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### ► **To cite this version:**

Flora Kochly, Christelle Haddad, Brahim Harbaoui, Claire Falandry, Pierre Lantelme, et al.. Therapeutic management and outcome of nonagenarians versus octogenarians admitted to an intensive care unit for acute coronary syndromes. Archives of cardiovascular diseases, 2020, 113 (12), pp.780-790. <10.1016/j.acvd.2020.05.020>. <hal-03149067>

**HAL Id: hal-03149067**

**<https://hal.science/hal-03149067v1>**

Submitted on 15 Dec 2022

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## **Therapeutic management and outcome of nonagenarians versus octogenarians admitted to an intensive care unit for acute coronary syndromes**

**Abbreviated title:** Acute coronary syndromes in the elderly

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## **Summary**

*Background.* – The number of very old patients admitted to intensive care units for acute coronary syndromes has increased gradually, but these patients are under-represented in randomized clinical trials.

*Aim.* – The aim of this study was to analyse mortality of nonagenarians compared with octogenarians admitted to an intensive care unit for acute coronary syndromes, to describe their management and to identify prognostic factors.

*Methods.* – Patients aged  $\geq 80$  years admitted to an intensive care unit (Croix-Rousse University Hospital, Lyon) with a diagnosis of acute coronary syndrome from 1 January 2013 to 31 December 2016 were included retrospectively. After exclusion of type 2 acute coronary syndromes, the data for 311 octogenarians and 92 nonagenarians were analysed using Kaplan-Meier curves and a multivariable Cox regression model.

*Results.* – More than 70% of patients received renin-angiotensin-system blockers, beta-blockers and statins, without significant difference between nonagenarians and octogenarians. Nonagenarians were treated significantly less frequently with ticagrelor than octogenarians ( $P = 0.028$ ). Overall, 97.8% of patients had a coronary angiogram, and 80.4% underwent percutaneous coronary intervention. At 5-year follow-up, the survival rate was 62.8% for nonagenarians compared with 73.1% for octogenarians ( $P = 0.007$ ), but no significant difference was observed for cardiovascular mortality ( $P = 0.17$ ). Global Registry of Acute Coronary Events (GRACE) score and increased age were significantly associated with higher mortality rate, while renin-angiotensin-system blockers, statins and ticagrelor were protective factors.

*Conclusions.* – Although overall mortality was higher in patients aged  $\geq 90$  years compared with those aged  $< 90$  years with acute coronary syndromes, the overall survival reported here is acceptable. In addition to the effect of age, the difference in prognosis according to age may be explained, in part, by a non-optimal treatment strategy for older patients.

## **Résumé**

*Contexte.* – La proportion des patients très âgés admis en soins intensifs cardiologiques (USIC) pour un syndrome coronaire aigu (SCA) a progressivement augmenté. Cette population est sous représentée dans les études randomisées.

*Objectif.* – L'objectif est d'évaluer la mortalité des nonagénaires en comparaison des octogénaires admis pour un SCA en USIC et d'identifier les facteurs influençant le pronostic.

*Méthodes.* – Les patients  $\geq 80$  ans admis à l'USIC (Hôpital de la Croix-Rousse, CHU de Lyon) avec un diagnostic de SCA ont été analysés rétrospectivement entre le 01 Janvier 2013 et le 31 décembre 2016. Après exclusion des SCA de type 2, les données de 311 octogénaires et 92 nonagénaires ont été analysés par les courbes de Kaplan-Meier et les modèles de Cox ajustés.

*Résultats.* – Plus de 70 % des patients ont été traités par les bloqueurs du système rénine-angiotensinogène (BSRA), les bêta-bloquants et statines sans différence significative selon l'âge. Les nonagénaires étaient moins fréquemment traités par le ticagrelor que les octogénaires ( $P = 0,0028$ ). 97,8 % des patients ont été explorés par une coronarographie, et 80,4 % une angioplastie coronaire. A 5 ans de suivi, la survie toute cause était de 62,8 % pour les nonagénaires contre 73,1 % pour les octogénaires ( $P = 0,007$ ) avec une tendance non significative pour la mortalité cardiovasculaire ( $P = 0,17$ ). L'âge avancé et le score de GRACE est significativement associé à la mortalité toute cause, à l'inverse les BSRA, les statines et le ticagrelor étaient des facteurs protecteurs.

*Conclusions.* – Malgré une mortalité supérieure chez les nonagénaires, leur survie globale paraît acceptable. Au-delà de l'effet de l'âge sur la mortalité, la surmortalité des nonagénaires pourrait s'expliquer par une moindre optimisation de la thérapeutique.

## **KEYWORDS**

Acute coronary syndromes;

Myocardial infarction;

Elderly;

Intensive care unit

## **MOTS CLÉS**

Syndrome coronaire aigu ;

Infarctus du myocarde ;

Personnes âgées ;

Soins intensifs cardiologiques

*Abbreviations:* ACS, acute coronary syndromes; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BARC, Bleeding Academic Research Consortium; DDD, defined daily dose; GRACE, Global Registry of Acute Coronary Events; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

## Background

Older patients account for an increasing proportion of patients admitted to hospital with acute coronary syndromes (ACS); currently about one-third are aged  $\geq 75$  years [1]. At the same time, older patients are either excluded or under-represented in randomized controlled trials investigating the benefits of ACS treatments [2-5]. This group of patients is known to be at higher risk of both ischaemic events and bleeding complications, making it difficult to determine the most appropriate therapy. Current guidelines do not detail a specific management strategy for this population, but propose performing an overall estimation of patient status, including general health, cognitive status and life expectancy [6-9]. In parallel, over the past decade, the added prognostic value of an invasive approach, particularly percutaneous coronary intervention (PCI), has been demonstrated for ST-segment elevation myocardial infarction (STEMI) [10-13] and non-STEMI (NSTEMI) [14, 15]. Such therapeutic management has moved progressively to the older population, and clinical benefit has been observed in this subgroup, mainly in cohort studies [16-19]. However, the concept of frailty, the higher prevalence of comorbidities, age-associated conditions (cognitive and functional impairment) and a higher risk of complications might explain why clinicians frequently use either conservative or selective invasive approaches in older patients in real-world practice [20, 21]. In the context of an ageing population, the prognosis of ACS in older patients appears to be of utmost importance. However, only a few studies have focused on daily routine practice concerning this specific population.

The aim of this study was therefore to analyse mortality of nonagenarians compared with octogenarians admitted to an intensive care unit (ICU) for ACS, to describe their therapeutic management and to identify prognostic factors.

## Methods

### Population

Patients aged  $\geq 80$  years and admitted for ACS to the ICU of the Croix-Rousse University Hospital (Hospices Civils de Lyon, France) were included retrospectively using the hospital discharge database (Programme de médicalisation des systems d'information [PMSI]). All patients with a hospital stay between 1 January 2013 and 31 December 2016 and with a diagnosis of ACS at admission were identified, and differential diagnoses were excluded after investigation of medical records. For patients with several hospital stays, only the first stay was considered in the analysis. Patients were classified

according to the type of myocardial infarction (STEMI, type 1 NSTEMI or type 2 NSTEMI) and age (80–90 or  $\geq 90$  years). Type 2 NSTEMI was defined when a specific clinical setting (anaemia, arrhythmias, sepsis) that might explain a myocardial oxygen demand mismatch was observed. Patients with type 2 NSTEMI were excluded from the analysis.

## **Data collection**

The following data were collected from electronic medical files: demographic characteristics (age, sex and residence in nursing home); comorbidities (hypertension, diabetes, atrial fibrillation and cognitive function); clinical presentation at admission (blood pressure, heart rate, Killip classification and cardiac arrest); laboratory data (plasma creatinine and haemoglobin); medical therapies; and invasive management. Significant valvular heart disease was defined after transthoracic echocardiography with the following criteria: mitral regurgitation  $\geq$  grade 3; aortic regurgitation  $\geq$  grade 3; moderate or severe aortic stenosis; and moderate or severe mitral stenosis. The defined daily dose (DDD) of administered drug was determined according to the World Health Organization Collaborating Centre for Drugs Statistics Methodology DDD system [22]. DDD is defined as “the assumed average maintenance dose per day for a drug used for its main indication in adults” [22]. This system makes it possible to perform standardized comparisons of antihypertensive drug use for patients on different drugs.

A Global Registry of Acute Coronary Events (GRACE) score at admission was calculated using the above-mentioned variables, as was a GRACE score excluding the variable age to compare patients aged 80–89 and  $\geq 90$  years [23]. Vital status was obtained using the last follow-up medical visit. Intrahospital haemorrhagic events were reported using Bleeding Academic Research Consortium (BARC) criteria [24].

## **Statistical analysis**

Continuous variables with normal distributions are summarized as means  $\pm$  standard deviations, and categorical variables as counts and percentages. Analysis of variance (ANOVA) and  $\chi^2$  tests were used for group comparisons for continuous and categorical variables, respectively. Paired comparisons were made between type of ACS, using the Tukey correction for multiple testing on continuous variables, and the Bonferroni correction for multiple testing on categorical variables. All-cause death and cardiovascular death (myocardial infarction, cardiogenic shock, cerebral infarction,

heart failure and sudden death) were estimated using the Kaplan-Meier method (log-rank statistic) according to different subgroups of patients (age 80–89 vs  $\geq 90$  years, type of ACS) and by univariate Cox regression models. The proportional hazards hypothesis was tested for each variable by introducing a variable-by-time interaction into the Cox regression model. These interactions were not statistically significant for all-cause or cardiovascular death. A backward multivariable Cox regression model was then built with the inclusion of variables with a  $P$  value  $< 0.10$  in the univariate analysis to determine the independent predictors of mortality. An additional sensitivity analysis was carried out after exclusion of patients who died during the initial hospital stay. Analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, IL, USA).  $P < 0.05$  was considered statistically significant.

## Results

### Baseline characteristics

Among the 476 patients considered, 403 were included with type 1 NSTEMI or STEMI (Fig. 1). Compared to included patients, patients with type 2 NSTEMI had different characteristics at admission, including significantly higher systolic blood pressure, heart rate and left ventricular ejection fraction (LVEF) and lower haemoglobin, and presented more frequently with atrial fibrillation and diabetes (Table A.1). Concerning included patients, nonagenarians less frequently had diabetes and smoked, but more frequently had dementia than octogenarians. There was also a significant difference in the number of coronary arteries affected according to age. Mean GRACE score (including or excluding age) was not significantly different between the two groups (Table 1). During their hospital stay, 43 patients (10.7%) developed new-onset atrial fibrillation, with no difference between nonagenarians and octogenarians ( $n = 12$ , 13.0% vs  $n = 31$ , 10.0%, respectively;  $P = 0.40$ ).

### Therapeutic management

Around three-quarters of patients received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE inhibitors/ARBs), beta-blockers or statins, without significant difference between age groups. Half of the patients received loop diuretics during their hospital stay, and 10.2% received inotropes/vasopressor agents. No ventilation was used in nonagenarian patients (Table 2). There was no significant difference in the proportions of patients receiving beta-blockers, ACE

inhibitors/ARBs and statins between the two age groups (Fig. 2A). However, nonagenarians received a lower mean DDD of drugs than octogenarians for beta-blockers, ACE inhibitors/ARBs and statins (Fig. 2B). Optimal doses of treatment were achieved in a minority of both nonagenarians (ACE inhibitors/ARBs 3.0%, beta-blockers 5.1%, statins 10.9%, mineralocorticoid receptor antagonists [MRAs] 1.1%) and octogenarians (ACE inhibitors/ARBs 18.3%, beta-blockers 13.3%, statins 28.3%, MRAs 3.2%). There was a significantly lower frequency of ticagrelor use in nonagenarians, whereas glycoprotein IIb/IIIa inhibitors (1.0%) and prasugrel (0.2%) were used infrequently in both groups. Low-molecular-weight heparin was the most frequently used anticoagulant drug in the two subgroups (41.2% and 39.1%, respectively) (Table 2 and Fig. 2C). Nearly all patients (97.8%) had a coronary angiogram during the hospital stay. PCI was performed in 80.4% of patients and radial access was used in 92.1% of cases (Table 2). Device closure was used in 19 patients (61.2%) in whom femoral access was used. Among nonagenarians, bare-metal stents were more frequent than drug-eluting stents, whereas the converse was found among younger patients ( $P = 0.001$ ; Table 2 and Fig. 2D). A small proportion of patients (6.1%) were treated without stent implantation (balloon angioplasty or aspiration thrombectomy). Haemorrhagic events, mostly of gastrointestinal, urological or vascular origin, occurred in 20.0% of nonagenarians and 11.7% of octogenarians ( $P = 0.052$ ); there was no significant difference in major bleeding (defined as BARC score  $> 2$ ) between the two subgroups ( $P = 0.42$ ; Fig. 3). Among the 43 patients who had new onset of atrial fibrillation during their hospital stay, nine were treated with vitamin K antagonists and three with direct oral anticoagulants at discharge. Among these 12 patients, only three were also treated with ticagrelor and aspirin; the others received clopidogrel and aspirin.

## Mortality and outcome

The mean length of hospital stay in ICU was  $2.4 \pm 2.2$  days in the whole cohort ( $n = 403$ ), with no significant difference between nonagenarians ( $2.5 \pm 2.4$ ) and octogenarians ( $2.4 \pm 2.2$  days) ( $P = 0.82$ ). The mean total length of full hospital stay was  $6.1 \pm 6.5$  days in the whole cohort, without difference between nonagenarians ( $6.4 \pm 6.9$ ) and octogenarians ( $6.0 \pm 6.3$ ) ( $P = 0.56$ ). The in-hospital mortality rate was 9.3% ( $n = 29$ ) for octogenarians and 15.2% ( $n = 14$ ) for nonagenarians. Before returning home, 37.2% of patients were admitted to a rehabilitation centre (40.2% of nonagenarians, 36.3% of octogenarians;  $P = 0.50$ ). During the follow-up period (mean duration  $3.2 \pm 1.8$  years), 108

deaths in the whole cohort ( $n = 403$ ) were recorded (34 in nonagenarians, 74 in octogenarians), 51 of which were from cardiovascular causes (15 in nonagenarians, 36 in octogenarians). At 5-year follow-up, the overall survival was estimated to be 62.8% for nonagenarians and 73.1% for octogenarians, with a significantly higher risk of all-cause mortality for nonagenarians during follow-up (log-rank  $P = 0.007$ ; Fig. 4A), and a similar (but non-significant) trend regarding cardiovascular mortality (log-rank  $P = 0.17$ ; Fig. 4B). After stratification according to the type of ACS (STEMI versus NSTEMI), a significant difference was found between nonagenarians and octogenarians for all-cause mortality (log-rank  $P < 0.001$ ; Fig. 4C) and for cardiovascular mortality (log-rank  $P = 0.004$ ; Fig. 4D).

Factors associated ( $P < 0.1$ ) with all-cause and/or cardiovascular mortality in the univariate analysis (Table A.2) were included in a multivariable Cox regression model. Significant risk factors for all-cause mortality were older age and the necessity for inotrope use. Protective factors were use of ACE inhibitors/ARBs, statins and ticagrelor. A trend towards a negative association with beta-blocker use and a positive association with higher GRACE score were also shown. Significant risk factors for cardiovascular mortality were a higher GRACE score and necessity for inotrope use. Protective factors were use of ACE inhibitors/ARBs, ticagrelor and statins, and non-invasive ventilation (Table 3). After exclusion of patients who died during their initial hospital stay ( $n = 43$ ), ticagrelor and ACE inhibitors/ARBs appeared to be protective factors against all-cause mortality, and inotropes and furosemide were associated with poorer survival. Finally, normal LVEF, ticagrelor and ACE inhibitors/ARBs were protective factors against cardiovascular mortality, whereas necessity for inotrope use was a strong predictor of pejorative outcome (Table A.3).

## Discussion

The therapeutic approach used here in a selected older population seems appropriate, highlighting the fact that such patients can benefit from ICU admission and an invasive management strategy. The present study has demonstrated that the survival of older patients aged  $\geq 90$  years admitted to an ICU for myocardial infarction (STEMI or type 1 NSTEMI) was significantly lower for all-cause mortality, and there was a trend towards it being lower for cardiovascular mortality in comparison with those aged 80–89 years. Prognostic factors were identified, and these included admission status (GRACE score, cardiogenic shock and requirement for non-invasive ventilation), as well as specific therapeutic classes (ACE inhibitors/ARBs, statins and ticagrelor). Moreover, we observed that patients aged  $\geq 90$

years were less frequently treated with optimal management, which may explain, at least in part, the difference in outcomes observed. The 5-year overall survival estimated in this cohort of ACS patients (73.1% for octogenarians and 62.8% for nonagenarians) appears acceptable, given that the median survival rates observed in France in the general population among those of same age and over the same period were 5.9 and 3.8 years, respectively [25].

The prognosis of patients with ACS is strongly influenced by age, and this variable has been included in the GRACE score that is recommended for risk stratification in the guidelines [23]. Previous studies performed between 2006 and 2013 demonstrated that nonagenarian patients had a 1-year mortality rate close to 50%, which was four times higher than that for the general population at the same time (10–13%) [12, 18, 26]. Many studies have highlighted temporal improvements in mortality from ACS, and most advances have concerned older patients [27]. Of note, in patients aged > 75 years, 5-year mortality decreased from 55% in the 1990s to 40% in 2008 [19]. The 5-year overall survival rate found in our study is indicative of an overall improvement during the past decade in a selected older population admitted to an ICU.

Medical practices have evolved quickly in the field of ACS, with new drugs (new P2Y<sub>12</sub> inhibitors) and interventional techniques (development of coronary angiogram preferentially through the radial route, superiority of drug-eluting stents, etc.) [28, 29]. Despite an increased number of older patients being admitted to ICUs, they are largely under-represented in randomized controlled trials. This is probably caused, in part, by the caution that can be applied concerning the safety of testing new drugs in elderly patients. Ticagrelor became available on the French market in 2012, just before the start of the study, which may explain why older patients in our study were found to be undertreated using this new drug. In the PLATO study, patients aged > 75 years represented around 15% of those included, but the proportions of patients aged > 80 years or > 90 years were not mentioned [30]. Nevertheless, in a substudy of PLATO, patients aged > 75 years had similar clinical benefit and overall safety to younger patients with ticagrelor compared with clopidogrel [31]. In the present cohort, ticagrelor was found to have a strong protective effect on mortality, sustaining the hypothesis that clopidogrel resistance might be more frequent in this population. This may encourage the prescription of ticagrelor in older patients who are not at very high risk of bleeding [32]. However, this option may sometimes be counterbalanced by the high frequency of atrial fibrillation in older patients (> 20% in our study), which

could explain the choice of clopidogrel in association with an anticoagulant to lower the risk of bleeding [6].

Other pharmacological treatments, including ACE inhibitors/ARBs, beta-blockers and statins, may be crucial for the outcome of patients after ACS. In the 2005 GRACE and CRUSADE studies, the use of beta-blockers and statins was reported to be less frequent among older patients at discharge [16, 32, 33]. Nevertheless, the rates of beta-blocker and statin prescriptions increased from 2003 to 2010 (49% to 56% and 61% to 68%, respectively) [34]. Importantly, these treatments, as well as ACE inhibitors, have demonstrated greater clinical benefit in those with heart failure and reduced LVEF [2, 35]. As nearly half of the present cohort presented with heart failure at admission, this could partly explain the observed protective effect of these different classes of treatments, which were prescribed frequently in our study.

In patients aged > 70 years admitted for STEMI or NSTEMI, the proportion who were treated by PCI increased progressively from 4% in 2001 to nearly 70% in 2012 [17, 20]. In our study, the majority of older patients admitted to the ICU had a coronary angiogram, and > 80% of them were treated by PCI. Drug-eluting stents were less frequently implanted in nonagenarians than in octogenarians, but the implantation rate was still 10 times higher than that reported for nonagenarians between 2003 and 2011 (4%) [36]. This is probably because of a change in practice during the study recruitment period, in accordance with clinical guidelines [6, 9]. The implantation of fewer drug-eluting stents may be explained, in part, by the desire to shorten the duration of dual antiplatelet therapy by using bare-metal stents for patients at high risk of haemorrhage. Of note, the current recommendations are moving to preferential use of drug-eluting stents instead of bare-metal stents, with tailored use of the duration of dual antiplatelet therapy [6].

Another important aspect when dealing with older patients is to reduce the side-effects – particularly the bleeding risk – of invasive procedures and antithrombotic agents. The frequency of major bleeding was reported to be 5% and 6% among patients aged > 85 years in the GRACE and CRUSADE studies, respectively [12, 37]. A similar result was found in our study, with no significant difference between octogenarians and nonagenarians. Vascular bleedings may have been limited in the present cohort by the infrequent use of the femoral approach to perform the coronary angiogram, a higher rate of radial access being reported here (92.1%) than in other cohorts (60%) [12].

## **Study limitations**

The major limitation of the present study is the selection bias related to ICU admission, which underlines that the population studied probably excluded patients with poor general health and cognitive status, who would have been treated non-invasively outside the ICU. This hypothesis is supported by previous reports demonstrating a lower admission to ICU for patients aged > 80 years compared with younger patients [31], and that selected older patients had a higher functional status score and a lower prevalence of frailty compared with those not admitted to an ICU [38]. However, this selection bias may be observed in clinical trials including older patients as well.

## **Conclusions**

Provided that nonagenarians are deemed in sufficiently good condition to be admitted to an ICU, their prognosis is not so far removed from that of octogenarians, and could possibly be improved by optimizing treatment. This does not account for the overall prognosis of nonagenarians, who frequently combine cardiac problems with many other comorbidities and frailty.

## **Acknowledgements**

We thank Véréna Landel and Philip Robinson (Direction de la Recherche Clinique et de l'Innovation, Hospices Civils de Lyon) for thorough editing of this article.

## **Sources of funding**

None.

## **Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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## Figure legends

**Figure 1.** Study flowchart. ACS: acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

**Figure 2.** Therapeutic management of different subgroups of patients with type 1 non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction ( $n = 403$ ). A. According to medical cardiac treatment. B. According to defined daily dose. C. According to antithrombotic and anticoagulant treatment. D. According to invasive procedure. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMS: bare-metal stent; DES: drug-eluting stent; LMWH: low-molecular-weight heparin; MRA: mineralocorticoid receptor antagonist; PCI: percutaneous coronary intervention; UFH: unfractionated heparin.

**Figure 3.** Frequency of haemorrhages, according to age and bleeding subtype. BARC: Bleeding Academic Research Consortium.

**Figure 4.** Survival rates. A. All-cause mortality according to age. B. Cardiovascular mortality according to age. C. All-cause mortality according to acute coronary syndrome subtype. D. Cardiovascular mortality according to acute coronary syndrome subtype. NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

**Table 1** Baseline characteristics of patients in the whole cohort and according to age subgroups after exclusion of type 2 non-ST-segment elevation myocardial infarction.

	All ( <i>n</i> = 403)	80–89 years ( <i>n</i> = 311)	≥ 90 years ( <i>n</i> = 92)	<i>P</i>
<b>General characteristics</b>				
Age (years)	86.4 ± 4.3	84.6 ± 2.9	92.6 ± 2.2	
Men/women	43.2/56.8	44.4/55.6	39.1/60.9	0.37
BMI (kg/m <sup>2</sup> )	25.0 ± 5.8	25.3 ± 6.2	22.7 ± 3.0	0.043
Resident in a nursing home	13.4	10.9	22.6	0.005
<b>Clinical characteristics at admission</b>				
Type of ACS				0.043
STEMI	36.7	34.1	45.7	
NSTEMI type 1	63.3	65.9	54.3	
SBP (mmHg)	128 ± 27	128 ± 27	125 ± 28	0.30
DBP (mmHg)	66 ± 16	66 ± 15	66 ± 19	0.98
Heart rate (bpm)	79 ± 19	78 ± 18	81 ± 18	0.24
Killip I/II/III/IV	57.3/20.8/16.1/5.8	58.2/18.0/17.0/6.8	54.3/30.4/13.0/2.2	0.033
Cardiac arrest	5.5	6.4	2.2	0.12
<b>Laboratory/imaging characteristics</b>				
Number of diseased vessels				0.35
Unknown	2.2	1.6	4.3	
One-vessel disease	30.0	28.6	34.8	
Two-vessel disease	27.0	27.3	26.1	
Three-vessel disease	40.7	42.4	34.8	
LVEF (%)	47.0 ± 12.4	47.2 ± 12.7	46.3 ± 11.3	0.56
Significant valvular heart disease	2.1	2.1	2.3	0.92
eGFR MDRD (mL/min/1.73m <sup>2</sup> )	65.3 ± 28.0	66.5 ± 28.1	62.5 ± 28.1	0.22
Haemoglobin (g/L)	124 ± 18	124 ± 19	125 ± 18	0.54
GRACE score	193 ± 40	192 ± 42	200 ± 37	0.12

GRACE score excluding age	101 ± 40	101 ± 42	100 ± 37	0.77
Co-morbidities				
History of atrial fibrillation	17.6	18.0	16.3	0.71
History of CAD	26.7	26.7	26.7	0.99
Diabetes	26.3	29.4	15.4	0.007
Hypertension	76.3	78.0	70.3	0.13
Smoking: no/former/current	80.5/15.5/4.0	78.0/17.1/4.9	88.8/10.3/0.9	0.032
Dementia	24.1	21.5	32.6	0.029

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Data are expressed as mean ± standard deviation or %. ACS: acute coronary syndrome; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; GRACE: Global Registry of Acute Coronary Events; LVEF: left ventricular ejection fraction; MDRD: modification of diet in renal disease; NSTEMI: non-ST-segment elevation myocardial infarction; SBP: systolic blood pressure; STEMI: ST-segment elevation myocardial infarction.

**Table 2** Treatment according to age subgroups after exclusion of type 2 non-ST-segment elevation myocardial infarction.

	All ( <i>n</i> = 403)	80–89 years ( <i>n</i> = 311)	≥ 90 years ( <i>n</i> = 92)	<i>P</i>
<b>Antiplatelets</b>				
Aspirin	385 (95.5)	293 (94.2)	92 (100.0)	0.018
Clopidogrel	247 (61.3)	177 (56.9)	70 (76.1)	0.001
Ticagrelor	130 (32.3)	109 (35.0)	21 (22.8)	0.028
Prasugrel	9 (0.2)	9 (0.3)	0 (0)	0.59
Glycoprotein IIb/IIIa inhibitor	4 (1.0)	4 (1.3)	0 (0)	0.27
<b>Anticoagulants</b>				
UFH	55 (13.6)	53 (17.0)	2 (2.2)	< 0.001
LMWH	164 (40.7)	128 (41.2)	36 (39.1)	0.73
Fondaparinux	34 (8.4)	22 (7.1)	12 (13.0)	0.070
VKA	59 (14.6)	49 (15.8)	10 (10.9)	0.24
NOAC	12 (3.0)	10 (3.2)	2 (2.2)	0.61
<b>Medical treatment</b>				
ACE inhibitor	241 (59.8)	181 (58.2)	60 (65.2)	0.22
ARB	45 (11.2)	39 (12.5)	6 (6.5)	0.11
ACE inhibitor or ARB	286 (71.0)	220 (70.7)	66 (71.7)	0.85
ACE inhibitor or ARB DDD	0.42 ± 0.28	0.45 ± 0.30	0.32 ± 0.19	0.001
Beta-blocker	320 (79.4)	242 (77.8)	78 (84.8)	0.15
Beta-blocker DDD	0.42 ± 0.26	0.44 ± 0.26	0.34 ± 0.21	0.002
MRA	55 (13.6)	43 (13.8)	12 (13.0)	0.85
MRA DDD	0.58 ± 0.24	0.60 ± 0.25	0.48 ± 0.21	0.14
Statin	290 (72.0)	228 (73.3)	62 (67.4)	0.27
Statin DDD	0.59 ± 0.32	0.62 ± 0.32	0.46 ± 0.29	< 0.001
Loop diuretic	207 (51.4)	156 (50.2)	51 (55.5)	0.47
Inotrope	41 (10.2)	32 (10.3)	9 (9.8)	0.89

Non-invasive ventilation	27 (6.7)	27 (8.7)	0 (0)	0.003
Invasive ventilation	21 (5.2)	21 (6.8)	0	0.010
Invasive therapy				
Coronary angiogram	394 (97.8)	306 (98.4)	88 (95.7)	0.12
Approach				0.39
Radial	363/394 (92.1)	280/306 (91.5)	83/88 (94.3)	
Femoral	31/394 (7.9)	26/306 (8.5)	5/88 (5.7)	
PCI	345 (80.4)	275 (88.4)	70 (76.1)	0.24
No stent/BMS/DES	6.1/36.2/57.7	6.9/31.3/61.8	2.9/55.7/41.4	0.001

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Data are expressed as number (%), mean  $\pm$  standard deviation or %. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMS: bare-metal stent; DDD: defined daily dose; DES: drug-eluting stent; LMWH: low-molecular-weight heparin; MRA: mineralocorticoid receptor antagonist; NOAC: non-vitamin K antagonist oral anticoagulant; PCI: percutaneous coronary intervention; UFH: unfractionated heparin; VKA: vitamin K antagonist.

**Table 3** Multivariable Cox regression model (exclusion of type 2 non-ST-segment elevation myocardial infarction).

	All-cause mortality		Cardiovascular mortality	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age ( $\geq 90$ vs $< 90$ years)	2.00 (1.30–3.08)	0.002	1.77 (0.93–3.38)	0.09
+ 1 vessel disease	1.22 (0.99–1.50)	0.06	-	-
LVEF (+ 1%)	-	-	-	-
GRACE score (+ 10 points)	1.06 (1.00–1.11)	0.050	1.08 (1.00–1.16)	0.043
STEMI vs NSTEMI	-	-	-	-
Haemoglobin (+ 10 g/L)	0.91 (0.82–1.02)	0.10	-	-
Ticagrelor (yes)	0.46 (0.28–0.75)	0.002	0.50 (0.25–0.97)	0.040
ACE inhibitor or ARB (yes)	0.60 (0.39–0.91)	0.017	0.45 (0.24–0.84)	0.012
Beta-blocker (yes)	0.64 (0.40–1.01)	0.05	-	-
Statin (yes)	0.52 (0.34–0.79)	0.002	0.53 (0.29–0.98)	0.041
Furosemide (yes)	-	-	-	-
Inotrope (yes)	4.24 (2.29–7.87)	$< 0.001$	5.94 (2.67–13.21)	$< 0.001$
Long-term use of anticoagulants (yes)	–	-	0.38 (0.13–1.07)	0.07
Non-invasive ventilation (yes)	1.89 (0.95–3.72)	0.07	3.00 (1.26–7.15)	0.013
Invasive ventilation (yes)	-	-	-	-
Coronary angiogram (yes)	-	-	-	-
PCI (yes)	-	-	-	-

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CI: confidence interval; GRACE: Global Registry of Acute Coronary Events; HR: hazard ratio; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

525 hospitalizations with a supposed diagnosis of ACS



33 hospitalizations with differential diagnosis

492 hospitalizations with a confirmed diagnosis of ACS



16 patients with more than 1 hospital stay

476 patients with one hospitalization for ACS



369 patients aged 80-89 years



107 patients aged ≥ 90 years



53 patients with type 2 NSTEMI



15 patients with type 2 NSTEMI

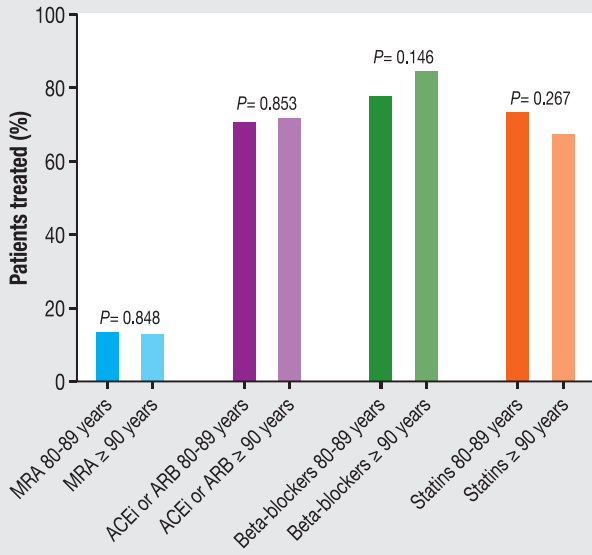
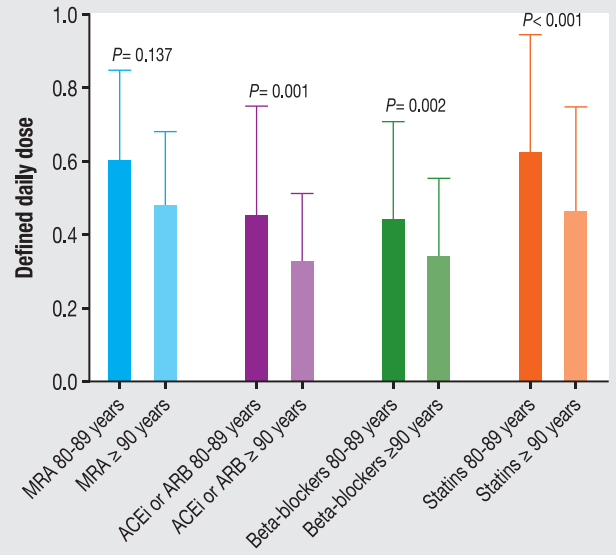
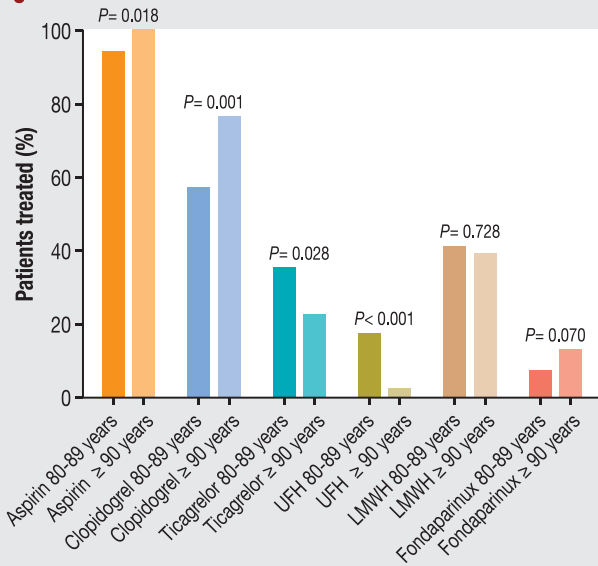
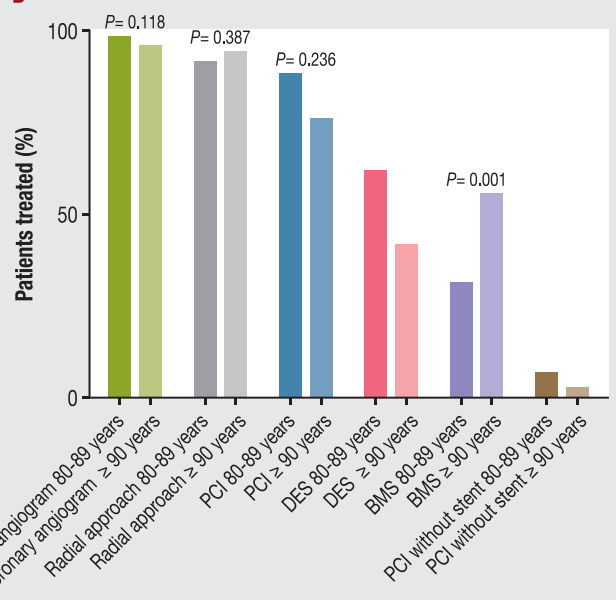
403 patients with type 1 NSTEMI or STEMI

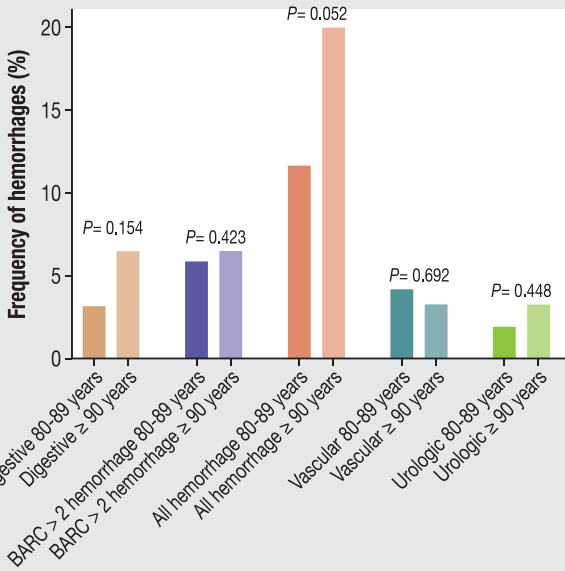


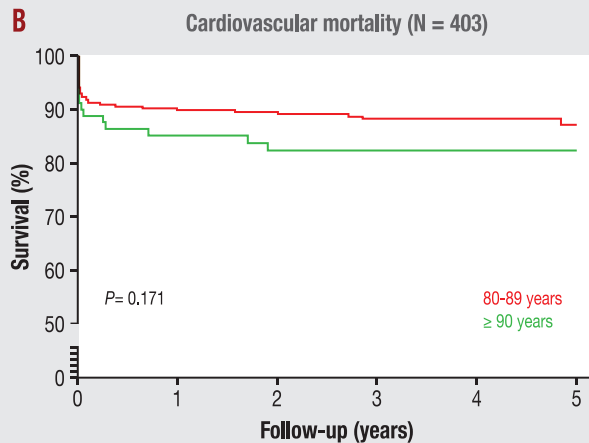
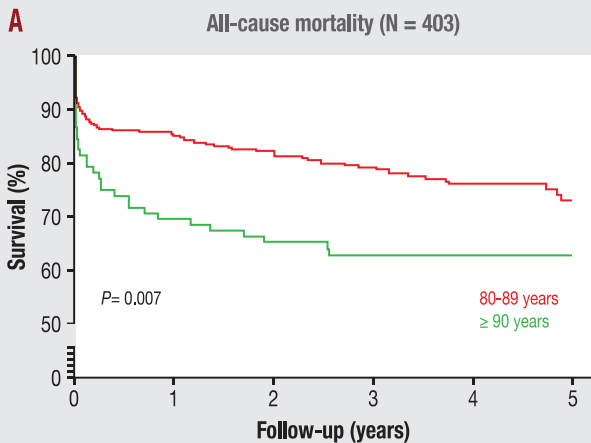
311 patients aged 80-89 years



92 patients aged ≥ 90 years

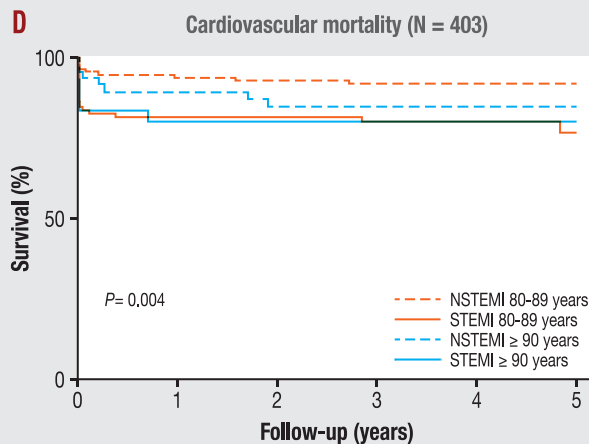
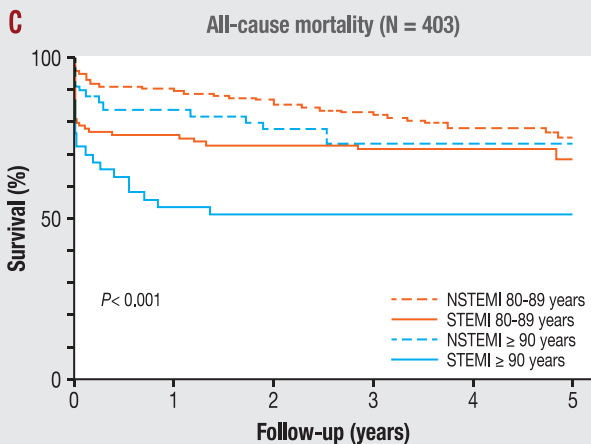
**A****B****C****D**





Number at risk

80-89 years	311	265	255	201	124	59
≥ 90 years	92	64	59	48	30	18



Number at risk

NSTEMI 80-89 years	212	190	184	143	80	42
STEMI 80-89 years	98	75	71	59	44	16
NSTEMI > 89 years	48	40	37	30	19	12
STEMI > 89 years	42	23	21	16	9	4