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TESI DI DOTTORATO DI RICERCA

Treatment of Acute Coronary Syndromes in Older Adults

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ABSTRACT

Background

Despite the increased proportion of elderly patients among those admitted for an acute coronary syndrome (ACS), elderly population has been underrepresented in prospective studies and randomized clinical trials. Nevertheless, older people are often frail, which means that they have low reserve capacity and decreased ability to manage complex physiologic stress, with a significant multimorbidity burden. Accordingly, they deserve dedicated studies to better improve clinical decision making in daily practice.

Aim

To provide additional information on risk factors and prognosis of elderly patients admitted to hospital for an ACS.

Methods

The project was based on three post-hoc analyses of the Elderly ACS 2 Randomized Trial-NCT01777503. The trial included ACS patients aged≥75 years and aimed to compare clopidogrel versus prasugrel 5 mg on top of acetyl salicylic acid for long term secondary prevention and bleeding events. Three main research questions (RQ) were addressed: 1) the role of a specific inflammatory disease (psoriasis) as risk factor for ACS, evaluated within a case-control study; 2) the role of ST-segment elevation myocardial infarction (STEMI) as presenting ACS type as risk factor for cardiovascular, non-cardiovascular death and stroke, evaluated through a cohort study with competing risk analysis; 3) the role of the residual angiographic burden (after percutaneous coronary intervention-PCI) in predicting 1-year mortality and cardiovascular events, evaluated through the change in net benefit (NB) over a core prediction model including the most relevant clinical variables and basal angiographic burden.

Results

RQ1: The prevalence of psoriasis was lower among cases (12/1455, 0.8%) than among controls (18/1108, 1.6%). The multivariate OR of ACS according to history of psoriasis (adjusted for age, sex and smoking) was 0.51 (95% confidence interval-CI-: 0.23–1.09).

RQ2: Patients with STEMI had a higher risk of cardiovascular death (cause-specific hazard ratio, cHR 1.85; 95% CI: 1.02-3.36), non-cardiovascular death (cHR 2.10; 95% CI, 1.01-4.38), and stroke (cHR 4.8; 95% CI, 1.7-13.7) as compared to patients with NSTEMI.

RQ3: The inclusion of angiographic residual burden gave little incremental value in the standardized NB compared to the core model.

Conclusions

Our data does not support an association between psoriasis and risk of ACS in the elderly.

In these patients, STEMI is an important predictor of cardiovascular death, non-cardiovascular death and stroke.

The residual angiographic burden does not improve 1-year prediction of adverse outcome compared with a model including clinical variables and the basal angiographic burden.

Elderly patients are a heterogenous, complex, and high- risk group whose management requires a multidimensional clinical approach beyond coronary anatomic variables.

***All the materials reported has been published in the referenced manuscripts*.**

- *Morici N, Ferri LA, Alicandro G, Tortorella G, Tondi S, Vitrella G, Bongioanni S, Ferrario M, Naldi L, La Vecchia C, Colombo D, De Servi S, Savonitto S. Psoriasis and the risk of acute coronary syndrome in the elderly. Int J Cardiol. 2018 Dec 15;273:44-46. doi: 10.1016/j.ijcard.2018.07.134.*
- *Morici N, Savonitto S, Ferri LA, Grosseto D, Bossi I, Sganzerla P, Tortorella G, Cacucci M, Ferrario M, Crimi G, Murena E, Tondi S, Toso A, Gandolfo N, Ravera A, Corrada E, Mariani M, Di Ascenzo L, Petronio AS, Cavallini C, Vitrella G, Antonicelli R, Piscione F, Rogacka R, Antolini L, Alicandro G, La Vecchia C, Piatti L, De Servi S; Elderly ACS-2 Investigators. Outcomes of Elderly Patients with ST-Elevation or Non-*

ST-Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. Am J Med. 2019 Feb;132(2):209-216. doi: 10.1016/j.amjmed.2018.10.027.

- *Morici N, Alicandro G, Ferri LA, Piatti L, Grosseto D, Sganzerla P, Tortorella G, Ferrario M, Crimi G, Bossi I, Tondi S, Petronio AS, Mariani M, Toso A, Ravera A, Corrada E, Cao D, Di Ascenzo L, La Vecchia C, De Servi S, Savonitto S. Residual SYNTAX Score and One-Year Outcome in Elderly Patients With Acute Coronary Syndrome. CJC Open. 2020 Mar 20;2(4):236-243. doi: 10.1016/j.cjco.2020.03.005.*

1.0 INTRODUCTION

Aging is a progressive condition without a universally accepted age threshold, though in most cardiovascular treatment studies a cutoff of 75 years is the most recurrent.[1] Now the elderly population account for the 6% of persons overall,[2] but by the year 2050 the predicted proportion in Western countries is expected to reach 11.5%, with octogenarians growing even faster than the number of older persons overall.[2] This increased number of older persons among overall population, named population aging, can be considered the result of a demographic success story and is becoming one of the most significant social transformations of this century.[2] It fosters an increased cardiovascular burden, being heart disease and its related consequences more common in older adults. Indeed, two-thirds of all patients with cardiovascular disease (CVD) are >60 years of age, and >85% of very elderly population live with some form of CVD.[3,4]

Patients aged ≥75 years admitted to the Italian intensive coronary care unit (ICCU) network represent about 40% of the Non ST-segment Elevation acute coronary syndrome (NSTEACS) population and 30% of the STEMI population.[5,6] (**Figure 1)** These proportions have been confirmed in other western countries.[7] Actually, the admission rate of elderly patients with ACS admitted to hospital is even larger, considering that up to 17% of patients with confirmed myocardial infarction are not included in ACS retrospective and prospective registries because of a conservative management and the admission outside a cardiology department.[8]

Evidence to guide treatment strategies for ACS in elderly was modest before 2010, since most randomized clinical trials had been performed in younger populations.[9,10] Observations coming from national ACS surveillance systems across the European and American countries have consistently shown that elderly patients are less likely to receive

guidelines recommended therapies compared to younger patients.[11-13] This is not surprising because of physicians' awareness that the benefit of a more intensive treatment, including any stay in ICCU, can be counterbalanced by concurrent geriatric syndrome, increased risk of bleeding events, diminished quality of life, and functional decline.[4,14] Moreover, bed rest in critical elderly patients may induce more pronounced muscle weakness and cognitive deterioration, leading to worse short-term outcome.[15-17] However, specific prospective trials in elderly patients have been carried out over the last decade, both comparing medical and interventional treatment in the acute phase and tailored antithrombotic therapy in the post-acute phase and up to one year (**Figure 2**). Moreover, temporal trends over a period of fifteen years have shown an increased use of revascularization throughout both percutaneous coronary intervention (PCI) and coronary artery bypass (CABG), along with evidence-based treatments at discharge and a positive association of this approach with improved outcome.[5,18] On the other hand, guideline recommendations on post-acute drug therapy, particularly antiplatelet therapy, have been built upon the evidence from RCTs whose populations had a mean age of about 60 years and a much lower bleeding risk as compared to older patients:[19,21] also for this component of ACS care, age-specific trials have been conducted over the second half of the 2010[s] (**Figure 2**). Finally, about 12% of the elderly ACS population have atrial fibrillation: these patients are also being increasingly invasively treated,[22] but recommendations about subsequent antithrombotic therapy need tailored adaptation.

Based upon this increased body of evidence, care towards elderly with ACS should be tailored on individual basis, considering several aspects which will be detailed in the dedicated following sections: 1) risk benefit ratio of a more invasive approach compared to a conservative one; 2) indications to complete revascularization versus revascularization of the culprit vessel; 3) management of the clinical complexity and

multiple comorbidities; 4) contribution of cardiovascular mortality to the total mortality; 4) strategies of secondary prevention; 5) end of life issues.

1.1 *Risk benefit ratio of a guideline-recommended pharmaco-invasive approach*

Coronary reperfusion and appropriate secondary prevention medicines after an ACS event have shown to improve prognosis across age groups, included elderly and very elderly people, even after adequate adjustment for comorbidities.[23,24] However, the care of elderly patients in this setting is often complicated by three main factors: 1) the increased atherothrombotic and thromboembolic risk as well as bleeding risk compared to younger population;[25-28] 2) the presence of geriatric syndrome, which involves frailty, multimorbidity and polypharmacy;[29] 3) the risk of bed rest and ICCU environment.[15-17,29]

The hemostatic system changes considerably with aging. General physical deterioration, frailty, the presence of multiple comorbidities, and polypharmacy affect changes in the hemostatic balance, which may explain, at least in part, the increased risk of thrombosis and bleeding in the older adults. Increased platelet activation, increased platelet-monocyte interactions and dysregulated inflammation[30] along with higher levels of pro-thrombotic factors as fibrinogen, von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), and t-PA antigen[29] may explain the increased risk of thrombosis (**Figure 3**). On the other hand, age is an important risk factor for bleeding. A consensus document recently released from the Academic Research Consortium (ARC) has considered age ≥75 years as a minor criterion for high bleeding risk (HBR) in patients undergoing percutaneous coronary intervention (PCI). Patients qualified on the basis of age alone would experience a Bleeding Academic Research Consortium (BARC)[31] 3 or 5 bleeding rates <4% at 1 year.[32] However, older age is associated with other risk factors for bleeding, such as upper and lower gastroenteric causes of bleeding, colorectal and bladder

cancer, risk of falls and concomitant use of anti-inflammatory agents and anticoagulants. An issue often overlooked in elderly patients is that frailty may increase during hospitalization. Prolonged bed rest associated with critical illness leads to a significant loss of lean body mass and atrophy, especially in lower extremities, throughout decreased muscle protein synthesis and increased urinary nitrogen excretion (indicating muscle catabolism).[15,17,33,34] Considering that approximately 71% of male and 42% of female Americans ≥ 65 years can already be characterized as moderately sarcopenic, it becomes increasingly likely that even a brief and clinically mandated period of bed rest could initiate a serious decline in muscle strength and functional capacity.[35] Moreover bed rest may affect the kidney function (increased mineral excretion, calcinuria and proteinuria and decreased blood volume), pulmonary system (increased airway resistance) and red blood cells size and quantity (throughout a downregulation of bone marrow production).[16] All these issues must be taken into account when deciding about the most appropriate allocation of elderly patients. In general, whereas STEMI justifies systematic admission to ICCU due to the higher risk of life-threatening arrhythmia and cardiogenic shock, for NSTACS the benefit of ICCU admission versus a more liberal admission to a telemetry ward must be judged on a case by case basis, since routine ICCU use is unlikely to be beneficial for hemodynamically stable NSTEACS patients.[36]

1.1.1 Risk benefit ratio of a guideline-recommended pharmaco-invasive approach in patients with NSTEACS

Excluding the first trials realized in the early 1990s [as the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial[37] and the Veterans Affairs Non–Q-Wave Infarction Strategies In Hospital (VANQWISH)[38] trial], which included a limited number of patients aged ≥75 years, without routine availability of coronary stents and use of concomitant

thrombolysis, the appropriateness of a routine invasive strategy compared to a selective invasive approach in elderly patients with Non-ST Elevation acute coronary syndrome (NSTE-ACS) has been the object of more recent investigations. In the TACTIS-TIMI 18,[39] NSTEACS patients aged ≥75 years experienced an absolute reduction of 10.8 percentage points (10.8% vs. 21.6%; p = 0.016) and a relative reduction of 56% in death or myocardial infarction (MI) at 6 months in the early invasive arm compared to a conservative strategy, but at the price of a significant increase in major bleeding (16.6% vs. 6.5%). However, the results are not generalizable in the current era because of the systematic use of the GP IIb/IIa inhibitor tirofiban and the almost universal use of the femoral approach to catheterization.

In a collaborative analysis of individual data from the FRISC (Fast Revascularization during Instability in Coronary artery disease) II - ICTUS (Invasive versus Conservative Treatment in Unstable Coronary Syndromes)– RITA (Randomized Intervention Trial of unstable Angina Investigators)-3 (FIR) trials, 839 patients aged ≥75 years were considered for the final analysis (though this older group had a mean age of 76 years).[40] At 5-year follow-up the revascularization rate was about 75% in the routine invasive arm and approximated 50% in the selective invasive arm, with coronary artery bypass performed more frequently in elderly patients (about 50% of overall revascularization) compared to the younger. Patients aged ≥75 years experienced a cumulative event rate for MI and cardiovascular (CV) death of 30.3%, compared to 12% in patients aged< 65 years, with the routine invasive strategy being associated with a lower hazard of cumulative adverse event in elderly patients (unadjusted hazard ratio -HR- 0.71, 95% confidence interval -CI- 0.55 to 0.91, p=0.007) compared to patients < 65 years (HR 1.11, 95% CI 0.90 to 1.38, p=0.33). The HR did not significantly change after adjustment for

body mass index (BMI), diabetes, hypertension, prior MI, and the presence of ST depression ≥0.1 mV. With regard to gender, in this analysis the benefit of a routine invasive strategy was observed in men, but not in women (**Figure 4**). The incidence of bleeding events (reported in the ICTUS and RITA-3 trial) was 6.1%, slightly higher in patients with the routine invasive approach compared to the selective one. However, GP IIb/IIIa antagonists were used in the 94% of the PCIs during initial hospitalization in the ICTUS trial and in the 25% of the PCI in the RITA-3 trial. Moreover, in the RITA-3 trial bleeding events were arterial access or wound-site bleeds in the 76% of the intervention patients.

In the 2012 the Italian Elderly ACS study was published which randomized 313 patients with NSTEACS aged ≥75 years to an early invasive (EA) versus an initially conservative (IC) approach.[41] Random allocation of the treatment strategy took place at the time of admission. The primary endpoint (consisting of a composite of death, myocardial infarction, disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding within 1 year) was significantly reduced in patients with elevated troponin on admission assigned to an EA strategy compared to the IC (HR: 0.43; 95% CI: 0.23 to 0.80), but not in those without troponin elevation. Major bleeding events were rare (<1%). This might be explained by the much lower use of GP IIb/IIIa antagonists (<25%), compared to the above-mentioned studies, and because >70% of the PCI procedures were by the radial approach.[41]

The After Eighty trials also randomized 557 patients with NSTEACS aged 80 years or older to either an invasive or a conservative strategy, after initial stabilization: the composite 1-year endpoint of myocardial infarction, need for urgent revascularization, stroke, and death occurred in 40.6% of patients assigned to the invasive group and 61.4%

of patients assigned to the conservative group (HR 0.53, 95% CI 0.41–0.69; p<0.001).[42] The study achieved 90% radial access in patients randomized to the invasive approach, and reported a major bleeding rate of 1.7%; only patients randomized to the invasive strategy performed coronary revascularization (50% of the patients enrolled in this arm).[42] The results of these two studies are not to be considered conflicting if the rate of revascularization and the interaction for the treatment effect according to troponin status are taken into account. An additional difference to be considered is the time of randomization: on admission for the Italian Elderly ACS study, rather than after stabilization in the After Eigthy study. In a metanalysis of TACTIS-TIMI 18,[39] RITA-3, FRISC II, ICTUS,[40] Italian Elderly ACS[41] and After Eighty trials[42] patients allocated to the routine invasive strategy experienced a lower risk of death and MI at the longest follow-up available (mean 36, interquartile range 6-60 months) (odds ratio -OR-, 0.65; 95% CI, 0.51-0.83; p<0.001) mostly driven by a statistically significant reduction of MI (OR, 0.51; 95% CI, 0.40-0.66; p<0.001) and a trend towards a lower death rate, with no heterogeneity among the included studies.[43] The incidence of major bleeding was not statistically different among the two different strategies (OR for routine invasive approach, 1.96; 95% CI, 0.97-3.97; p=0.06).[43] When the pooled analysis was extended in order to include 9 observational studies (all prospective except one), which allowed to include 21.864 elderly NSTEACS patients, the early invasive strategy, compared to a initially conservative approach, was associated with a lower risk of death (relative risk -RR- 0.65, 95% CI 0.59–0.73, p < 0.001), MI (RR 0.58; 95% CI 0.46–0.72, p < 0.001), and stroke (RR 0.54; 95% CI 0.30–0.97, p = 0.040) up to 5 years of follow-up; major bleedings were comparable, whereas if any in-hospital bleeding was considered, the incidence was increased in patients treated with an early invasive approach.[44] In the real-word cohort of 968.542 octogenarians with NSTEACS included in the Nationwide

Inpatient Sample (NIS) database, the largest publicly available all-payer inpatient care database in the United States, patients treated with an early invasive strategy (806.902, 83.3%) experienced lower rates of in-hospital intracranial hemorrhage (adjusted OR 0.59; 95% CI, 0.51-0.70) and gastrointestinal bleeding (adjusted OR 0.63; 95% CI, 0.60-0.65) compared to the 161.640 patients (16.7%) managed with an initial conservative approach; in-hospital death was consistently lower in patients with an early invasive approach, with a similar benefit in men (adjusted OR 0.74; 95% CI, 0.71-0.77, p<0.001) and women (adjusted OR 0.78; 95% CI, 0.75-0.81, p <0.001).[45] Technological advances such as less thrombogenic intracoronary stents and tailored use of antithrombotic treatments, along with less selection biases for an early invasive approach may explain this favorable and consistent decrease in adverse ischemic and bleeding events in elderly patients managed with an invasive approach in the more recent studies[39-46] compared to previous randomized and observational data.[38,47] Indeed, in the MOSCA (coMOrbilidades en el Síndrome Coronario Agudo) study, which included 106 patients aged ≥70 years randomized to an invasive versus a conservative strategy in patients with NSTEACS, the radial approach was used in 91% of the procedures and drug eluting stents were implanted in 47% of the procedures. Any bleeding classified as TIMI≥2 was 13% in the invasive group and 18% in the conservative approach; the invasive approach led to an advantage in the first 3-month follow up, which decreased thereafter.[48]

These results are further confirmed by the recently published SENIOR-NSTEMI cohort study, performed including bid data of NSTEMI patients aged ≥ 80 years obtained from five collaborating hospitals hosting the National Institute for Health Research (NIHR) Biomedical Research Centres, throughout the target trial approach.[49,50] A propensity score model was applied selecting 655 patients included in the early invasive strategy and 845

in the initially conservative management (evaluated by intention-to treat). The rate of revascularization in the invasive arm was 74%. At 5-year follow death the adjusted risk of dying was reduced by 44% in the early invasive group (HR 0.56; 95% CI 0.45-0.70), with lower mortality emerging from 1 year of follow-up onwards.[50] Rehospitalization for heart failure was decreased too (16% in the early invasive group versus 22% in the early conservative). The adjusted HR for re-hospitalization for bleeding was neutral (5.0% in the invasive group versus 4.7% in the non-invasive group; HR 0.93; 95% CI 0.52-1.65; p=0.801). According the above presented results there is therefore a general consensus that an early invasive approach in elderly patients admitted for NSTEACS should not be denied a priori and at least evaluated on an individual basis. In the recently released ESC guidelines on NSTE-ACS it is recommended for older people to apply the same diagnostic and interventional strategies used for younger (IB), considering on individual case basis "ischaemic and bleeding risks, estimated life expectancy, comorbidities, the need for non-cardiac surgery, quality of life, frailty, cognitive and functional impairment, patient values and preferences".[51]

Stronger evidence will be available with the results of the SENIOR-RITA trial, aimed to compare an invasive to a non-invasive management strategy in patients aged 75 years or older with NSTEMI. The main endpoint will be a composite of cardiovascular death and non-fatal myocardial infarction and the final completion date is expected in the 2029.[52]

1.1.2 Risk benefit ratio of a guideline-recommended pharmaco-invasive approach in patients with STEMI

The European Society of Cardiology Guidelines state that "There is no upper age limit with respect to reperfusion, especially with primary PCI (PPCI)".[53]

However, concerns about high comorbidity prevalence [eg, chronic kidney failure, chronic obstructive coronary disease (COPD), diabetes mellitus and previous coronary heart disease or stroke], often lead to lower indication of catheterization and PPCI in elderly patients.[6,54]

In a registry conducted in Spain from 2003 to 2012 and including 302.471 patients, 116.621 received PCI (38.6%), 46.720 fibrinolysis (15.4%) and 139.130 had no indication of reperfusion (46%). The mean age of each group was 63.4, 63.7 and 71.8 years old, respectively, with mortality ranging from 4.8% in the PCI-treated patients versus 17.3% for the group without any reperfusion therapy.[54]

This therapeutic nihilism was partly justified in the thrombolytic era due to the fear of bleeding complication in elderly patients. Indeed, despite preliminary evidence from subgroup analyses and meta-analyses that thrombolytic therapy could lead to net benefits and cost-effective results in elderly patients,[55,56,57] well-conducted nationwide retrospective registries suggested that thrombolytic therapy for patients >75 years old was unlikely to confer a significant survival disadvantage because of an increased hemorrhagic risk.[58] Conversely, randomized trials and metanalysis of primary angioplasty versus thrombolysis in elderly patients have showed that PCI is more effective compared to lytic strategy [58,59,60] and its more widespread use has significantly improved patients outcome.[6,61] In consecutive CCU registries conducted in Italy from 2001 to 2014, a progressive shift from predominantly lytic to predominantly PCI reperfusion treatment was observed in the overall population, including elderly patients.[6] In the older age group, lytic therapy decreased from 36% to 2% in men, and from 28% to 1% in women; primary PCI increased from 10% to 74% in men and from 8 to 71% in women; and no-reperfusion decreased from 54% to 23% in men and from 64% to 27% in women. Over the

observation period, in-hospital mortality among men aged ≥75 years declined from 18% to 7%, and among women from 23% to 11%. Similar temporal trends were observed in Spain, with a 50% reduction in 30-day and 5-year mortality from 1988 to 2008 in elderly patients with organization of the STEMI network, reduction in the rates of no reperfusion and the progressive shift from lytic therapy to PCI.[62]

A retrospective analysis recently performed among 979 patients with STEMI aged ≥ 75 years has suggested, in a regression model adjusted by propensity score, a lower risk of dying or presenting with reinfarction, acute pulmonary oedema or cardiogenic shock during the hospitalization for patients treated with primary PCI (PPCI) (OR 0.55, 95% CI 0.34-0.89).[63]

1.1.3 *Risk benefit ratio of a guideline-recommended pharmaco-invasive approach: the Gender issue*

Several reports have addressed the age-gender issue in patients admitted with ACS, showing that sex-based differences in the rates of events varied according to age.[64-69]

The younger the patients are, the worst short and long-term outcome usually is for women compared to men, because of a different pathophysiology of CAD in pre- menopausal and middle-aged women. Younger women most probably benefit from hormonal protection against ischemic heart disease, but those who experience ACS are more prone to ischemic events because more cardiovascular factors, as smoking, diabetes, hypertriglyceridemia, and metabolic syndrome have accrued over time.[70] Moreover, sex-related differences in arterial size and remodeling have been demonstrated and linked to ischemic heart disease.[71,72] Conversely, postmenopausal women with an ACS have less

extensive coronary disease as compared to men of same age[73] and have similar rates of in-hospital adverse outcomes and similar or better follow-up course.[63-68]

Despite differences in treatments have been reported and reinforced the myth of sex-related bias,[72] it appears from observational studies that different outcome might be explained by advanced age and clustering of comorbidities.[66]

To further test this hypothesis, we have performed a pooled analysis of a prospective cohort of patients presenting with an ACS enrolled in three Italian multicentre studies (the Italian Elderly ACS study- NCT00510185,[41] the LADIES ACS study- NCT01997307[73] and the Elderly ACS 2 Randomised Trial- NCT01777503[74]). Whereas the first two studies enrolled exclusively patients aged >74 years, LADIES ACS enrolled patients >55 years. Details on study design and results have been described elsewhere.[41,73,74] From the overall cohort of 2,776 patients, 425 (15.3%) (enrolled in the LADIES ACS study) aged <75 years were excluded from the present analysis. Ninety-eight patients (3.4%) were further excluded because of missing information after discharge. Therefore, the final population included 2,253 ACS patients aged ≥75 years. Elderly women showed a lower prevalence of vascular history, in both ACS presentations. (**Figure 5**) Female gender was not associated with worse outcome, after adjustment for main relevant baseline covariates (age, prior PCI, prior CABG, prior MI, current smoker, dyslipidemia, history of peripheral vascular disease, creatinine values on admission) and invasive management during the index event both in patients with STEMI (HR 1.46, 95% CI 0.88-2.46, p=0.143) as well as in patients with NSTEACS (HR 0.63; 95% CI 0.38-1.067, p=0.087). (data not published)

In light of the above reported consideration, prevention strategies towards the underlying risk factors and the best pharmaco-invasive approach, based on reasoned clinical judgment, should be similar in older women and men.

1.1.4 *Risk benefit ratio of a guideline-recommended pharmaco-invasive approach: cardiogenic shock*

A final consideration should be deserved to elderly patients with myocardial infarction complicated by cardiogenic shock. Even if data coming from the SHOCK trial in patients aged ≥75 years shown no benefit from early revascularization, elderly patients were widely underrepresented and highly selected.[75] Actually, data drawn from a more rea-world setting showed opposite results suggesting that despite higher rates of high-risk comorbidities in elderly patients with ACS complicated by cardiogenic shock, their survival rates in hospital and at 1 year were not significantly different from survival rates in the younger group. There were also no significant differences about major adverse cardiovascular events (MACE), MI, target lesion revascularization, and target vessel revascularization rates.[76]

1.2 Complete revascularization versus culprit only

Approximately 50% of patients presenting with STEMI have other obstructive lesion in a non-culprit vessel at index presentation,[77,78] with this finding associated with worse short- and long-term outcomes.[79]

The prognostic advantage of complete revascularization compared to a culprit lesion only strategy has been investigated in ACS patients both with[80] and without cardiogenic shock,[81,82] achieving different results in stable versus unstable setting.

In STEMI patients without cardiogenic shock and multivessel coronary artery disease enrolled in the COMPLETE trial, the revascularization of angiographically significant non-culprit lesions significantly decreased the incidence of cardiovascular death and myocardial infarction at a median follow-up of 3 years (HR 0.74; 95% CI 0.60 to 0.91; P=0.004), independently of the intended timing of non-culprit lesion PCI.[55] These results were confirmed in a recent meta-analysis (mostly driven by the COMPLETE study data, the larger among the ten included trials).[82] Details about the representativity and outcome of the elderly population were not reported. However, in the subgroup analysis of the COMPLETE trial comparing patients aged <65 years to patients aged ≥65 years, the benefit of complete revascularization was lost in the latter, even though the age per treatment interaction was not statistically significant.[81]

Conversely, in the CULPRIT-SHOCK trial, including patients with STEMI complicated by cardiogenic shock, 30% of the overall study had ≥75 years and experienced the same treatment effect of the overall trial population. The primary endpoint of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization occurred in 70 out of 115 patients in the culprit only arm (60%) compared to 72 out of the 99 patients enrolled in the multivessel arm (72.7%) (HR 0.84; 95% CI 0.69-1.01).[80]

In this context we have explored the research project 3.[83]

1.3 Management of the clinical complexity and comorbidities

Since its first definition in 1970,[84] comorbidity, i.e. the combination of additional diseases beyond an index disorder, has been regarded as a dominant health care burden strongly related to aging.[85] Moreover, epidemiological researches indicate that longstanding illnesses have increased over decades in older people with independent additive

significant effects of gender, age and education on the odds of having complex health problems.[86] Indeed, elderly people may experience multimorbidity, defined by two or more coexisting chronic conditions in 55-98% of the cases, with multimorbidity being associated with functional impairment, poor quality of life and health adverse outcomes.[85,87-89] This is not surprising, considering that older people are often frail, which means that they have low reserve capacity and decreased ability to manage complex physiologic stress.[86] Along this line, in a recently published research by our group on the definition of a prognostic score for patients discharged alive after an ACS event, a multiparametric evaluation, including complete blood count (as marker of well-being and frailty out of the acute event) and patient comorbidities (measured throughout the age-adjusted Charlson Comorbidity index), could better classify patient risk and allow for a tailored and improved management.[89]

However, there are not enough data so far to provide evidence-based recommendations for the care of patients affected by multimorbidity, that are mostly managed using a case by case approach.

Clinical decision making with multimorbidity requires complex communications and collaborations among generalists, specialists, nurses, and patients. An assessment of the social context (general home conditions, caregivers) is an essential part of the initial patient evaluation.

In a systematic review exploring the experience of clinical management with multimorbidity of 257 general practitioners in 7 different countries, four domains were identified as critical areas to be addressed: a) disorganization and fragmentation of healthcare, with specialists blamed for not considering the wider harms and benefits of organ-specific intervention; b) the inadequacy of guidelines and evidence-based

medicine, usually set for optimum conditions rather than real-life complexity; 3) challenges in delivering patient-centered care, by incorporating non-medical or psychosocial issues; 4) barriers to shared decision-making, considering the difficulty in eliciting patient's preferences.[90]

In a systematic assessment of the comorbidity-related content of clinical practice guidelines (CPGs), along with the evidence that supports their content, 20 guidelines were analyzed. Among them, 17 (85%) addressed the issue of comorbidity, fourteen (70%) provided specific treatment recommendation for patients with comorbid conditions, but none of them specified the management of patients with more than one comorbid condition. Moreover, the comorbidities taken into account were mostly concordant, i.e. representing the same overall pathophysiological risk profile, and the level of evidence of the studies was generally weak.[91]

In 2010 an interesting epidemiological study on multiple-diseased elderly patients admitted to hospital with NSTEACS was conducted among 370 cardiologists in Sweden. Multiple-diseased elderly were defined as follows: "Individuals 75 years of age or older, who have received inpatient hospital care three or more times during the past 12 months and who have three or more diagnoses in three or more diagnostic groups according to the ICD-10 classification system".[92] Although about 80% of the included cardiologists reported to use CPGs in these patients, the most frequently used sources in their clinical decision-making were the individual cardiologist's own clinical experience and patient views. This behavior could be a reasonable approach given the limited generalizability of currently available guidelines to elderly patients with comorbidities who may experience futility or damage of using polypharmacy.[92]

Organizational and patient-oriented interventions are advocated for these patients.[93]

A first step is to decide which multimorbidity measure to use in research and clinical practice. Five multimorbidity measures (disease counts, selected conditions count, Charlson comorbidity index, RxRisk-V, medication counts) were tested among 862 elderly community-dwellers followed-up for 2 years, in order to assess their performance in predicting emergency admission and ambulatory care sensitive admission and functional decline.[94] All these measures demonstrated poor discrimination (c-statistic range: 0.62, 0.65) and, according the optimal cut-point chosen, the percentage of population categorized as multimorbid changed considerably. A feasible approach already tested could be to define as multimorbid elderly patients with two or more chronic conditions prescribed four or more medications.[95] For the prognostic assessment of elderly patients discharged alive after an ACS, complete blood count and age-adjusted Charlson Comorbidity index should be evaluated.[88] A simplified comorbidity assessment comprising 6 comorbidities (renal failure, anemia, diabetes, peripheral artery disease, cerebrovascular disease and chronic lung disease) could provide useful risk stratification too.[96] A clinical judgments about frailty developed using the clinical frailty scale (CFR) would complete patient assessment in order to tailor more invasive management and discharge approach.[97,98]

A main shortcoming in patient management is the tendency to focus on a single diagnosis. A Norwegian randomized trial performed in elderly patients admitted for acute disease showed consistent benefit in decreasing early mortality (up to 3-month follow up) within Geriatric Evaluation Management Units (GEMUs). They are based on an interdisciplinary evaluation to treat all relevant diseases, prevent iatrogenic complications, provide early mobilization and plan early discharge in collaboration with family members and representative from the home services.[99]

Finally, a therapeutic approach that takes into account frailty in older people should consider specific aims related to prescribed medications. International consensus principles have just been generated by the Optimizing Geriatric Pharmacotherapy through Pharmacoepidemiology Network.[100] They are based on medication reconciliation and appropriate deprescribing in order to minimize medication burden. The contribution of medications to the geriatric syndrome should always be considered.

Nevertheless, an invasive strategy with coronary angiography and revascularization should not be denied only on the basis of frailty, but it should be carefully evaluated on individual basis. Several studies demonstrated that even though frailty does confer a higher mortality risk, PCI in this frailer older group hospitalized for MI provides strong survival benefit,[101,102] with a rate of in-hospital complications not significantly different between frail and non-frail patients [procedural complications were 3.3% in frail vs. 5.7% in non-frail (p=0.377), whereas in-hospital complications were 8.2% vs. 3.3% (p=0.136), respectively].[103]

1.4 Cardiovascular versus Non-cardiovascular mortality in elderly ACS patients

Even if ageing can contribute mostly to the general decline and death, when pre-specified adjudication criteria are adopted and observations are limited to elderly patients admitted for ACS, several reports have confirmed the importance of cardiac causes, mostly ischemic, to the global burden of overall death. This contribute ranges from 50% to 80%,[21,104] dependent on the inclusion of the secondary causes of death.[105]

In a population of United States acutely sick frail patients aged 75 and older admitted to a department of internal medicine, heart disease was the major cause of death (50% of the patients who died) at both 3 and 12 months, followed by infectious disease.[87]

In the Italian Elderly ACS trial of patients ≥75 years of age with NSTEACS (41% undergoing revascularization) cardiovascular death was defined according to the MONItoring trends and determinants of CArdiovascular disease (MONICA) criteria[106] and contributed to the 80% of the overall death at 1-year follow up.[104] In the Elderly ACS-2 clinical study (100% undergoing PCI), cardiovascular death was defined as death due to atherosclerotic coronary heart disease, cerebrovascular accident or (complication of) peripheral embolization, and includes deaths due to acute MI, stroke, sudden death, non-sudden death, unwitnessed death, and procedure-related deaths: 1-year cardiovascular death was 59% of the overall death.[74]

In a post-hoc analysis of the AleCardio trial, testing the effect on cardiovascular outcomes of the dual peroxisome proliferator-activated receptor agonist aleglitazar in patients with type 2 diabetes mellitus and recent acute coronary syndrome, the predictors of long-term mortality were investigated. Among the 7226 patients included (median age 61, range interquartile 54-68, 77.7% with revascularization in the acute phase) all-cause mortality at 2-year follow-up was 4%, with cardiovascular death contributing for 73% of the overall causes.[107] When only patients aged ≥75 years were selected, among a final population of 634 patients enrolled (71% with acute revascularization), overall mortality raised to 21%, with cardiovascular death still contributing for the 55% of the total burden.[107]

In the POPular AGE trial, including NSTEACS patients aged ≥70 years (65% with acute revascularization) randomized to different $P2Y_{12}$ inhibitors treatments, the following causes of death were captured: vascular, cardiovascular, cerebrovascular, bleeding and unknown. At 1-year follow-up, cardiovascular death contributed for the 45% of the overall mortality.[108]

Figure 6 described the pooled association between cardiovascular death and invasive management, adjusted by age in patients aged >74 years enrolled in the Elderly ACS, Elderly ACS 2, Ladies and Alecardio Trial.

All the above reported results suggest that mortality after admission for ACS, even in elderly and very elderly multimorbid people, is largely dominated by markers of ischemic damage. This finding should prompt greater efforts toward improving strategies of secondary prevention and tight follow-up in elderly patients discharged alive after an ACS index event.

1.5 Strategies of secondary prevention

Long-term secondary prevention in ACS patients requires balancing the risk of ischemic and bleeding complications. This is mostly true in elderly patients, who are at increased risk of both ischemic and bleedings events.[109-111]

In the general population, the residual risk of death, myocardial infarction and stroke up to 1 year after an ACS achieves 10%, with major bleeding events ranging from 1 to 3%.[112] In elderly patients the residual risk of death, myocardial infarction and stroke is higher up to 18-20%,[21,74] rising to 50% if urgent revascularization is included.[34] Severe bleeding, defined as any intracranial bleeding or bleeding leading to hospitalization and/or blood transfusion, occurring within the first year after discharge after an ACS index event, has been reported in 5.6% of the patients.[110]

Therefore, optimizing the balance between ischemic and bleeding risk still represents a challenge for physicians managing elderly ACS patients.

1.5.1 Secondary prevention and acetylsalicylic acid

The Antiplatelet Trialists' Collaboration reported a 4.5% absolute reduction in vascular events in at-risk patients aged ≥ 65 years. The number needed to treat (NNT) to prevent 1 death was 67, whereas the NNT for 1 non-fatal gastrointestinal event was 100.[113]

In the second International Study of Infarct Survival trial, patients randomized to one month of 160 mg/day enteric-coated ASA experienced a 21% event reduction compared to placebo (17.6% vs 22.3%) with a relative treatment effect even larger in patients aged 70 and over versus 60-69.[114]

Finally, among 5490 consecutive Medicare beneficiaries who survived an acute myocardial infarction, the 4149 patients (76%) who were prescribed aspirin at hospital discharge had better left ventricular ejection fraction and lower mortality 6 months after discharge compared with no prescribed aspirin (odds ratio, 0.77; 95% CI 0.61 to 0.98), even after adjustment for baseline differences in demographic, clinical, and treatment characteristics between the two groups.[115]

1.5.2 Secondary prevention and dual antiplatelet therapy (DAPT)

$P2Y_{12}$ inhibitors associated to ASA have become the cornerstone of secondary antithrombotic treatment since the routine use of coronary stents.[116] However, the selection of optimal type and duration of $P2Y_{12}$ inhibitor in the elderly remains an open issue.[117]

The focused update on dual antiplatelet therapy (DAPT) released by the European Society of Cardiology in 2017 defined elderly patients as a high-risk underrepresented subgroup.[118] Based on the available data, this consensus did not provide specific recommendation for elderly people, but did suggest to customize the choice of type and

length of $P2Y_{12}$ therapy, optimizing radial artery access for any invasive procedure and using proton pump inhibitors to avoid gastrointestinal hemorrhages.[118]

Since the landmark CURE trial[19] the standard of care of DAPT regimen in elderly patients has been represented by the thienopyridine-type $P2Y_{12}$ receptor blocker clopidogrel, in association with aspirin. Despite slower speed of onset and higher rates of poor response, as compared to the newer agents, this association has long represented the standard of care in DAPT regimens in elderly patients with ACS, mainly because of safety concerns.[18]

Indeed, the TRITON-TIMI 38 trial randomized ACS patients treated with PCI to prasugrel 10 mg versus clopidogrel 75 mg, showing the superiority of prasugrel in reducing ischemic events (including myocardial infarction, urgent target vessel revascularization and stent thrombosis).[20] However, in patients aged 75 or older the benefit was counterbalanced by an excess in life-threatening bleeding events. This can be explained by higher levels of prasugrel active metabolite, as shown by a pharmacokinetic sub-study from the same trial.[119]

More recent pharmacodynamic studies have shown higher platelet reactivity in elderly patients ,[109,120] and that switching from clopidogrel to prasugrel 5 mg (rather than the full 10 mg dose) may be sufficient to enhance platelet inhibition.[121] However, fine tuning of the $P2Y_{12}$ antagonist effect, by adjusting the dosage based on the results of platelet function tests, has not been found to improve outcome as compared to the standard combination of aspirin and clopidogrel, both for patients treated with an invasive[122] and a conservative strategy.[123]

The Elderly ACS 2 study was a randomised trial comparing a daily maintenance dose of prasugrel 5 mg with the standard clopidogrel 75 mg in patients >74 years undergoing PCI

during index admission for an ACS. At 1-year follow-up, the primary endpoint (composite of mortality, myocardial infarction, disabling stroke and re-hospitalization for cardiovascular causes or bleeding) occurred at almost the same rate in the two arms (HR 1.007, 95% CI, 0.78-1.30; p =0.955), with neutral effect in the ischemic outcome and increased, even though not statistically significant, BARC bleeding events >2 in the prasugrel group (4.1% vs 2.7%; OR 1.52, C.I. 0.85-3.16, p= 0.18).[74] Improved pharmaco-invasive strategies and generally low rates of adverse event, may partly explain these findings.

In the PLATO trial the reversible, direct-acting inhibitor of the adenosine diphosphate receptor $P2Y_{12}$ ticagrelor was compared to clopidogrel in a randomized fashion. Among the 18,624 patients, the primary end point (a composite of death from vascular causes, myocardial infarction, or stroke) had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (HR 0.84; 95% CI 0.77 to 0.92; P<0.001).[21]

In a subanalysis of the PLATO trial[124] investigating the interaction between age and treatment effect, patients aged ≥ 75 years experienced the same benefit of the overall cohort in terms of decreased ischemic event, without a relevant increase in PLATO-defined major bleeding events (HR 1.02; 95% CI 0.82– 1.27). The rate of TIMI non–CABG-related major bleeding was lower for patients aged >75 years treated with clopidogrel versus ticagrelor (2.0%/year versus 2.4%/year; P=0.02), and the same difference occurred for the GUSTO mild bleeding (9.3%/year versus 10.4%/year; P=0.02). These results were partly contradicted in a subsequent analysis of the same study showing a significant interaction between age and treatment effect with age dichotomized at 65 years: in the 5416 patients treated by PCI during admission (similar to the TRITON-

TIMI 38 population), the primary endpoint was reduced by ticagrelor in patients <65 years of age (HR 0.59, 95% CI 0.41-0.85), but not in those ≥65 years (HR 1.17, 95% CI 0.85-1.61; P for interaction <0.01).

In the most recently published POPular AGE trial, which enrolled 1002 patients with NSTE-ACS aged 70 or older to clopidogrel versus stronger $P2Y_{12}$ inhibitors (ticagrelor in 95% of the cases), PLATO-defined major and minor bleeding events were lower with clopidogrel compared to the ticagrelor strategy (18% versus 24%; HR 0.71, 95% CI 0.54-0.94; p=0.02 for superiority) without paying the price of an increased risk of ischemic events (28% vs 32%; absolute risk difference –4%, 95% CI –10·0 to 1·4; p=0.03 for non-inferiority).[108]

Overall considered, these results suggest that standard 12-month treatment using either prasugrel or ticagrelor, rather than clopidogrel, have an unfavorable trade-off between ischemic and bleeding risk in frailer patients.

1.5.3 De-escalating antiplatelet potency after the acute phase

An ideal approach should be to perform an accurate patients' stratification able to drive the best antithrombotic treatment. However, available tools need ad hoc validation and at the moment cannot be generalizable in a contemporary elderly population.[111]

In order to overcome the bleeding risk related to a stronger inhibition, a de-escalation strategy, able to harmonize the time-dependency of thrombotic and bleeding risk, has been recently suggested.[125,126]

Data coming from real-word ACS population[127] and from post-hoc analysis of the Elderly ACS 2 study,[125] confirmed that the ischemic risk is particularly high in the first month

and up to three months after an ACS event, especially in patients with STEMI. Afterwards, the bleeding risk may overcome the ischemic burden. This perspective opens two scenarios: de-escalate from prasugrel/ticagrelor to clopidogrel after the first 1-3 months of stronger $P2Y_{12}$ inhibition or consider monotherapy with ticagrelor/prasugrel (optimal dose to be established), or even clopidogrel. Monotherapy is an interesting option considering that 10% of elderly patients admitted for ACS will need concomitant anticoagulant therapy for atrial fibrillation.[127] The GLOBAL LEADERS was a multi-center, multinational, open-label trial that compared two strategies of antiplatelet treatment: an experimental strategy of 1-month aspirin and ticagrelor, followed by 23 months of ticagrelor alone compared to a reference strategy of 12-month DAPT consisting of aspirin in combination with either clopidogrel (for stable CAD) or ticagrelor (for ACS patients).[128] The frequency of all-cause mortality, new Q-wave myocardial infarction, definite stent thrombosis, or investigator-reported BARC grade 3 or 5 events did not differ significantly between groups at 2-year follow-up, both for the ACS and stable CAD populations. A pre-specified analysis involved the 2.565 patients out of 15.968 (16.1%) aged >75 years.[129] The primary endpoint of two-year all-cause mortality or new Q-wave core lab-adjudicated MI occurred in 7.2% and 9.4% of patients in the ticagrelor monotherapy and the reference group, respectively, (HR 0.75, 95% CI 0.58-0.99; p=0.041) with a favorable interaction of age and treatment towards protection of stent thrombosis with ticagrelor monotherapy; BARC 3 to 5 bleeding events occurred in 5.2% and 4.1%, respectively (HR 1.29; 95% CI 0.89- 1.86; p=0.180). However, this approach requires further evidence.

Figure 5 reports a suggested algorithm based on a summary of the above reported data.

1.5.4 Secondary prevention and Statins

Data on the use and dose of statin therapy in elderly patients with ACS are relatively scanty and often conflicting.[24, 130-134]

Pooling together the available evidence, statin administration seems mostly a marker of less frail patients and optimal pharmaco-invasive treatment.[24, 130-134]

Moderate dose could provide the same benefit than higher doses.[133]

2.0 AIM

Three main issues were explored: 1) the role of a specific inflammatory disease (psoriasis) as risk factor for ACS, evaluated within a case-control study (research project 1); 2) the role of ST-segment elevation as presenting ACS type as risk factor for cardiovascular, noncardiovascular death and stroke, evaluated through a cohort study with competing risk analysis (research project 2) ; 3) the role of the residual angiographic burden (after percutaneous coronary intervention-PCI) in predicting 1-year mortality and cardiovascular events, evaluated through the change in net benefit (NB) over a core prediction model including the most relevant clinical variables and basal angiographic burden (research project 3).

3.0 RESEARCH PROJECTS

The three papers performed for each PhD course will be discussed in detail.

3.1 Research project 1:

3.1.1 Population and study design of the manuscript: Psoriasis and the risk of acute coronary syndrome in the elderly.[135]

We conducted a case-control study based on 1455 cases of ACS and 1108 population controls. Cases were all patients enrolled in the Elderly-ACS 2 trial, a randomized clinical trial aiming to evaluate different antiplatelet treatment strategies in patients aged ≥75 years with ACS undergoing PCI during index admission.[47] The study was carried out at 32 centers in Italy between November 2012 and April 2017. Patients were interviewed during index admission by each site investigator. The following set of information were collected: cardiovascular risk factors, previous medical history (with a specific question regarding history of psoriasis), and previous medications. Information on psoriasis included duration of disease, Psoriasis Area Severity Index (PASI)[51] and ongoing treatment.

Controls were selected from patients included in the Prevalence of Actinic Keratoses in the Italian Population Study (PraKtis).[52] This was an observational study based on a sample of 12,483 subjects' representative of the whole Italian population aged 45 years and over.

3.1.2 Statistical Analysis

Sex, age distribution and smoking prevalence were compared between cases and controls by the χ^2 test. We computed the odds ratio (OR) of ACS according to history of psoriasis, the corresponding 95% confidence interval (CI), using unconditional multiple logistic regression, including terms for age, sex, and smoking. Analyses were performed using R version 3.2.3.

3.1.3 Results

Patients with ACS were more likely to be male and older than controls (Table 1A). The percentage of ever smokers was similar in cases and controls (34.2% vs. 35.4%).

All but one psoriasis patients were men. The mean PASI score was 4.9 (range 1–20), with only one patient being affected by psoriatic arthritis. Six patients were on no psoriasis treatment, three on topic therapy only, one on methotrexate and calcipotriole, one on betamethasone and calcipotriole, and one on sekukinumab. Psoriasis duration was >20 years in 10 cases and >10 years in two.

The prevalence of psoriasis was lower among ACS cases (12/1455, 0.8%) than among controls (18/1108, 1.6%), corresponding to an unadjusted OR of 0.50 (95% CI: 0.24–1.04). After adjusting for sex, age and smoking status the OR did not substantially change (OR: 0.51, 95% CI 0.23–1.09) (Table 2A).

3.1.4 Tables

Table 1A. Sex, age distribution and smoking prevalence among cases and controls

	Cases	**Controls**	**P value** [a]
	n (%)	n (%)	
Number of patients	1455 (100)	1108 (100)	
Sex			<0.0001
Males	873 (60.0)	427 (38.5)	
Female	582 (40.0)	681 (61.5)	
Age categories (years)			<0.0001
75-79	678 (46.6)	738 (66.6)	
80-84	481 (33.1)	287 (25.9)	

85+	296 (20.3)	83 (7.5)	
Ever smokers	498 (34.2)	392 (35.4)	0.57

[a] between-group comparison by χ^2 test

Table 2A. Distribution of 1455 cases of acute coronary syndrome (ACS) and 1108 controls according to prevalence of psoriasis and corresponding odds ratios (ORs) and 95% confidence intervals (95%CIs)

History of psoriasis	ACS Cases N (%)	Controls (%) N (%)	OR[a] (95%CI)	OR[b] (95%CI)
No	1443 (99.2)	1090 (98.4)	1	1
Yes	12 (0.8)	18 (1.6)	0.49 (0.22-1.06)	0.51 (0.23-1.09)

[a] estimated from an unconditional multiple logistic regression model adjusted for sex and age

[b] further adjusted for smoking

3.1.5 Discussion

We did not find a higher prevalence of psoriasis in our ACS population compared to a representative sample of the general Italian population aged >75 years.

The present results are in broad agreement with some of the previous reports. In a record linkage study, based on the UK General Practice Research Database,[136] an excess risk of MI was reported in patients with psoriasis. However, the association was stronger in younger subjects and decreased in subjects aged 60 or over, with relative risks of 1.29

and 3.10 in younger and 1.08 and 1.36 in older subjects for mild and severe psoriasis, respectively.[136] Similar results were obtained from the same UK data source when the crude incidence rates (IRs) of MI were assessed in patients with psoriasis and compared in a nested case-control analysis: the OR was 1.66 for patients aged <60 years and 0.99 in patients aged ≥60 years.[137] Among a UK cohort of 48,523 patients with psoriasis and 208,187 controls (median age 48 years), the presence of severe psoriasis was associated with an increased risk of composite major cardiovascular events (myocardial infarction, acute coronary syndrome, unstable angina, and stroke) in the age-and gender-adjusted analysis (HR 1.40 (95% CI: 1.07–1.84), whereas in the fully adjusted model the HR was not significant (HR 1.28 (95% CI: 0.96–1.69).[138]

A possible explanation is that in younger patients with less comorbidities, the inflammatory status generated by psoriasis, particularly if severe, may especially affect the atherothrombotic risk, whereas in older patients who have a baseline increased risk of MI for multiple factors, the RR of MI related to psoriasis becomes attenuated.

We did not have information on the prevalence of ACS in the control group or on body mass index, diabetes, hypertension and other potentially relevant risk factors, except smoking. The absence of information of ACS in the control group is an important limit for the concept of the case-control study. The number of subjects with psoriasis was limited in both cases and controls and this could substantially affect results. However, we were able to exclude a 10% excess ACS risk reported in previous studies.[136]

3.2 RESEARCH PROJECT 2:

3.2.1 Population and study design of the manuscript: Outcomes of Elderly Patients with ST-Elevation or Non-ST-Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention.[139]

Overall, 1443 patients were enrolled across the ACS spectrum, including STEMI and NSTEACS. The original endpoint of the Elderly ACS-2 study was a composite of all-cause mortality, myocardial (re)infarction, disabling stroke, and re-hospitalization for cardiovascular causes or bleeding, within 1 year. For this post-hoc analysis we considered cardiovascular mortality and, in addition, non-cardiovascular mortality, reinfarction, and overall stroke.

3.2.2 Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test and are reported as mean and standard deviation if normally distributed, or medians and 25th and 75th percentiles if they did not satisfy the normal assumption. Categorical variables are shown as frequencies and percentages in each ACS group.

To describe the first signal of unfavourable outcome, the numbers and percentages of first events observed during the follow-up were reported in a table separately by ACS group. The data were provided separately for the type of first event (cardiovascular mortality, non-cardiovascular mortality, re-infarction, stroke) distinguishing between the events observed up to the first 30 days and in the whole follow-up.

In each ACS group, the cumulative probability of observing the single type of first event (crude cumulative incidence function, CCI) was estimated as a function of time by the Aalen Johansen estimator for competing risks. This estimator was used to remove the bias due to the presence of right censoring from the percentages of events observed up to 30 days and in the whole follow-up. The CCIs of a given type of first event were compared

between ACS groups by the Gray's test. Of note, the CCI of the single type of first event is affected by the indirect protection of the competing events, since the more the competing event occurs as first, the lower is the proportion of patients that may develop the type of first event under analysis. This motivates that to evaluate the prognostic role of the ACS group we resorted to cause specific rates in time windows and cause specific hazard of each type of first event. The rate of the single type of first event was calculated in each ACS group splitting follow-up time in the first 30 days and from the 31st day on. The rates of a given type of first event were compared between ACS groups by the exponential model.

The cause specific hazard ratio (cHRs) and corresponding 95% confidence intervals (Cis) for patients with STEMI versus NSTEACS were calculated by using univariate Cox regression models. Cox regression models were also adjusted for age (entered as the following four dummy variables: 75-79, 80-84, 85-89, ≥90 years), gender and previous MI. Visual inspection of the Shoenfeld residual plot and the test proposed by Grambsch [8] were used to assess the proportional hazards assumption. The analyses were performed using STATA version 14 (Stata Corp., College Station, TX) and R software 3.5.1, and R version 3.4.1 (2017-06-30).

3.2.3 Results

The distribution of patients' baseline clinical characteristics, features of the index ACS event, angiographic and PCI data, and drug therapy during admission and at discharge, are summarized in **TABLES 1-3B** by ACS group (STEMI vs NSTEACS). On the presenting ECG, 595 (41.0%) were classified as STEMI, whereas 848 (59.0%) had NSTEACS. Based on cardiac troponin levels, 100% of the ST Elevation patients were classified as STEMI, whereas among the NSTEACS patients 694 (82%) were Non-ST Elevation myocardial infarction and 154 (18%) unstable angina. Women were more

frequent among STEMI patients, whereas age and body mass index were almost comparable. Diabetes, hypertension, hypercholesterolemia, chronic respiratory failure as well as previous cardiovascular events (prior myocardial infarction, prior PCI, prior bypass surgery and peripheral vascular disease) were less frequent among STEMI as compared to NSTEACS patients, whereas the prevalence of current smokers was comparable. Ongoing cardiovascular medications were also less frequent in the STEMI group.

STEMI patients had less extensive coronary artery disease, including left main and 3-vessel disease. However, STEMI patients had significantly lower residual left ventricular ejection fraction. Among the patients treated with stenting [539 STEMI (96.4%) and 787 with NSTEACS (94.2%)], the proportion of patients who implanted drug eluting stents was significantly smaller in STEMI patients (66% vs 75% in NSTEACS, $p<0.001$).

Finally, STEMI patients were more commonly treated with glycoprotein IIb/IIIa antagonists and bivalirudin in the periprocedural period. Medications at discharge were comparable.

The length of hospital stay was significantly longer for STEMI patients (median 6 days, IQR 5-9 days) compared to patients with NSTEMI (median 6, IQR 4-8 days) ($p<0.01$).

The median follow-up duration was 12 months (range, 3–13 months), with 23 patients (1.5%) lost to follow-up. The number of observed events (as first event) in STEMI and NSTEACS patients is shown in **TABLE 4B**. Among STEMI patients, a total of 44 deaths from any cause (7.4%) were observed. Three out of 7 patients with reinfarction and 4 out of 15 patients with stroke died within the end of follow up; among the 3 patients died after reinfarction, 2 died the same day when MI occurred, whereas in the third death occurred 6 months after MI. Among the 4 patients dead after stroke, death occurred a few

days after stroke in 3 cases, whereas in 1 case the patient experienced a non-disabling in-hospital stroke and died after 11 months.

Among NSTEACS patients, a total of 35 deaths from any cause were observed. Four patients out of 31 with reinfarction died within the end of follow up, in 3 cases a few days after MI and in 1 case 5 months later.

Nineteen patients experienced stent thrombosis (ST), classified as definite in 5 cases [2 (0.3%) among STEMI and in 3 (0.3%) among NSTEACS patients] and probable in 14 [9 (1.5%) among STEMI and 5 (0.5%) among NSTEACS patients]. Three patients had non-fatal MI, 14 had sudden cardiac death, whereas 2 patients (both with STE as presenting ECG) had fatal MI (in 1 patient death occurred after 6 months and in 1 patient occurred the same day, 6 days after study inclusion). Eleven patients (2.0%) among STEMI and 38 (4.5%) among NSTEACS patients had BARC 2-5 bleeding events (p=0.02). Only one patient with NSTEACS at admission experienced a fatal bleeding.

The CCI functions for cardiovascular mortality, non-cardiovascular mortality, re-infarction and stroke are displayed in **Figure 1B.** A higher incidence of cardiovascular mortality, non- cardiovascular mortality and stroke was observed among STEMI patients, whereas the incidence of re-infarction was higher among patients with NSTEACS. The 30-day and one-year crude cumulative rates of study outcomes according to the presenting ECG are reported in **TABLE** 4B.

Results on the prognostic impact of the ACS group regarding the different types of first events are reported in **TABLE** 5B. As compared to NSTEACS patients, those with STEMI had a higher rate of cardiovascular mortality in the first 30-day time window, a lower rate of infarction and a higher rate of stroke in the time window from the 31st day on. In the Cox regression model, the presence of STEMI was associated to higher cardiovascular (cHR 1.70; 95% CI 0.97-3.01) and non-cardiovascular mortality (cHR

2.01; 95% CI 0.99-4.11), stroke (cHR 4.25; 1.55-11.7) and with a lower risk of myocardial infarction (cHR 0.33; 95% CI 0.14-0.74). After adjusting for sex, age and previous MI, STEMI remained a significant and independent predictor of cardiovascular death (cHR 1.85; 95% CI 1.02-3.36), non-cardiovascular death (cHR 2.10; 95% CI 1.01-4.38) and stroke (cHR 4.80; 95% CI 1.68-13.7), whereas the association with reinfarction became nonsignificant (cHR 0.44, 95% CI 0.19-1.03).

3.2.4 Tables

Table 1B: Baseline clinical characteristics

	STEMI (n=595)	**NSTEACS** (n=848)	**p value**
Age (median, IQR)	80 (77-84)	80 (77-83)	0.232
Sex			
Female	264 (44.4)	312 (36.8)	0.004
Male	331 (55.6)	536 (63.2)	
Body-mass index (kg/m^2)	25.4 (23.5-27.8)	25.8 (23.5-28.3)	0.125
Medical history			
Family history of cardiovascular disease	88 (14.8)	127 (15.0)	0.995
Diabetes	151 (25.4)	269 (31.7)	0.009
Hypertension	426 (71.6)	694 (81.8)	<0.001
Hypercholesterolemia	228 (38.3)	416 (49.1)	<0.001

Current smoker	63 (10.6)	68 (8.0)	0.094
Chronic respiratory failure	23 (3.9)	64 (7.5)	0.004
Liver disease	10 (1.7)	14 (1.6)	0.965
eGFR[a] at admission (ml/min)	55 (43-67)	55 (42-68)	0.781
Hemoglobin at admission (g/dL)			
males	14.0 (1.4)	13.6 (1.5)	< 0.001
females	12.8 (1.4)	12.6 (1.4)	0.091
Neurological disorders	18 (3.0)	28 (3.3)	0.768
Malignancies	23 (3.9)	22 (2.6)	0.171
Previous cardiovascular events			
Myocardial infarction	52 (8.7)	222 (26.2)	<0.001
Percutaneous coronary interventions	62 (10.4)	202 (23.8)	<0.001
Coronary artery bypass grafting	22 (3.7)	106 (12.5)	<0.001
Peripheral vascular disease	36 (6.1)	89 (10.5)	0.003
Atrial fibrillation	16 (2.7)	40 (4.7)	0.050
Ongoing cardiovascular medications[b]			
Aspirin	208 (47.1)	508 (67.8)	<0.001
Clopidogrel	39 (8.8)	175 (23.4)	<0.001
Betablockers	152 (34.4)	342 (45.7)	<0.001
Calcium antagonists	147 (33.1)	202 (27.0)	0.026
ACE-inhibitors/ARBs	290 (65.7)	500 (66.7)	0.075
Diuretics	125 (28.3)	297 (39.6)	<0.001
Nitrates	34 (7.7)	177 (23.6)	<0.001
Statins	135 (30.5)	394 (52.6)	<0.001

Data are n (%) for categorical variables and median (IQR) for continuous variables. STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor antagonist.

[a]estimated Glomerular Filtration Rate by the Cockroft-Gault formula.

[b]Data available on 1191 patients (442 STEMI and 749 NSTEACS), where percentages were calculated on available data.

Table 2B: Characteristics of index ACS event

	STEMI	**NSTEACS**	**p Value**
	(n=595)	(n=848)	
Left ventricular ejection fraction	45 (40-55)	50 (45-55)	<0.001
Coronary angiography			
Radial access	457 (76.8)	652 (76.9)	0.702
Number of vessels with critical stenosis[a]			<0.001
One-vessel disease	263 (44.4)	314 (37.1)	
Two-vessel disease	183 (30.9)	240 (28.4)	
Three-vessel disease or greater	141 (23.8)	291 (34.4)	
Left main	16 (2.7)	83 (9.8)	<0.001
PCI performed	587 (98.7)	846 (99.8)	0.012
Procedural treatment[b]			0.032
Stenting[b]	539 (96.4)	787 (94.2)	0.085

Drug eluting stents implanted	354 (65.7)	590 (75.0)	
Bare metal stents implanted	131 (24.3)	124 (15.8)	
Other (unknown type)	54 (10.0)	73 (9.2)	
Drug Eluting Balloons	4 (0.70)	22 (2.7)	
Plain balloon angioplasty	16 (2.9)	26 (3.1)	
Procedural success	569 (95.6)	818 (96.5)	0.891
Length of hospital stay (days)	6 (5-9)	6 (4-8)	<0.01

Data are n (%) for categorical variables and median (IQR) for continuous variables. STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome.
[a]Data available on 1438 patients (592 STEMI and 846 NSTEACS), where percentages were calculated on available data.
[b]Data available on 1384 patients (556 STEMI and 828 NSTEACS), where percentages were calculated on available data.

Table 3B: Drug therapy during admission and at discharge

	STEMI (n=595)	**NSTEACS** (n=848)	**p Value**
Peri-procedural medications[a]			
Aspirin	550 (93.2)	813 (97.1)	0.001
Glycoprotein IIb/IIIa antagonists	154 (26.1)	81 (9.7)	<0.001
Unfractionated heparin	520 (88.1)	626 (74.8)	<0.001
Low molecular weight heparin	35 (5.9)	241 (28.8)	<0.001
Bivalirudin	88 (14.9)	36 (4.3)	<0.001
Medications at discharge[b]			

Aspirin	569 (98.8)	830 (99.3)	0.329
Proton Pump Inhibitors	551 (95.7)	756 (90.4)	<0.001
Betablockers	444 (77.1)	661 (79.1)	0.375
Calcium antagonists	70 (12.1)	225 (26.9)	<0.001
ACE-inhibitors or ARBs	484 (83.3)	689 (81.4)	0.365
Diuretics	224 (38.9)	335 (40.1)	0.655
Nitrates	57 (9.9)	126 (15.1)	0.004
Statins	554 (96.2)	790 (94.5)	0.147
Oral anticoagulant	20 (3.5)	17 (2.0)	0.096

Data are n (%). ACE=angiotensin-converting enzyme.
STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome. ARB=angiotensin-receptor antagonist.
[a]Data available on 1427 patients (590 STEMI and 837 NSTEACS), where percentages were calculated on available data. [b]Data available on 1412 patients (576 STEMI and 836 NSTEACS), where percentages were calculated on available data.

Table 4B. Thirty-day and one-year crude cumulative incidence (CCI) and 95% confidence intervals (CIs) of study outcomes according to presenting ECG

Study outcome	Group	30-day events (n, %)	CCI at 30 days (% of patients) (95% CI)	1-year events (n, %)	CCI at 1 year (% of patients) (95% CI)
Cardiovascular death	STEMI	20 (3.4)	3.38 (3.24-3.53)	26 (4.4)	4.43 (4.26-4.60)
	NSTEACS	12 (1.4)	1.43 (1.35-1.51)	22(2.6)	2.98 (2.85-3.11)
Non-Cardiovascular death	STEMI	5 (0.8)	0.85 (0.78-0.93)	18 (3.0)	3.63 (3.45-3.80)
	NSTEACS	2 (0.2)	0.24 (0.21-0.27)	13 (1.5)	1.73 (1.64-1.83)
Myocardial infarction	STEMI	4 (0.7)	0.68 (0.61-0.74)	7 (1.2)	1.25 (1.16-1.35)
	NSTEACS	5 (=.6)	0.59 (0.54-0.64)	31 (3.7)	4.46 (4.30-4.62)
Stroke	STEMI	5 (0.8)	0.85 (0.77-0.92)	15 (2.5)	3.34 (3.16-3.51)
	NSTEACS	0	0	5 (0.6)	1.19 (1.09-1.30)

STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome. CCI: Crude Cumulative Incidence

Table 5B. Estimated rates (per person-year) with lower/upper bounds of 95% confidence intervals (CIs) and cause-specific hazard ratios (HRs) with corresponding 95% CIs.

First event	*Estimated rates (95% CI) 0-30 days*	*p value*	*Estimated rates (95% CI) 31-365 days*	*p value*	HR[ac] (95%CI)	HR[bc] (95%CI)
Cardiovascular death STEMI NSTEACS	0.428 (0.276-0.664) 0.177 (0.100-0.312)	*0.016*	0.012 (0.005-0.027) 0.014 (0.007-0.261)	*0.805*	1.70 (0.97-3.01)	1.85 (1.02-3.36)
Non-Cardiovascular death STEMI NSTEACS	0.107 (0.044-0.257) 0.029 (0.007-0.118)	*0.124*	0.026 (0.015-0.046) 0.015 (0.008-0.028)	*0.179*	2.01 (0.99-4.11)	2.10 (1.01-4.38)
Myocardial Infarction STEMI NSTEACS	0.085 (0.032-0.228) 0.074 (0.030-0.177)	*0.826*	0.006 (0.002-0.020) 0.036 (0.025-0.053)	*0.004*	0.33 (0.14-0.74)	0.44 (0.19-1.03)
Stroke STEMI NSTEACS	0.107 (0.044-0.257) not estimable	*na*	0.020 (0.011-0.038) 0.007 (0.003-0.017)	*0.049*	4.25 (1.55-11.7)	4.80 (1.68-13.7)

STEMI=ST-segment elevation myocardial infarction. NSTEACS=non-ST elevation acute coronary syndrome.

[a] estimated from cause specific regression analysis for patients with STEMI compared to NSTEACS.

[b] further adjusted for age classes, gender, previous myocardial infarction.

[C] estimated over 365-day follow up

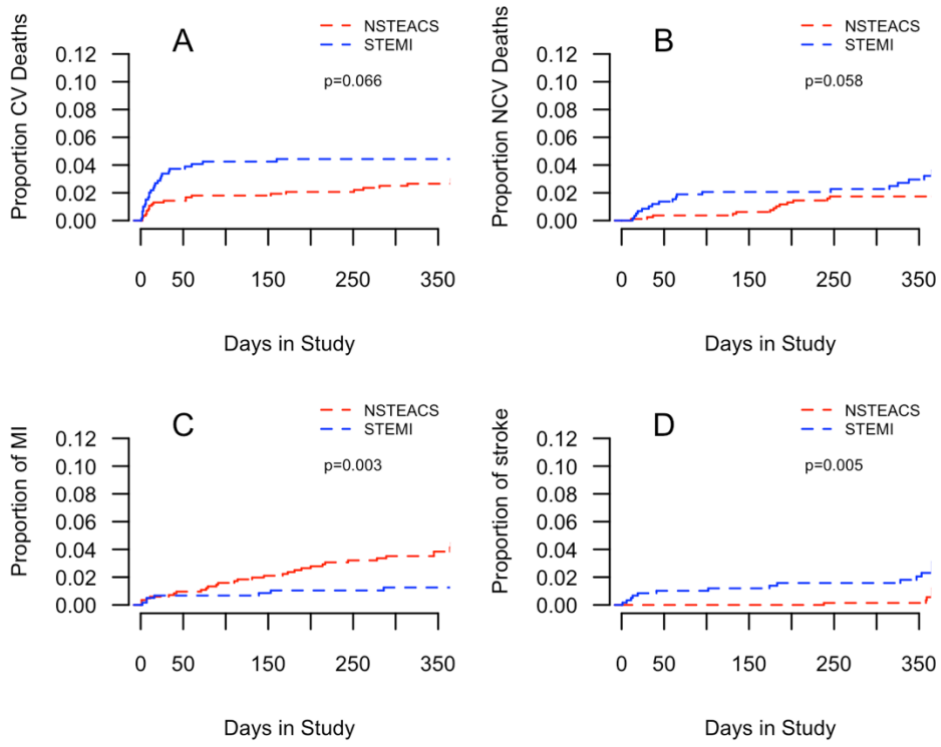

Figure 1B. One-year crude cumulative incidence (CCI) of study outcomes according to presenting ECG. CV: cardiovascular; NSTEACS: Non-ST Elevation Acute Coronary Syndrome; STEMI: ST Elevation Myocardial infarction; MI: Myocardial Infarction

3.2.5 Discussion

The present study confirms that, even in older adults, STEMI and NSTEACS are 2 different clinical syndromes of acute coronary artery disease. It has long been established that, as compared with STEMI patients, those with NSTEACS are older and have a longer history of coronary artery disease, including prior MIs end revascularization procedures.[140]

These worst characteristics persist at the present time and are independent from the age difference between the 2 patient populations. Therefore, even in the elderly, the STEMI presentation is indicative of an abrupt closure of a major coronary segment in the lack of

collateral circulation and myocardial preconditioning; these 2 conditions being more typical of patients with longer history of coronary artery disease and revascularization procedures.

A surprising and new finding of the present study is the 50% higher risk of cardiovascular and non-cardiovascular death at 12 months observed among STEMI patients, as compared with those with NSTEACS. This finding was observed with similar post-discharge drug therapy in the 2 groups. To this regard, it should be considered that the whole study population consisted of patients undergoing percutaneous coronary intervention during the index admission, a feature that has selected a subset of NSTEACS patients suitable for percutaneous coronary intervention procedures. The low mortality rate observed in the whole study, and particularly among NSTEACS patients, may well reflect current mortality rates among elderly ACS patients treated by percutaneous coronary intervention, and has been observed in similar contemporary trials[122] and registries.[141]

The characteristic of the present study, based on a population enrolled in a randomized clinical trial, limits the applicability of our findings to patients treated by percutaneous coronary intervention early during index admission. However, the study exclusion criteria were limited to patients with recent severe bleeding and those with an indication to anticoagulant therapy, including atrial fibrillation.

3.3 RESEARCH PROJECT 3

3.3.1 Population and study design of the manuscript: Residual SYNTAX score and one-year outcome in elderly patients with acute coronary syndrome.[83]

We conducted a post-hoc analysis of data collected in the Elderly-ACS 2 multicenter randomized trial of patients aged ≥75 years with an ACS undergoing PCI during index

admission.[74] Included in the present analysis were patients with multivessel coronary disease and available data for baseline SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score (bSS) and residual SS (rSS). To reduce variability in acquisition methods, we collected data from centers having enrolled at least 25 patients in the original study.

3.3.2 Statistical analysis

Baseline characteristics were compared between patients with complete and incomplete revascularization using the anatomical definition of incomplete revascularization adopted in other studies, i.e. rSS >8.[142,143] Continuous data are presented as mean ± SD or median (interquartile range, IQR) and were compared between groups (complete vs. incomplete revascularization) using the Student's t test or Mann-Whitney test, as appropriate. Categorical variables were compared between groups using the χ^2 test.

Correlation between the bSS and rSS was assessed through the Spearman's coefficient of correlation.

We estimated the cumulative incidence of the composite outcome across strata of rSS ($\leq$8 vs. >8) using the Kaplan-Meier method and we assessed the univariate association between the rSS and the event rate using the log-rank test.

We fitted multivariable Cox proportional hazard models to estimate the hazard ratios (HRs) and the corresponding 95% confidence intervals (CI) for each potential predictor of the 1-year composite outcome. We first defined a core model by selecting all predictors that had an HR <0.8 or >1.2 (for binary variables) and a *P* value <0.10 among a set of potential predictors, including sex, age, prior MI, type of ACS, left ventricular ejection fraction, diabetes, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, glomerular filtration rate, blood haemoglobin and body mass index (BMI). Then,

we compared three prediction models including: 1) the predictors of the core model plus the bSS; 2) only the rSS; 3) the predictors of the core model plus the rSS.

In the main analysis, bSS and rSS were included in the models as continuous variables, whereas in a secondary analysis we categorized both scores. Categories for bSS were defined by tertiles of the frequency distribution, while rSS was used as binary variable (<8 vs. >8).

To replace missing values for left ventricular ejection fraction, glomerular filtration rate, hemoglobin and BMI we used multiple imputation with chained equations.[57] We carried out five imputations and we used the Rubin's rules to combine the results across the imputed datasets.

We computed the c-statistic to evaluate the discrimination ability of the models. For internal validation, the optimism of the models was estimated by using 300 bootstrapping samples. The estimated optimism was then subtracted from the c-statistic calculated in the original cohort to obtain the optimism-corrected c-statistic. We assessed the model calibration by comparing the predicted probabilities at 1 year, and the corresponding Kaplan-Meier estimate, stratifying on intervals of predicted probabilities. To obtain the predicted probabilities, we combined the regression coefficients with the baseline survival function. The baseline survival function was based on zero values for centred continuous variables with all binary predictor set to zero.

According to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement,[144] the change in net benefit (NB) was calculated in order to evaluate the clinical utility of including the rSS in a prediction model.

The NB is a simple indicator that can be used to evaluate the clinical utility of a prediction model when it is designed to make clinical decisions, for instance, to refer patients

predicted to be at high risk of worse outcome to a more intensive treatment. The indicator balances benefits and harms and put them on the same scale so that they can be compared directly.[145,146]

We calculated the NB obtained from the application of each prediction model as:

$$(1)\ NB = \frac{TP}{N} - \frac{FP}{N} \bullet \frac{p}{1-p}$$

Where TP are the true positives, i.e. the patients classified at high risk who developed the event, FP are the false positives, i.e. the patients classified at high risk but who did not have the event, p is the decision threshold or cut-off used to classify the patient at high risk, and N is the total sample size. TP and FP were obtained according to the method described in Vickers et al.[147] The NB was then divided by the proportion of patients who experienced the composite outcome to obtain the standardized NB (sNB). This facilitates the interpretation of the NB since the sNB represents the proportion of the maximum clinical utility than can be achieved when all patients who had the event and no patients without the event are classified in the high-risk category.

We computed the sNB and the change in the sNB resulting from the inclusion of the rSS in prediction models at three different pre-specified plausible thresholds of 1-year event rate of 0.10, 0.20 and 0.30, i.e. patients were classified at high risk if their predicted probability of 1-year death or cardiovascular event exceeds the threshold. The 95% confidence intervals (CI) for the change in the sNB were obtain by bootstrap with 1000 replications.

Decision curves were also drawn to show the sNB for decision thresholds up to 0.50.

The analyses were performed using STATA version 14 (Stata Corp., College Station, TX) and R software version 3.5.1.

3.3.3 Results

Among the 25 Centers enrolling 1443 patients in the Elderly ACS II trial, 15 contributed with ≥25 patients each, for a total 1085 subjects (75.2 % of the whole study population). Among them, 630 patients (58%) had multivessel coronary artery disease. The median bSS was 18 (IQR: 12-25, range: 2-68), whereas the median rSS was 6 (IQR: 2-11, range: 0-51). The correlation between bSS and rSS was 0.68 (P<0.001). A rSS=0 was achieved in 116 patients (18.4%).

Patients with incomplete revascularization (rSS >8) were older, had a higher burden of several cardiovascular risk factors (hypertension, dyslipidemia, decreased kidney function, decreased hemoglobin value) as well as a higher rate of prior MI in their medical history (**Table 1C**). Left main disease was more common in patients with incomplete revascularization, whereas the other angiographic characteristics were comparable. Patients with incomplete revascularization were more likely to receive anti-ischemic therapy and diuretics at discharge (**Table 2C**).

At 1-year follow up 68 patients experienced the composite event of mortality, MI and stroke, with an estimated cumulative incidence of 12.9% (95% CI: 9.8-16.0%).

All-cause mortality occurred in 41 (6.5%) patients, 18 (4.6%) in patients with rSS score ≤8 and 23 (9.7%) in those with higher rSS. Recurrent MI occurred in 20 (3.17%) patients, 6 (1.5%) in patients with rSS score ≤8 and 14 (5.6%) in patients with higher rSS. Stroke occurred in 14 (2.2%) patients, 7 (1.8%) in patients with rSS score ≤8 and 7 (2.9%) in the group with higher rSS. Other clinically meaningful events were higher in patients with rSS >8 as shown in **(Table 3C)**

Figure 1C shows the cumulative incidence function for patients with rSS below and above 8. A rSS above 8 was associated with higher 1-year event rates.

Table 4C shows the results of the Cox regression model including sex, age and all potential clinical predictors. Sex, ventricular ejection fraction, glomerular filtration rate, hemoglobin, diabetes, peripheral vascular disease and COPD were not significantly associated with the event rate, and therefore were not included in the core model.

Table 5C gives the HRs and corresponding 95% CI estimated from the three prediction models. The HR for one-point increase in the rSS was 1.06 (1.03-1.08) when the rSS was the only predictor of the model and 1.05 (1.02-1.07) in the multivariable model. **Table 6C** shows the results of the models with bSS and rSS used as categorical variables. When the rSS was considered as categorical variable, patients with values >8 had a higher cumulative incidence of events with an adjusted HR of 2.47 (95%CI: 1.51-4.06).

As shown by the c-statistic, the inclusion of the rSS instead of the bSS in the core model did not materially change the discrimination ability (**Table 5C**). The discrimination ability of the model including the rSS as the only predictor was lower as compared to the other models. All models were well calibrated (**Figure 2C**).

Table 7C gives the sNB obtained from each prediction model when used to classify patients at high or low risk of the composite outcome based on three selected decision thresholds with estimated event rates of 0.10, 0.20 and 0.30. The inclusion of the rSS in the core model resulted in little improvement in the sNB only for the decision threshold of 0.10. For this threshold, the core model including also the rSS would correctly identify 4 additional cases and yield 63 less false positives as compared to the core model with the bSS; in a population of 1000 patients with a cumulative incidence of the composite event of 12.9%.

Figure 3C shows the decision curves with the sNB estimated for decision thresholds up to 0.50. No clear improvement in risk prediction emerged from the model with the rSS.

Results were similar when the bSS and the rSS were included in the model as categorical variables. (**Table 8C, Figure 4C**).

Table 1C. Baseline clinical characteristics

	RSS 0-8 (n=392)	RSS >8 (n=238)	*P* value
Age	79 (76-83)	81 (78-85)	<0.001
Male sex	250 (63.8)	146 (61.3)	0.540
Body-mass index (kg/m^2)	25.5 (23.5-27.8)	25.7 (23.6-28.4)	0.485
Family history of cardiovascular disease	63 (16.1)	20 (8.4)	0.006
Diabetes	111 (28.3)	74 (31.1)	0.458
Hypertension	292 (74.5)	194 (81.5)	0.042
Hypercholesterolemia	154 (39.3)	113 (47.5)	0.044
Current smoker	30 (7.6)	19 (7.9)	0.881
Chronic respiratory failure	16 (4.1)	11 (4.6)	0.745
Liver disease	5 (1.3)	4 (1.7)	0.678
eGFR at admission (mL/min)*	69.3 (53.6-85.1)	61.7 (48.9-80.8)	0.005
Hemoglobin at admission (g/dL)			
Males	14 (13-15)	13.8 (12.6-14.6)	0.055
Females	12.5 (11.7-13.8)	12.2 (11.7-13.2)	0.070
Neurological disorders	15 (3.8)	4 (1.7)	0.127
Malignancies	9 (2.3)	6 (2.5)	0.857
Previous cardiovascular events			
Myocardial infarction	54 (13.8)	52 (26.0)	<0.001
Percutaneous coronary interventions	61 (15.6)	45 (18.9)	0.276
Peripheral vascular disease	32 (8.2)	24 (10.1)	0.411
Atrial fibrillation	13 (3.3)	9 (3.8)	0.758
Ongoing cardiovascular medications			
Aspirin	184 (46.9)	119 (47.2)	0.133
Clopidogrel	92 (11.9)	42 (13.6)	0.161
Betablockers	121 (30.8)	89 (37.4)	0.078
Calcium antagonists	99 (25.3)	66 (27.3)	0.088
ACE-inhibitors or ARBs	200 (51.0)	137 (57.6)	0.117
Diuretics	109 (27.8)	65 (27.3)	0.109
Nitrates	39 (9.9)	49 (20.6)	<0.001
Statins	111 (28.3)	102 (42.9)	0.001

Data are no. (%) for categorical variables and median (IQR) for continuous variables. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor antagonist. *estimated Glomerular Filtration Rate by the Cockroft-Gault formula.

Table 2C: Characteristics of index ACS event

	RSS 0-8 (n=392)	RSS >8 (n=238)	*P* value
Left ventricular ejection fraction	50 (45-55)	50 (40-55)	0.548
Coronary angiography			
Radial access	320 (81.6)	180 (75.6)	0.071
Left main	77 (19.6)	63 (26.5)	0.046
Procedural treatment			
Stenting	381 (97.4)	222 (94.9)	0.035
Drug Eluting Balloons	8 (2.1)	4 (1.7)	0.760
Plain balloon angioplasty	6 (1.5)	10 (4.3)	0.037
Procedural success	378 (96.4)	227 (95.4)	0.794
Length of hospital stay (days)	6 (5-8)	6 (5-10)	0.183
Peri-procedural medications			
Aspirin	359 (91.6)	223 (93.7)	0.557
Glycoprotein IIb/IIIa antagonists	77 (19.6)	43 (18.1)	0.880
Unfractionated heparin	330 (84.2)	176 (73.9)	0.005
Low molecular weight heparin	65 (16.6)	60 (25.1)	0.031
Bivalirudin	24 (6.1)	17 (7.1)	0.878
Medications at discharge			
Aspirin	385 (98.2)	228 (95.8)	0.117
Proton Pump Inhibitors	362 (92.3)	209 (97.8)	0.068
Betablockers	304 (77.5)	191 (80.2)	0.040
Calcium antagonists	87 (22.2)	51 (21.4)	0.117
ACE-inhibitors or ARBs	329 (83.9)	184 (77.3)	0.039
Diuretics	135 (34.4)	103 (43.3)	0.005
Nitrates	42 (10.7)	37 (15.5)	0.019
Statins	365 (93.1)	221 (92.8)	0.056
Oral anticoagulant	8 (2.0)	9 (3.8)	0.047

Data are no. (%) for categorical variables and median (IQR) for continuous variables.
ACE=angiotensin-converting enzyme; ARB=angiotensin-receptor antagonist.

Table 3C: Other Follow-up events

	RSS 0-8 (n=392)	RSS >8 (n=238)	P value
Stent Thrombosis	3 (0.8)	8 (3.4)	0.016
Definite	1 (0.2)	2 (0.8)	
Re-hospitalization for cardiovascular causes	28 (7.1)	29 (12.2)	0.032
Re-hospitalization for bleeding events	4 (1.0)	9 (3.8)	0.018
Bleeding events according to BARC classification			
BARC 2	4 (1.0)	4 (1.7)	
BARC 3a	1 (0.2)	6 (2.5)	
BARC 3b	2 (0.5)	0	
BARC 3c	0	1 (0.4)	
BARC 4	1 (0.2)	0	

Data are no. (%).

Table 4C. Hazard ratios (HRs) and 95% confidence intervals of 1-year mortality or cardiovascular event estimated from a Cox regression model including sex, age and a set of potential clinical predictors.

Predictors	HR (95% CI)	P value
Male sex	1.02 (0.60-1.73)	0.952
Age (years)	1.08 (1.02-1.13)	0.007
Prior MI	2.34 (1.35-4.06)	0.002
STEMI	1.87 (1.12-3.13)	0.017
Diabetes	1.36 (0.81-2.28)	0.242
COPD	1.56 (0.60-4.02)	0.359
PVD	1.67 (0.82-3.38)	0.157
LVEF (5-unit increase)	0.94 (0.82-1.07)	0.758
eGFR (5-unit increase)	0.98 (0.93-1.04)	0.558
Hemoglobin	0.89 (0.76-1.06)	0.187
BMI	1.03 (0.96-1.10)	0.439

BMI – Body mass index; COPD – Chronic obstructive pulmonary disease; LVEF – Left ventricular ejection fraction, eGFR – estimated Glomerular filtration rate; MI – Myocardial infarction; PVD – Peripheral vascular disease; STEMI – ST-elevation myocardial infarction.

Table 5C Hazard ratios (HRs) and 95% confidence intervals of 1-year mortality or cardiovascular event estimated from multivariable Cox regression models.

Predictors	Core model[a] + bSS	Model including only rSS	Core model[a] + rSS
Age (years)	1.08 (1.03-1.13)	-	1.08 (1.03-1.14)
Prior MI	2.15 (1.25-3.69)	-	2.02 (1.17-3.49)
STEMI	1.87 (1.14-3.06)	-	1.88 (1.14-3.09)
bSS	1.04 (1.01-1.06)	-	-
rSS	-	1.06 (1.03-1.08)	1.05 (1.02-1.07)
AIC	822	832	819
c-statistic	0.690	0.644	0.700
Optimism-corrected *c*-statistics	0.681	0.643	0.691

Abbreviations: AIC – Akaike information criterion; BMI – Body mass index; bSS – baseline SYNTAX score; MI – Myocardial infarction; rSS – Residual SYNTAX score; SE – Standard error; STEMI – ST-elevation myocardial infarction.
[a] The core model included only the predictors that had a HR <0.8 or >1.2 (for binary variables) and a *P* value <0.10 in a starting model including terms for sex, age, previous myocardial infarction, type of acute coronary syndrome, diabetes, peripheral vascular disease and chronic pulmonary disease.

Table 6C. Hazard ratios (HRs) and 95% confidence intervals of 1-year mortality or cardiovascular event estimated from multivariable Cox regression models with baseline and residual SYNTAX scores used as categorical predictors.

Predictors	Core model[a] + bSS	Core model[a] + rSS
Age (years)	1.09 (1.04-1.14)	1.08 (1.03-1.14)
Prior MI	2.34 (1.37-3.99)	2.20 (1.29-3.76)
STEMI	1.88 (1.14-3.09)	1.99 (1.20-3.28)
bSS (15-22)[b]	1.24 (0.64-2.39)	-
bSS (23-68)[b]	1.87 (1.02-3.44)	-
rSS >8	-	2.47 (1.51-4.06)
AIC	829	818
c-statistic	0.681	0.705
Optimism-corrected *c*-statistics	0.672	0.700

Abbreviations: AIC – Akaike information criterion; BMI – Body mass index; bSS – baseline SYNTAX score; MI – Myocardial infarction; rSS – Residual SYNTAX score; STEMI – ST-elevation myocardial infarction.
[a] The core model included only the predictors that had a HR <0.8 or >1.2 (for binary variables) and a *P* value <0.10 in a starting model including terms for sex, age, previous myocardial infarction, type of acute coronary syndrome, diabetes, peripheral vascular disease and chronic pulmonary disease.
[b] Baseline SYNTAX score was categorized using tertiles, with values below the first tertile (<15) as reference category.

defined by tertiles of the frequency distribution. Residual SYNTAX score was included as categorical variable (<8 vs. >8).

Table 7C. Clinical utility of the prediction models at different plausible threshold probabilities of 1-year mortality or cardiovascular event.

	sNB			Change in sNB (95% CI)	
Threshold probability	Core model[a] + bSS (Model #1)	Model including only rSS (Model #2)	Core model[a] + rSS (Model #3)	Model #2 vs. Model #1	Model #3 vs. Model #1
0.10	0.38	0.36	0.47	-0.02 (-0.16; 0.11)	0.09 (0.02; 0.16)
0.20	0.17	0.05	0.11	-0.12 (-0.28; 0.04)	-0.06 (-0.19; 0.07)
0.30	0.05	0.02	0.07	-0.03 (-0.13; 0.06)	0.02 (-0.06; 0.09)

Abbreviations: bSS – Baseline SYNTAX score; rSS – Residual SYNTAX score, sNB – standardized net benefit

[a] The core model included age, prior myocardial infarction and type of acute coronary syndrome as predictors

Table 8C. Clinical utility of the prediction models at different plausible threshold probabilities of 1-year mortality or cardiovascular event with baseline and residual SYNTAX scores used as categorical predictors.

	Core model[a] + bSS	Core model[a] + rSS	
Threshold probability	sNB	sNB	Change in sNB (95% CI)
0.10	0.39	0.39	0 (-0.08; 0.09)
0.20	0.18	0.17	-0.01 (-0.14; 0.12)
0.30	0.04	0.05	0.01 (-0.07; 0.09)

Abbreviations: bSS – Baseline SYNTAX score; rSS – Residual SYNTAX score, sNB – standardized net benefit

[a] The core model included age, prior myocardial infarction and type of acute coronary syndrome as predictors. Baseline SYNTAX score was included in the model as categorical variable with categories

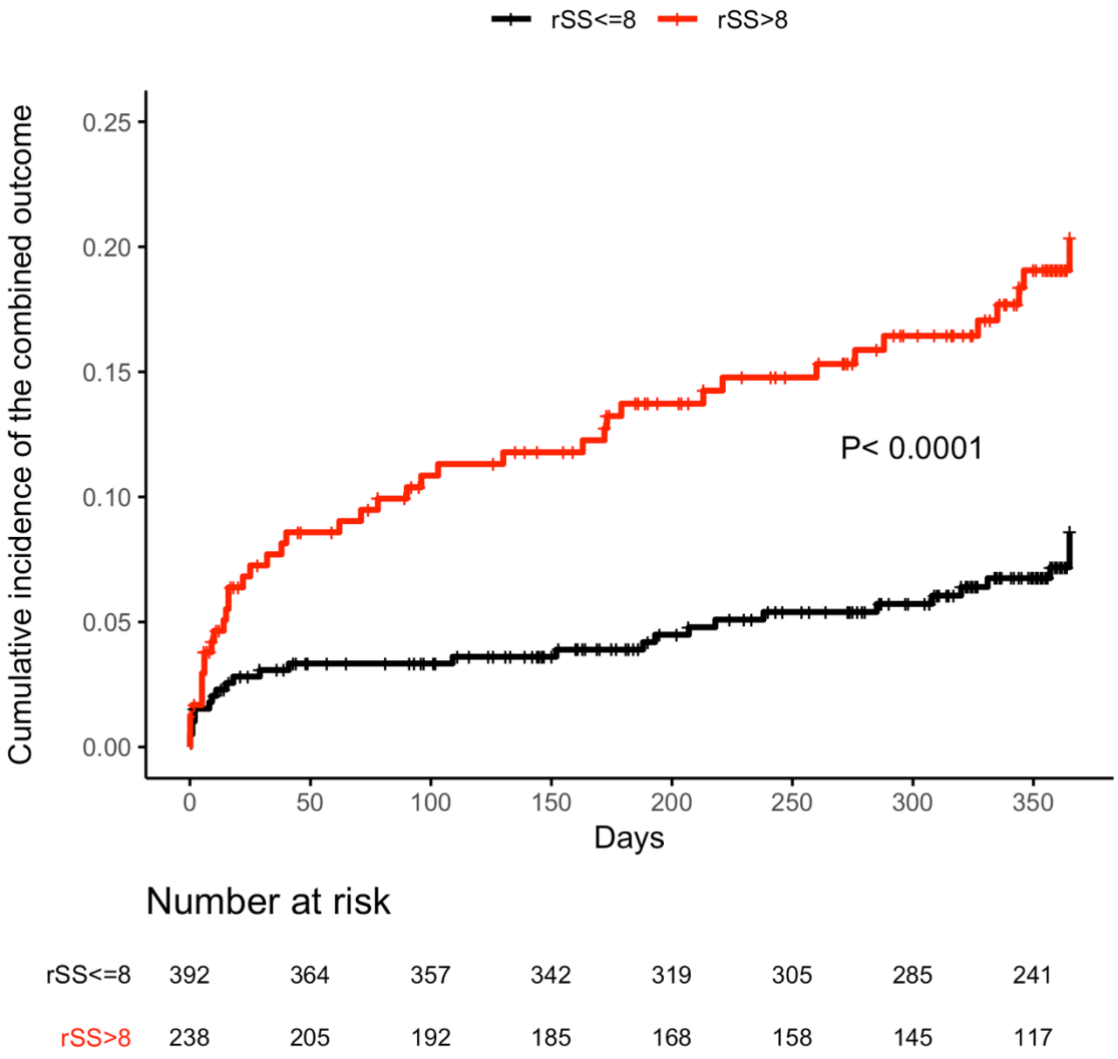

Figure 1C. Kaplan-Meier estimates of the cumulative incidence functions of the combined outcome (cardiovascular event or death) according to residual SYNTAX score (rSS). Log-rank test *P* value for comparison between cumulative incidence functions.

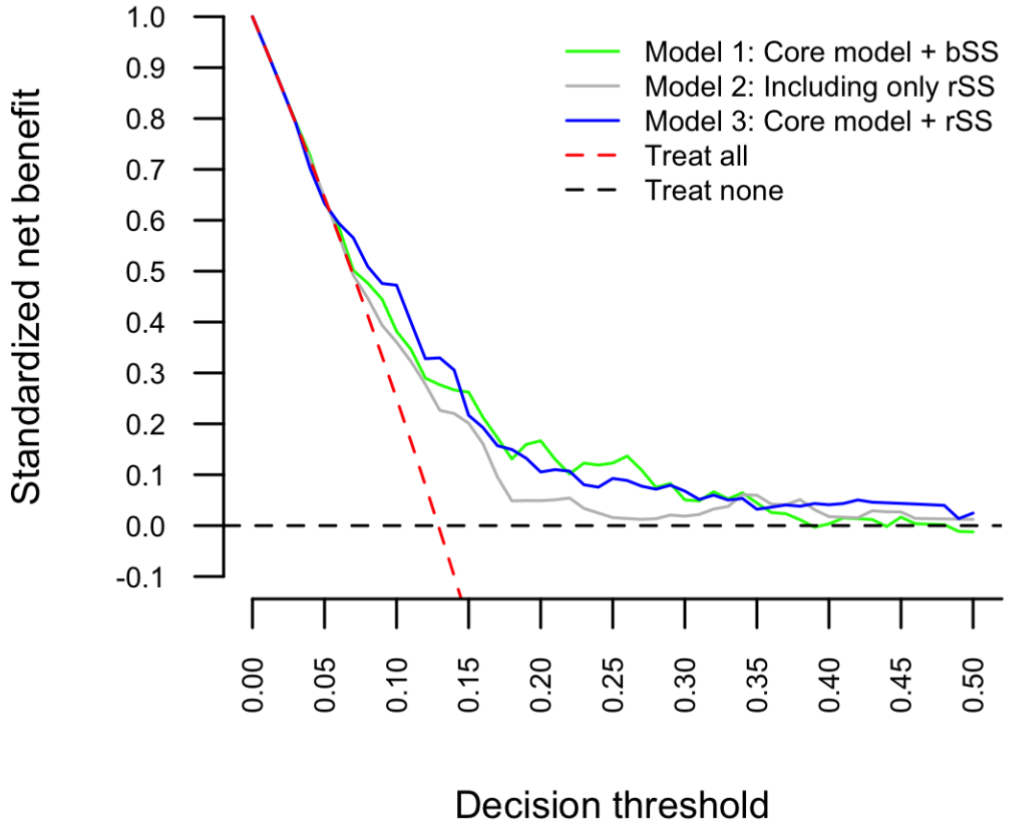

Figure 2C. Decision curves with standardized net benefit computed using the predictions obtained from three different models: 1) a core model plus the baseline SYNTAX score (bSS); 2) a model including only the residual SYNTAX score (rSS); 3) a core model plus the rSS. The core model included age, prior myocardial infarction and type of acute coronary syndrome. The standardized net benefit is also shown for the two extreme conditions: i.e. all patients assumed to be at high risk and all patients assumed to be at low risk.

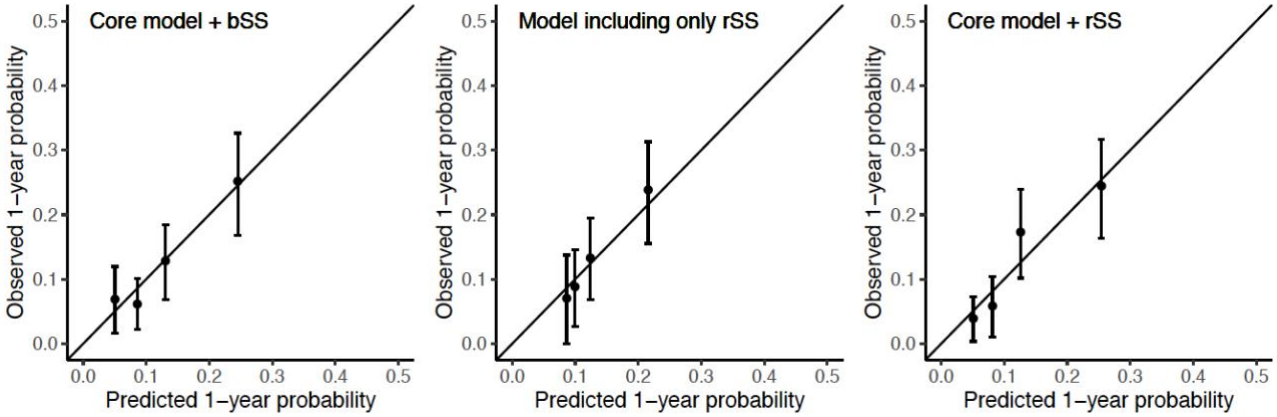

Figure 3C. Predicted and observed 1-year probabilities of the combined outcome of death and new cardiovascular event. Prediction were obtained from three different models: 1) a core model plus the baseline SYNTAX score (bSS); 2) a model including only the residual SYNTAX score (rSS); 3) a core model plus the rSS. The core model included age, prior myocardial infarction and ST-elevation myocardial infarction.

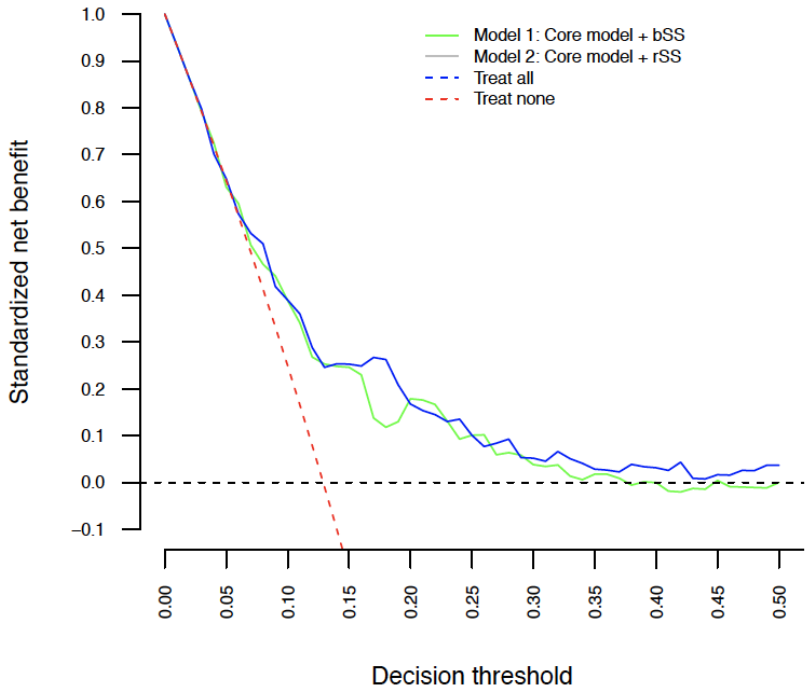

Figure 4C. Decision curves with standardized net benefit computed using the predictions obtained from two different models: 1) a core model plus the baseline SYNTAX score (bSS); 2) a core model plus the residual SYNTAX score (rSS). bSS score was included in the model as categorical variable with categories defined by tertiles of the frequency distribution. rSS was included as categorical variable (≤8 vs. >8). The core model included age, prior myocardial infarction and type of acute coronary syndrome. The standardized net benefit is also shown for the two extreme conditions: i.e. all patients assumed to be at high risk and all patients assumed to be at low risk.

3.3.4 Discussion

The present analysis, performed in a cohort of elderly and very elderly patients admitted to hospital for an ACS and treated with PCI, provides relevant insight on the prognostic role of residual critical coronary artery disease, as quantified by the rSS, after ACS treatment. The main findings are the following: in elderly ACS patients, the residual burden of untreated CAD is associated with worse outcome at 1-year follow up; however, the rSS does not substantially improve risk prediction when added to a core prediction model including selected clinical variables and bSS. This information may assist

clinicians in deciding whether to pursue complete revascularization in elderly patients with ACS after PCI of the presumably culprit artery.

Our study provides unique data on an elderly population, which are consistent with data drawn from the all-comers SYNTAX trial and other cohort studies, which confirm the prognostic role of rSS in patients with stable CAD, ACS and cardiogenic shock.[148,149] However, they add relevant information assessing the specific and incremental role of residual coronary artery disease in elderly ACS patients, evaluated throughout the decision curves analysis. According to this analysis, the model including rSS on top of core variables (age, prior MI and ACS type) and bSS did not significantly improve patients' risk stratification.

A possible limitation of the study lies on its design with data collected in an experimental setting with strict monitoring and aggressive management of risk factors and complications. This may reduce the generalizability of the results to real-life. However, this may also be a strength, considering the standardized, approach toward patients' management and follow-up.

The partial predictive ability of the models may result from unmeasured factors, such as poor social network, impaired cognitive function, dementia and depression symptoms, which were not assessed in the Elderly ACS 2 study but may have significant impact on the prognosis of this elderly population with a high burden of comorbidities.

4.0 CONCLUSIONS

Changes in the epidemiological and demographic landscape have extended the end-of-life horizon for many years, allowing many people to survive with life-limiting conditions, often associated with ageing.[150] The consequence has been the need of redesigning the healthcare system in multimorbid older patients towards "management of illness" rather than "being able to cure". This approach is mostly challenging implying an overwhelming effort to understand patients' complexity and preferences and to approach a shared decision-making process.[151] Actually, most health care systems, along with medical research and medical education, are configurated as single-disease framework, far from a patient-center perspective.

In 2009, ***Carl May***, professor of medical sociology, ***Victor M Montori***, professor of medicine and ***Frances S Mair***, professor of primary care research, wrote on the ***British Medical Journal***: "chronic disease is the great epidemic of our times, but the strategies we have developed to manage it have created a growing burden for patients. This treatment burden induces poor adherence, wasted resources, and poor outcomes. Against this background, we call for minimally disruptive medicine that seeks to tailor treatment regimens to the realities of the daily lives of patients. Such an approach could greatly improve the care and quality of life for patients".[152]

At the moment "disruptive medicine" often affects elderly end of life issues. They are not allowed to give up cures and interventions and to put their own life in a more compassionate perspective.

Why does it happen? Because cardiovascular care is usually perceived by patients and practitioners as a curative discipline, unlike what happens for cancer disease. Because it

requires a paradigm shift in relationships and network and in the healthcare system organization, with deep understanding of social and cultural aspects. Because it requires to cope with unrealistic expectations and over-optimism created by technology advancements.

Evidence based practice standards for starting palliative care, family counseling and clear communication may allow to achieve the goal: generate comfort and improve quality of life.[153] Throughout an informative communication, the patient can be able to express advanced directive. The awareness of end-of-life, for the patient and his/her family, requires time. This time is valuable in order to reset expectations. A collaborative effort will lead towards acceptation and alternative, but not less adequate, care options.

In conclusion, elderly patients are a special high-risk population with its own peculiarities in terms of biological vulnerability, risk stratification assessment and management approaches. (**Infographic**). A case by case decision supported by a holistic vision should always been considered.

5.0 References

1. Tzoran I, Hoffmann R, Monreal M. Hemostasis and Thrombosis in the Oldest Old. Semin. *Thromb. Hemost*. 2018; 44: 624-631.
2. United Nations Department of Economic and Social Affairs. Population Division. World Population Ageing. Available at: http://www. un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2017.pdf. Accessed November 1, 2017.
3. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics 2020 update: a report from the American heart association. *Circulation*. 2020; 141: e139-e596
4. Sahyoun NR, Lentzner H, Hoyert D, Robinson KN. Trends in causes of death among the elderly. *Aging Trends*. 2001; 1: 1–10.
5. De Luca L, Olivari Z, Bolognese L, et al. A decade of changes in clinical characteristics and management of elderly patients with non-ST elevation myocardial infarction admitted in Italian cardiac care units. *Open Heart*. 2014; 13;1(1): e000148.
6. De Luca L, Marini M, Gonzini L, et al. Contemporary Trends and Age-Specific Sex Differences in Management and Outcome for Patients With ST-Segment Elevation Myocardial Infarction. *J Am Heart Assoc* 2016; 5:e004202.
7. Schoenenberger AW, Radovanovic D, Windecker S, et al. AMIS Plus Investigators. Temporal trends in the treatment and outcomes of elderly patients with acute coronary syndrome. *Eur Heart J*. 2016; 37:1304-1311.

8. Leonardi S, Montalto C, Casella G, et al. "The Clinical Governance Programme in Patients with Acute Coronary Syndrome: Design and Methodology of a Quality Improvement Initiative". *Open Heart*. In press.
9. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: the era of reperfusion: section 1: acute coronarysyndromes (acute myocardial infarction). The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation*. 2000;102(8 Suppl): I172-203.
10. 2000 ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a practical summary for emergency physicians. Pollack CV Jr, Gibler WB. *Ann Emerg Med*. 2001; 38:229-40. doi: 10.1067/mem.2001.117955.
11. Schoenenberger, A.W. Radovanovic, D. Stauffer, J.C. Windecker, S. Urban, P. Eberli, F.R. Stuck, A.E. Gutzwiller, F. Erne, P. Acute Myocardial Infarction in Switzerland Plus Investigators. Age-related differences in the use of guideline-recommended medical and interventional therapies for acute coronary syndromes: a cohort study. J. Am. Geriatr. Soc. 56:510–516 (2008).
12. Zaman MJ, Stirling S, Shepstone L, et al. The Association Between Older Age and Receipt of Care and Outcomes in Patients with Acute Coronary Syndromes: A Cohort Study of the Myocardial Ischaemia National Audit Project (MINAP). *Eur Heart J*. 2014; 35:1551-8. doi: 10.1093/eurheartj/ehu039.
13. Avezum A, Makdisse M, Spencer F, et al. GRACE Investigators. Impact of Age on Management and Outcome of Acute Coronary Syndrome:

Observations From the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*. 2005; 149 :67-73. doi: 10.1016/j.ahj.2004.06.003.

14. Forman DE, Rich MW, Alexander KP, et al. Cardiac Care for Older Adults. Time for a New Paradigm. *J Am Coll Cardiol*. 2011; 57: 1801-1810. doi: 10.1016/j.jacc.2011.02.014.
15. Truong AD, Fan E, Brower RG, Needham DM. Bench-to-bedside Review: Mobilizing Patients in the Intensive Care Unit--From Pathophysiology to Clinical Trials. *Crit Care*. 2009; 13:216. doi: 10.1186/cc7885. Epub 2009 Jul 13.
16. Winkelman C. Bed Rest in Health and Critical Illness: A Body Systems Approach. AACN. *Adv Crit Care.* 2009; 20:254-66. doi: 10.1097/NCI.0b013e3181ac838d.
17. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 Days of Bed Rest on Skeletal Muscle in Healthy Older Adults. *JAMA*. 2007; 297:1772-1774. doi: 10.1001/jama.297.16.1772-b.
18. De Luca L, Leonardi S, Cavallini C. et al. EYESHOT Investigators. Contemporary antithrombotic strategies in patients with acute coronary syndromes admitted to cardiac care units in Italy: the EYESHOT study. *Eur Heart J Acute. Cardiovasc Care*. 2015; 4:441–452.
19. Yusuf S, Zhao F, Mehta SR, Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001; 345: 494-502.
20. Wiviott SD, Braunwald E, McCabe CH, et al. TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; 357:2001–2015.

21. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009; 361:1045-57. doi: 10.1056/NEJMoa0904327.
22. De Luca L, Casella G, Rubboli A, et al. Recent trends in management and outcome of patients with acute coronary syndromes and atrial fibrillation. *Int J Cardiol*. 2017; 1; 248:369-375. doi: 10.1016/j.ijcard.2017.08.019.
23. Hoenig MR, Aroney CN, Scott IA. Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. *Cochrane Database Syst Rev*. 2010. PMID: 20238333 Updated.
24. Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol*.2008; 51:37–45.
25. Gharacholou SM, Becker RC. Hemostasis and Thrombosis in Older Adults. *J Thromb Thrombolysis*. 2009; 27:249-251. doi: 10.1007/s11239-009-0308-4.
26. Yayan J, Bals R. Relative risk of deep vein thrombosis in very elderly patients compared with elderly patients. *Clin Appl Thromb Hemost*. 2014; 22 77–84.
27. Hernández B, Fuentes E, Palomo I, Alarcón M. Increased platelet function during frailty. *Exp. Hematol*. 2019; 77: 12–25.
28. Fuentes F, Palomo I, Fuentes E. Platelet oxidative Stress as a Novel Target of Cardiovascular Risk in Frail Older People. *Vascul Pharmacol* 2017; 93-95:14-19. doi: 10.1016/j.vph.2017.07.003
29. Damluji AA, Forman DE, van Diepen S, et al. American Heart Association Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing. Older Adults in the Cardiac Intensive Care Unit: Factoring Geriatric Syndromes in the Management, Prognosis, and Process of Care: A Scientific

Statement From the American Heart Association. *Circulation*. 2020; 141: e6-e32. doi: 10.1161/CIR.0000000000000741.

30. Montenont E, Rondina MT, Campbell RA. Altered functions of platelets during aging. *Curr Opin Hematol*. 2019 26: 336-342. doi: 10.1097/MOH.0000000000000526
31. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus re- port from the Bleeding Academic Research Consortium. *Circulation*. 2011; 123: 2736–2747.
32. Urban P, Mehran R, Colleran R, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. *Circulation*. 2019; 140 :240-261. doi: 10.1161/CIRCULATIONAHA.119.040167.
33. Buck M, Chojkier M. Muscle wasting and dedifferentiation induced by oxidative stress in a murine model of cachexia is prevented by inhibitors of nitric oxide synthesis and antioxi- dants. *EMBO J*. 1996; 15:1753-1765.
34. Reid MB, Li YP. Tumor necrosis factor-alpha and muscle wasting: a cellular perspective. *Respir. Res*. 2001; 2:269-272.
35. English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care*. 2010; 13: 34-39. doi: 10.1097/MCO.0b013e328333aa66.
36. Fanaroff AC, Chen AY, van Diepen S, Peterson ED, Wang TY. Association Between Intensive Care Unit Usage and Long-Term Medication Adherence, Mortality, and Readmission Among Initially Stable Patients with Non-ST-Segment-Elevation Myocardial Infarction. *J Am Heart Assoc*. 2020; 9(6):e015179. doi: 10.1161/JAHA.119.015179.

37. Anderson HV, Cannon CP, Stone PH, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. *J Am Coll Cardiol*. 1995; 26:1643e50.
38. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non- Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med*. 1998; 338:1785e92.
39. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med*. 2004; 141:186-95. doi: 10.7326/0003-4819-141-3-200408030-00007.
40. Damman P, Clayton T, Wallentin L, Effects of age on long- term outcomes after a routine invasive or selective invasive strategy in patients presenting with non-ST segment elevation acute coronary syndromes: a collaborative analysis of individual data from the FRISC II - ICTUS - RITA-3 (FIR) trials. *Heart*. 2012; 98 :207-213. doi: 10.1136/heartjnl-2011-300453.
41. Savonitto S, Cavallini C, Petronio AS, et al. Italian Elderly ACS Trial Investigators. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. *JACC Cardiovasc Interv*. 2012; 5:906-916. doi: 10.1016/j.jcin.2012.06.008.

42. Tegn N, Abdelnoor M, Aaberge L, et al. After Eighty study investigators. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label rand- omised controlled trial. *Lancet*. 2016; 387 :1057-1065. doi: 10.1016/S0140-6736(15)01166-6
43. Garg A, Garg L, Agarwal M, et al. Routine invasive versus selective invasive strategy in Elderly patients older than 75 years with Non-ST Elevation Acute coronary Syndrome. A systematic review and meta-analysis. *Mayo Clin Proc*. 2018; 9 :436-444. doi: 10.1016/j.mayocp.2017.11.022.
44. Ma W, Liang,Y, Zhu J. Early Invasive Versus Initially Conservative Strategy in Elderly Patients Older Than 75 Years with Non-ST-Elevation Acute Coronary Syndrome: A Meta-Analysis. *Heart Lung Circ*. 2018; 27:611-620. doi: 10.1016/j.hlc.2017.06.725.
45. Kolte D, Khera S, Palaniswamy C, et al. Early invasive versus initial conservative treatment strategies in octogenarians with UA/NSTEMI. *Am J Med*. 2013; 126 :1076-83. doi: 10.1016/j.amjmed.2013.07.024.
46. Sui YG, Teng SY, Qian J, et al. Invasive versus conservative strategy in consecutive patients aged 80 years or older with non-ST-segment elevation myocardial infarction: a retrospective study in China. *Geriatr Cardiol*. 2019; 16: 741-748. doi: 10.11909/j.issn.1671-5411.2019.10.006.
47. Bhatt DL, Roe MT, Peterson ED, et al. CRUSADE Investigators. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA*. 2004; 292: 2096-2104. doi: 10.1001/jama.292.17.2096.

48. Sanchis J, Núñez E, Barrabés JA, et al. Randomized comparison between the invasive and conservative strategies in comorbid elderly patients with non-ST elevation myocardial infarction. *Eur J Intern Med*. 2016; 35: 89-94. doi: 10.1016/j.ejim.2016.07.003.
49. Hernán MA, Robins JM. Using Big Data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol.* 2016; 183: 758–64.
50. Kaura A, Sterne JCS, Trickey A, et al. Invasive versus non-invasive management of older patients with non-ST elevation myocardial infarction (SENIOR-NSTEMI): a cohort study based on routine clinical data. Lancet. 2020; 396:623-634. doi: 10.1016/S0140-6736(20)30930-2.
51. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020 Aug 29:ehaa575. doi: 10.1093/eurheartj/ehaa575.
52. The British Heart Foundation SENIOR-RITA Trial (SENIOR-RITA). https://clinicaltrials.gov/ct2/show/ NCT03052036 (accessed April 4, 2020)
53. Ibañez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2018; 39:119–77.
54. Cequier A, Ariza-Solé A, Elola FJ, et al. Impact on Mortality of Different Network Systems in the Treatment of ST-segment Elevation Acute Myocardial Infarction. The Spanish Experience. *Rev Esp Cardiol.* 2017; 70:155–61.
55. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative

overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet*. 1994; 343:311-322.

56. Krumholz HM, Pasternak RC, Weinstein MC, et al. Cost-effectiveness of thrombolytic therapy with streptokinase in elderly patients with suspected acute myocardial infarction. *N Engl J Med*. 1992; 327:7-13.
57. White HD, Barbash GI, Califf RM, et al. for the GUSTO-I investigators. Age and outcome with contemporary thrombolytic therapy: results from the GUSTO-I trial. *Circulation*. 1996; 94:1826 –1833.
58. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation*. 2000; 101:2239 –46
59. O'Neill WW, de Boer MJ, Gibbons RJ, et al. Lessons from the pooled outcome of the PAMI, Zwolle and Mayo clinic randomized trials of primary angioplasty versus thrombolytic therapy of acute myocardial infarction. *J Invasive Cardiol*. 1998; 10:4–10.
60. de Boer MJ, Ottervanger JP, van 't Hof AWJ, et al. for Zwolle Myocardial Infarction Study Group. Reperfusion therapy in elderly patients with acute myocardial infarction: a randomized comparison of primary angioplasty and thrombolytic therapy. *Am Coll Cardiol*. 2002; 39:1723-8. doi: 10.1016/s0735-1097(02)01878-8.
61. Bueno H, Betriu A, Heras M, et al. TRIANA investigators. Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) randomized trial and pooled analysis with previous studies. *Eur Heart J*. 2011; 32: 51-60. doi: 10.1093/eurheartj/ehq375.

62. Viana-Tejedor A, Loughlin G, Fernández-Avilés F, et al. Temporal trends in the use of reperfusion therapy and outcomes in elderly patients with first ST elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2015; 4:461-7. doi: 10.1177/2048872614565928.

63. Fernández-Bergés D, Degano IR, Gonzalez Fernandez R, et al. Benefit of primary percutaneous coronary interventions in the elderly with ST segment elevation myocardial infarction. Open Heart. 2020;7:e001169. doi: 10.1136/openhrt-2019-001169.

64. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex- based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med*. 1999; 341:217–225. doi: 10.1056/NEJM199907223410401

65. Champney KP, Frederick PD, Bueno H, et al. NRMI Investigators. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. *Heart*. 2009; 95:895–899. doi: 10.1136/hrt.2008.155804.

66. Gupta T, Kolte D, Khera S, et al. Contemporary Sex-Based Differences by Age in Presenting Characteristics, Use of an Early Invasive Strategy, and In hospital Mortality in Patients With Non-ST-Segment-Elevation Myocardial Infarction in the United States. Circ Cardiovasc Interv. 2018; 11 :e005735. doi: 10.1161/CIRCINTERVENTIONS.117.005735.

67. Pagidipati NJ, Peterson ED. Acute coronary syndromes in women and men. *Nat Rev Cardiol*. 2016; 13: 471-480. doi:10.1038/nrcardio.2016.89.

68. De Carlo, M. Morici, N. Savonitto, et al. Sex-Related Outcomes in Elderly Patients Presenting with Non-ST segment Elevation Acute Coronary

Syndrome: Insights From the Italian Elderly ACS Study. *JACC Cardiovasc Interv*. 2015; 8 :791-796. doi: 10.1016/j.jcin.2014.12.240.

69. Anderson RD, Pepine CJ. Gender differences in the treatment for acute myocardial infarction: bias or biology? *Circulation*. 2007;115:823–826. doi: 10.1161/CIRCULATIONAHA.106.685859.
70. Herity NA, Lo S, Lee DP, et al. Effect of a change in gender on coronary arterial size: a longitudinal intravascular ultrasound study in transplanted hearts. *J Am Coll Cardiol.* 2003; *41*: 1539–1546.
71. Holubkov R, Karas RH, Pepine CJ, et al. Large brachial artery diameter is associated with angiographic coronary artery disease in women. *Am Heart J.* 2002; 143: 802–807
72. Pitzalis M. Yentl syndrome. The underestimate of cardiovascular risk in women. *Heart J Suppl*. 2005; 6:72-76.
73. Savonitto S, Colombo D, Franco N, et al. LADIES ACS Study Investigators. Age at Menopause and Extent of Coronary Artery Disease Among Postmenopausal Women with Acute Coronary Syndromes. *Am J Med*. 2016; 129:1205-1212. doi: 10.1016/j.amjmed.2016.05.031
74. Savonitto S, Ferri LA, Piatti L, et al. Elderly ACS 2 Investigators. Comparison of reduced dose prasugrel and standard dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revaacularization. *Circulation*. 2018; 137 :2435-2445. doi: 10.1161/CIRCULATIONAHA.117.032180.
75. Dzavik V, Sleeper LA, Picard MH, et al. SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK Investigators. Outcome of patients aged ≥75 years in the SHould we emergently revascularize Occluded

Coronaries in cardiogenic shocK (SHOCK) trial: do elderly patients with acute myocardial infarction complicated by cardiogenic shock respond differently to emergent revascularization? *Am Heart J*. 2005; 149:1128e34.

76. Lim HS, Farouque O, Andrianopoulos N, et al. Melbourne Interventional Group. Survival of elderly patients undergoing percutaneous coronary intervention for acute myocardial infarction complicated by cardiogenic shock. *JACC Cardiovasc Interv*. 2009; 2:153–155.
77. Tripathi B, Yeh RW, Bavishi CP, et al. Etiologies, trends, and predictors of readmission in ST-elevation myocardial infarction patients undergoing multivessel percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2019; 94: 905–14.
78. Qamar A, Bhatt DL. Culprit-only vs. complete revascularization during ST-segment elevation myocardial infarction. *Prog Cardiovasc Dis*. 2015; 58:260–6.
79. Sorajja P, Gersh BJ, Cox DA, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J*. 2007; 28: 1709–16.
80. Thiele H, Akin I, Sandri M, et al. CULPRIT-SHOCK Investigators. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. *N Engl J Med*. 2017; 377:2419-2432. doi: 10.1056/NEJMoa1710261.
81. Mehta SR, Wood DA, Storey RF, et al. COMPLETE Trial Steering Committee and Investigators. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019; 381:1411-142. doi: 10.1056/NEJMoa1907775.

82. Atti V, Gwon Y, Narayanan MA, et al. Multivessel Versus Culprit-Only Revascularization in STEMI and Multivessel Coronary Artery Disease: Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv*. 2020; 13:1571-1582.
83. Morici N, Alicandro G, Ferri LA, et al. Residual SYNTAX Score and One-Year Outcome in Elderly Patients With Acute Coronary Syndrome. *CJC Open*. 2020; 2:236-243. doi: 10.1016/j.cjco.2020.03.005.
84. Feinstein AR. The pretherapeutic classification of comorbidity in chronic disease. *J Chronic Dis*. 1970; 23: 455–468.
85. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10 :430-439. doi: 10.1016/j.arr.2011.03.003.
86. Meinow B, Parker MG, Kàreholt I, Thorslund M. Complex health problems in the oldest old in Sweden 1992–2002. *Eur J Ageing*. 2006; 3: 98–106.
87. Marengoni A, Winblad B, Karp A, Fratiglioni L. Prevalence of chronic diseases and multimorbidity among the elderly population in Sweden. *Am J Public Health*. 2008; 98:1198–1200.
88. Fillenbaum GG, Pieper CF, Cohen HJ, Cornoni-Huntley JC, Guralnik JM. Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. *J Gerontol A Biol Sci Med Sci*. 2000; 55:M84–M89.
89. Morici N, Molinari V, Cantoni S, et al. Long-Term Risk of Major Adverse Cardiovascular Events in Patients With Acute Coronary Syndrome: Prognostic Role of Complete Blood Cell Count. *Angiology*. 2020; 8:3319720938619. doi: 10.1177/0003319720938619.

90. Sinnott C, McHugh S, Browne J, Bradley C. GPs' perspectives on the management of patients with multimorbidity: systematic review and synthesis of qualitative research. *BMJ Open*. 2013; 3:e003610. doi: 10.1136/bmjopen-2013-003610
91. Lugtenberg M, Burgers JS, Clancy C, Westert GP, Schneider EC. Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. PLoS One. 2011; 6, e25987.
92. Ekerstand N, Löfmark R, Carlsson P. Elderly people with multi-morbidity and acute coronary syndrome: doctors' views on decision-making. *Scand J Public Health*. 2010; 38: 325-31. doi: 10.1177/1403494809354359.
93. Xu X, Mishra GD, Jones,M. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. *Ageing Research Reviews*.2017; 37: 53–68.
94. Wallace E, McDowell R, Bennett K, et al. Comparison of count-based multimorbidity measures in predicting emergency admission and functional decline in older community-dwelling adults: a prospective cohort study. *BMJ Open*. 2016; 6: e013089. doi: 10.1136/bmjopen-2016-013089.
95. Garvey J, Connolly D, Boland F, Smith SM. OPTIMAL, an occupational therapy led self-management support programme for people with multimorbidity in primary care: a randomized controlled trial. *BMC Fam Pract.* 2015 16:59.
96. Sanchis J, Soler M, Núñez J, et al. Comorbidity assessment for mortality risk stratification in elderly patients with acute coronary syndrome. *Eur J Intern Med.* 2019; 62:48-53. doi: 10.1016/j.ejim.2019.01.018.

97. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005; 173:489-95. doi: 10.1503/cmaj.050051.

98. Wall SJ, Wall J, Biram RWS, Romero-Ortuno R. Association of the clinical frailty scale with hospital outcomes. *QJM*. 2015; 12: 943-9. doi: 10.1093/qjmed/hcv066.Epub 2015 Mar 15.

99. Saltvedt I, Mo ES, Fayers P, Kaasa S, Sletvold O. Reduced mortality in treating acutely sick, frail older patients in a geriatric evaluation and management unit. A prospective randomized trial. *J Am. Geriatr Soc*. 2002; 50:792-798. doi: 10.1046/j.1532-5415.2002.50202.x.

100. Liau SJ, Lalic S, Sluggett JK, et al. Optimizing Geriatric Pharmacotherapy through Pharmacoepidemiology Network (OPPEN). Medication management in frail older people: consensus principles for clinical practice, research and education. *J Am Med Dir Assoc*. 2020 12: S1525-8610(20)30371-6. doi: 10.1016/j.jamda.2020.05.004

101. Ricci B, Cenko E, Vasiljevic Z. Impact of the age of frailty on outcomes after percutaneous coronary intervention in acute coronary syndromes. *J Am Coll Cardiol*. 2018; 71:30752–6.

102. Damluji A, Bandeen-Roche K, Forman D, et al. Frailty as an effect measure modifier in older adults with acute myocardial infarction. *J Am Coll Cardiol*. 2019; 73:30629.

103. Veerasamy M, Sinclair H, Qiu W. Procedural and in-hospital complications, time from presentation to invasive treatment and length of hospital stay in frail versus non-frail older (≥75 years) patients with non-ST elevation acute coronary syndrome. *J Am Coll Cardiol*. 2015; 65:60089.

104. Morici N, Savonitto S, Murena E, et al. Causes of death in patients ≥75 years of age with non-ST-segment elevation acute coronary syndrome. *Am J Cardiol*. 2013; 112:1-7. doi: 10.1016/j.amjcard.2013.02.043.

105. Maynard C, Lowy E, McDonell M, Fihn SD. Cause of death in Washington state veterans hospitalized with acute coronary syndromes in the veterans health administration. *Pop Hlth Metric*. 2008; 6:3.

106. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation*. 1994. 90:583e612.

107. Savonitto S, Morici N, Nozza A, et al. Predictors of mortality in hospital survivors with type 2 diabetes mellitus and acute coronary syndrome. *Diab Vasc Dis Res*. 2018; 15:14:23.

108. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomized open-label, non-inferiority trial. *Lancet.* 2020; 395: 1374-1381.

109. De Rosa R, Palmerini T, De Servi S, et al. High on-treatment platelet reactivity and outcome in elderly with non-ST-segment elevation acute coronary syndrome - insight from the GEPRESS study. *Int J Cardiol*. 2018; 259: 20-25.

110. Garay A, Ariza-Solé A, Formiga F, et al. Predictors of post-discharge bleeding in elderly patients with acute coronary syndromes: insights from the BleeMACS registry. *Thromb Haemost*. 2018; 118: 929-938 (2018).

111. Montalto C, Crimi G, Morici N, Savonitto S, De Servi S. Use of Clinical Risk Score in an Elderly Population: Need for Ad Hoc Validation and Calibration. *J Am Coll Cardiol*. 2019; 74:157–166.

112. Roe MT, Ohman EM. A new era in secondary prevention after acute coronary syndrome. *N Engl J Med*. 2012; 366: 85-87.

113. Antiplatelets Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelets therapy: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994; 308:81-106.

114. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988; II:349-360.

115. Krumholz HM, Radford MJ, Ellerbeck EF, et al. Aspirin for secondary prevention after acute myocardial infarction in the elderly: prescribed use and outcomes. *Ann Intern Med*. 1996; 124:292-298. doi: 10.7326/0003-4819-124-3-199602010-00002.

116. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med.* 1998; 339:1665-71. doi: 10.1056/NEJM199812033392303.

117. Nusdeo G, Terrosu P, Parodi G. Optimal antiplatelet therapy after an acute coronary syndrome in the elderly: An old issue. *Int J Cardiol*. 2018; 259:49-50. doi: 10.1016/j.ijcard.2018.02.061

118. Valgimigli M, Bueno H, Byrne RA, et al. ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018; 39:213-260. doi: 10.1093/eurheartj/ehx419.

119. Riesmeyer JS, Salazar DE, Weerakkody GJ, et al. Relationship between exposure to prasugrel active metabolite and clinical outcomes in the TRITON-TIMI 38 substudy. *J Clin Pharmacol*. 2012; 52:789-797. doi: 10.1177/0091270011406280.

120. Silvain J, Cayla G, Hulot JS, et al. High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study. *Eur Heart J*. 2012; 33:1241-1249.

121. Capranzano P, Tamburino C, Capodanno D, et al. Platelet function profiles in the elderly: results of a pharmacodynamic study in patients on clopidogrel therapy and effects of switching to prasugrel 5 mg in patients with high platelet reactivity. *Thromb Haemost*. 2011; 106:1149-1157.

122. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomized controlled superiority trial. *Lancet*. 2016; 388:2015–2022.

123. Roe MT, Goodman SG, Ohman EM, et al. Elderly patients with acute coronary syndromes managed without revascularization: insights into the

safety of long-term dual antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. *Circulation*. 2013; 128:823-33. doi: 10.1161/CIRCULATIONAHA.113.002303

124. Lindholm D, Varenhorst C, Cannon CP, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial . *Eur Heart J*. 2014;35 :2083-2093. doi: 10.1093/eurheartj/ehu160.

125. Crimi G, Morici N, Ferrario M, et al. Time course of ischemic and bleeding burden in elderly patients with acute coronary syndromes randomized to low-dose prasugrel or clopidogrel. *J Am Heart Assoc*. 2019; 8:e010956. doi: 10.1161/JAHA.118.010956

126. Crimi G, De Rosa R, Mandurino-Mirizzi A, et al. De-escalating dual antiplatelet therapy in patients with acute coronary syndromes: the right strategy to harmonize time-dependent ischemic and bleeding risk in elderly patients? *J Cardiovasc Med*. (Hagerstown).2020; 21:281-285. doi: 10.2459/JCM.0000000000000929.

127. Menditto A, Antonicelli R. Is dual therapy the correct strategy in frail elderly patients with atrial fibrillation and acute coronary syndrome? *J Geriatr Cardiol*. 2020; 17: 51-57. doi: 10.11909/j.issn.1671-5411.2020.01.004

128. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month,followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018; 392 :940-949. doi: 10.1016/S0140-6736(18)31858-0.

129. Tomaniak M, Chichareon P, Modolo R, et al.. Ticagrelor monotherapy beyond one month after PCI in ACS or stable CAD in elderly patients: a pre-specified analysis of the GLOBAL LEADERS trial. *EuroIntervention*. 2020; 15:e1605-e1614. doi: 10.4244/EIJ-D-19-00699.

130. Alexander KP, Blazing MA, Rosenson RS, et al.. Management of hyperlipidemia in older adults. *J Cardiovasc Pharmacol Ther*. 2009; 14:49–58.

131. Rich MW. Secondary prevention of cardiovascular disease in older adults. *Prog Cardiovasc Dis*. 2014; 57:168–75.

132. Phan BA, Bittner V. Lipid-lowering therapy in patients 75 years and older: clinical priority or superfluous therapy? *Prog Cardiovasc Dis*. 2014; 57:187–96.

133. Choudhry NK, Levin R, Winkelmayer WC. Statins in elderly patients with acute coronary syndrome: an analysis of dose and class effects in typical practice. *Heart*. 2007; 93: 945–51.

134. Vicent L, Ariza-Solé A, Díez-Villanueva P, et al. Statin Treatment and Prognosis of Elderly Patients Discharged after Non-ST Segment Elevation Acute Coronary Syndrome. Cardiology. 2019; 143:14-21. doi: 10.1159/000500824.

135. Morici N, Ferri LA, Alicandro G, et al. Psoriasis and the risk of acute coronary syndrome in the elderly. *Int J Cardiol*. 2018; 273:44-46. doi: 10.1016/j.ijcard.2018.07.134.

136. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006; 296: 1735–1741.

137. Brauchli YB, Jick SS, Miret M, et al. Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case-control analysis. *Br J Dermatol*. 2009; 160: 1048–1056.

138. Parisi R, Rutter MK, Lunt M, Young HS, Symmons DPM, Griffiths CEM, Ashcroft DM; Identification and Management of Psoriasis Associated ComorbidiTy (IMPACT) project team. Psoriasis and the Risk of Major Cardiovascular Events: Cohort Study Using the Clinical Practice Research Datalink. *J Invest Dermatol*. 2015; 135:2189-2197. doi: 10.1038/jid.2015.87.

139. Morici N, Savonitto S, Ferri LA, et al; Elderly ACS-2 Investigators. Outcomes of Elderly Patients with ST-Elevation or Non-ST-Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *Am J Med*. 2019;132 :209-216. doi: 10.1016/j.amjmed.2018.10.027.

140. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA*. 1999;281:707–713.

141. Casella G, Di Pasquale G, Oltrona Visconti L, et al. Management of patients with acute coronary syndromes in real-world practice in Italy: an outcome research study focused on the use of ANTithRombotic Agents: the MANTRA registry. *Eur Heart J Acute Cardiovasc Care*. 2013; 2:27–34.

142. Farooq V, Serruys PW, Bourantas CV, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation*. 2013; 128:141-151.

143. Fujino A, Kadohira T, Redfors B, et al. Significant association among residual SYNTAX score, non-culprit major adverse cardiac events, and greyscale and virtual histology intravascular ultrasound findings: a substudy from the PROSPECT study. *EuroIntervention*. 2019; 14:1676-1684.

144. Moons KG, Altman DG, Reitsma JB,et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162: W1-73.

145. Kerr KF, Brown MD, Zhu K, Janes H. Assessing the Clinical Impact of Risk Prediction Models With Decision Curves: Guidance for Correct Interpretation and Appropriate Use. *J Clin Oncol*. 2016; 34:2534-40.

146. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ*. 2016;352: i6.

147. Vickers AJ, Cronin AM, Elkin EB, Gonen M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Med Inform Decis Mak*. 2008; 8:53-70.

148. Malkin CJ, George V, Ghobrial MS, et al. Residual SYNTAX score after PCI for triple vessel coronary artery disease: quantifying the adverse effect of incomplete revascularization. *EuroIntervention*. 2013; 8: 1286-1295.

149. Adachi H, Yasuoka Y, Kume K, et al. The residual syntax score for mortality risk assessment in acute coronary syndrome with cardiogenic shock. *J Am Coll Cardiol*. 2013;61(10 Supplement): E20.

150. May CR, Eton DT, Boehmer K, et al. Rethinking the patient: using Burden of Treatment Theory to understand the changing dynamics of illness. *BMC Health Serv Res*. 2014; 14:281. doi: 10.1186/1472-6963-14-281.

151. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. J Gen Intern Med. 2012; 27:1361–1367.

152. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *BMJ.* 2009; 339:b2803. doi: 10.1136/bmj.b2803.

153. Eues SK. End-of-life care: improving quality of life at the end of life. *Prof Case Manag.* 2007; 12:339-344. doi: 10.1097/01.PCAMA.0000300408.00325.1c.

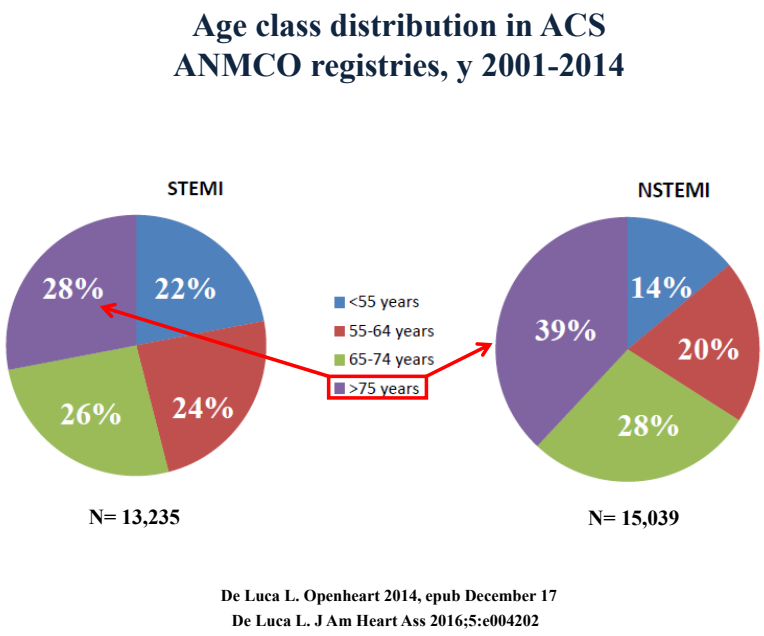

Figure 1. Age class distribution in ACS patients (data from Italian registries)

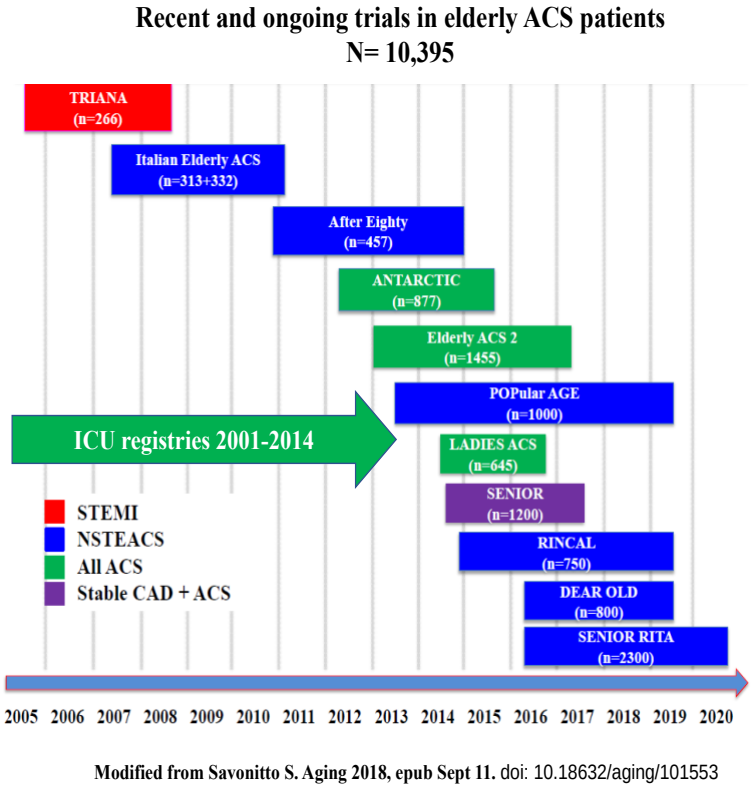

Figure 2. Recent and ongoing trials in elderly ACS patients

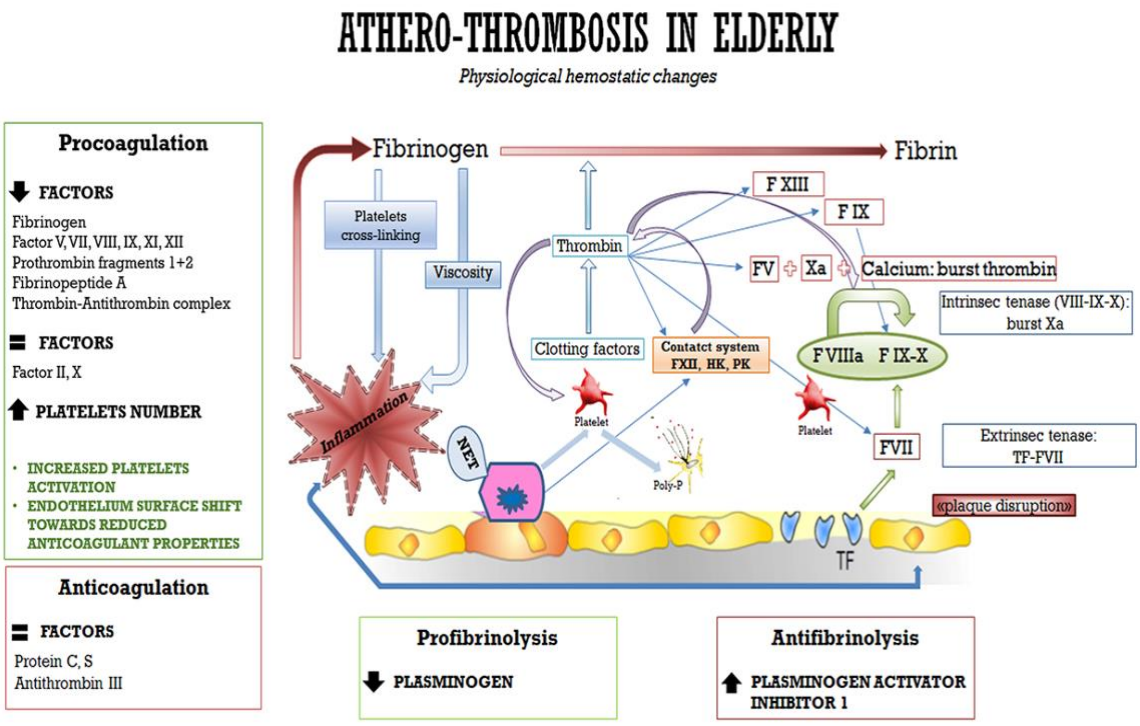

Figure 3. Specific hemostatic pathways in elderly patients

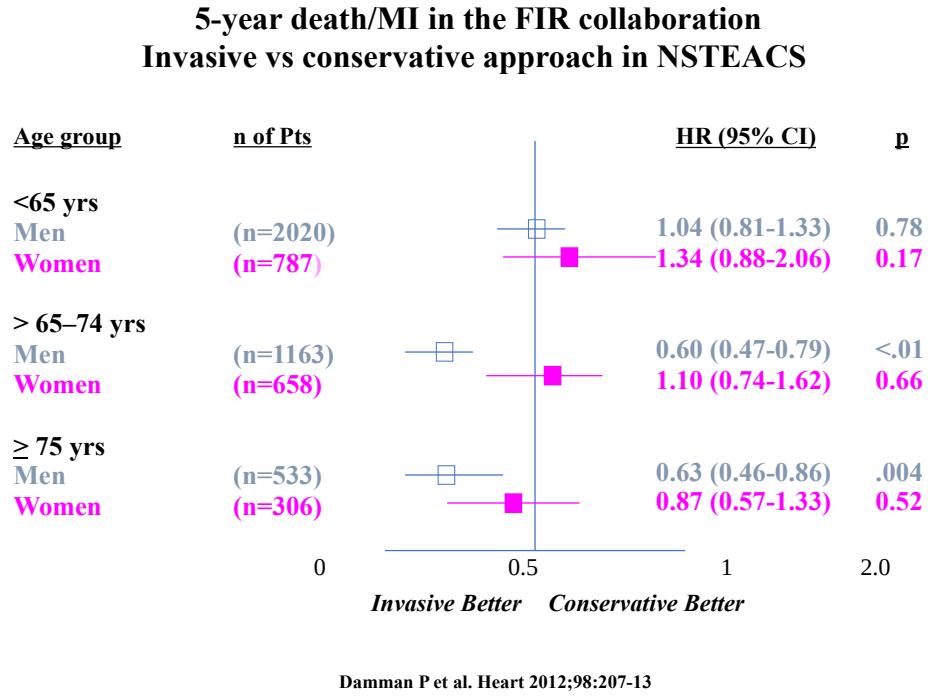

Figure 4. 5-year death/MI in the FIR collaboration according to invasive strategies, age classes and gender.

Italian Elderly ACS study, the Elderly ACS 2 Randomized Trial, and LADIES ACS study

Combined Data=2253 patients

STEMI=687 patients (30.5%)

	Women (n=334;48.6%)	Men (n=353;51.4%)	*p Value*
Age, years	82 (79-86)	80 (77-83)	<0.001
Diabetes	27.8%	22.2%	0.491
Hypertension	78.0%	70.0%	0.017
Dyslipidemia	41.4%	35.2%	0.094
Prior MI*	7.5%	12.5%	0.030
Prior CABG°	2.7%	4.3%	0.267
Prior PCI§	9.0%	13.3%	0.072
Perior PVD^	7.5%	13.9%	0.007
Any IHR**	98.1%	98.8%	0.498
Composite¶ Endpoint	21.9%	17.3%	0.130

NSTE-ACS=1566 patients (69.5%)

	Women (n=682;43.7%)	Men (n=882;56.3%)	*p Value*
Age, years	81 (78-85)	80 (77-84)	0.002
Diabetes	19.0%	16.7%	0.229
Hypertension	87.9%	81.5%	0.002
Dyslipidemia	49.0%	49.0%	0.981
Prior MI*	16.7%	25.1%	<0.001
Prior CABG°	9.2%	14.9%	0.003
Prior PCI§	16.8%	25.8%	<0.001
Perior PVD^	20.8%	25.1%	0.080
Any IHR**	68.8%	77.3%	<0.001
Composite¶ Endpoint	14.0%	16.5%	0.171

*MI=Myocardial Infarction; °CABG=Coronary Artery Bypass Graft; §PCI:Percutaneous Coronary Intervention; ^PVD: Peripheral Vascular Disease; **IHR: any revascularization during hospital stay for the index event; ¶Composite Endpoint: overall death, re-MI, stroke at the follow up of at a median follow-up of 367 days (interquartile range 355-397 days).

Figure 5. Description of STEMI and NSTEACS characteristics, according to gender.

Association between cardiovascular death at follow up & revascularization during index ACS admission

ALECARDIO TRIAL: 7226 patients; 634 aged >74 years

median follow-up of 104 weeks

CVD	Conservative	Invasive	total
no	170 (91.4)	434 (96.9)	604
yes	16 (8.6)	14 (3.1)	30
	186	448	634

Elderly ACS 1, 2 & Ladies: 2776 patients; 2264 aged >74 years, without missing

median follow-up of 52 weeks

CVD	Conservative	Invasive	Total
no	363 (83.4)	1749 (95.6)	2112
yes	72 (16.5)	80 (4.4)	152
	435	1829	2264

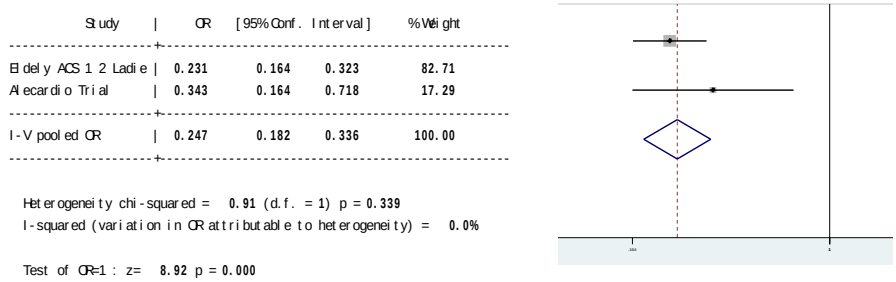

Figure 6. Association between cardiovascular death at follow up and revascularization during index ACS admission in Alecardio trial and pooled analysis of Elderly ACS 1, Elderly ACS 2 and Ladies.

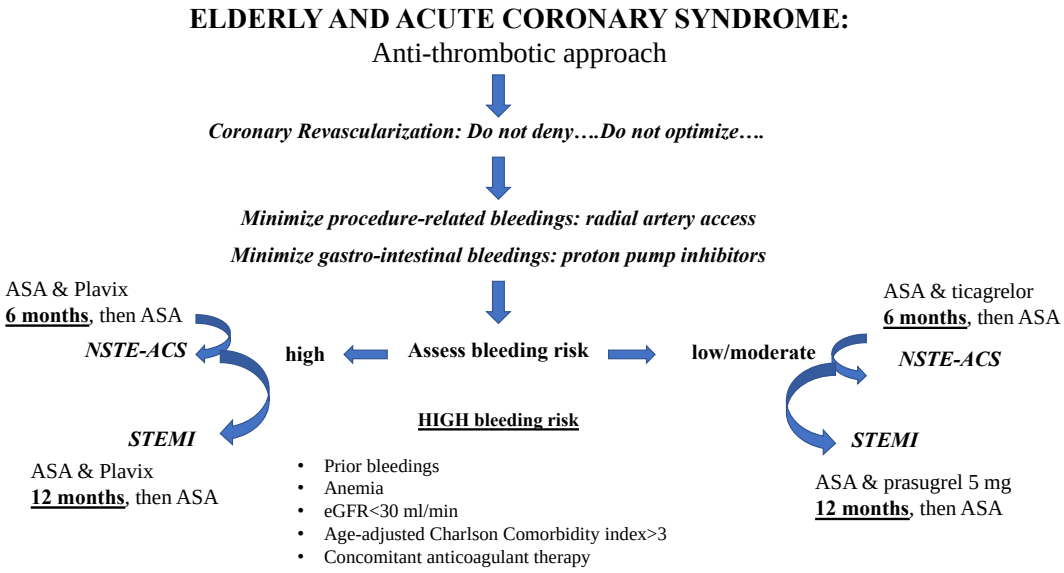

Figure 7. Elderly and ACS: a therapeutic approach.

CENTRAL ILLUSTRATION:

ELDERLY PATIENTS AND ACUTE CORONARY SYNDROME