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CLINICAL RESEARCH

The major element of 1-year prognosis in acute coronary syndromes is severity of initial clinical presentation: Results from the French MONICA registries

La majorité du pronostic à un an des syndromes coronariens aigus est associée à la sévérité de la présentation clinique initiale. Résultats des registres français MONICA

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Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

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KEYWORDS
Coronary artery disease;
Acute coronary syndrome;
Sudden death;
Mortality;
Prognosis

Summary

Background. — While the death rate from acute coronary syndromes (ACS) has been in decline for more than 50 years, out-of-hospital mortality remains high despite improvements in care.

Aim. — To evaluate the importance of out-of-hospital mortality and identify the main predictors of in-hospital and 1-year mortality in France.

Methods. — Analyses were based on data from the French MONICA population-based registry, which included all cases of ACS occurring in people aged 35—74 years during 2006 in three geographic areas in France. We first evaluated out-of-hospital mortality; then, using data from patients with incident ACS who reached hospital alive, Cox models were performed to determine the main predictors of 1-year mortality. The number of attributable deaths was assessed for variables of interest.

Results. — After 1-year follow-up, case-fatality was 29.3% for incident events (n = 2547); the proportion of out-of-hospital deaths was 70.3%, and 91.5% of deaths occurred in the 28 days following the ACS. On multivariable analysis, the number of attributable deaths associated with three scenarios (out-of-hospital life-and-death emergency, hospitalization before ACS occurrence, and lack of coronary angiography) was 130 (accounting for 59% of deaths occurring after reaching the hospital) during 1-year follow-up. These scenarios corresponded to patients with an initial severe clinical presentation in whom rates of use of specific treatments and invasive procedures were very low.

Conclusion. — A large proportion of fatalities after an ACS occurs in the out-of-hospital phase. Moreover, the major component of 1-year mortality is associated with a poor prognosis at initial presentation. This finding highlights the importance of cardiovascular prevention, population education and better out-of-hospital emergency management in improving prognosis after an ACS.

MOTS CLÉS
Maladie coronaire ;
Syndrome coronaire aigu ;
Mort subite ;
Mortalité ;
Pronostic

Résumé

Rationnel. — La mortalité des syndromes coronariens aigus diminue depuis 50 ans. La mortalité extrahospitalière reste élevée malgré les améliorations de soins.

Objectif. — Évaluer l'importance de la mortalité extrahospitalière et les principaux facteurs prédictifs de la mortalité à un an en France.

Méthodes. — Données de l'année 2006 des registres français MONICA incluant exhaustivement tous les syndromes coronariens aigus entre 35 et 74 ans dans trois bassins géographiques. La mortalité extrahospitalière a été évaluée, les facteurs prédictifs de la mortalité à un an des SCA inauguraux hospitalisés ont été analysés par modèles de Cox. Le nombre de décès attribuables a ensuite été calculé pour des variables d'intérêt.

Résultats. — La létalité à un an des 2547 épisodes inauguraux était de 29,3 %. La proportion de décès extrahospitaliers était de 70,3 % ; 91,5 % des décès survenant dans les 28 jours suivant l'hospitalisation. Le nombre de décès attribuables à trois situations identifiées à partir de l'analyse multivariée (menaces vitales pré-hospitalières, sujets déjà hospitalisés et patients sans coronarographie) était de 130 à un an, soit 59 % des décès survenant chez les sujets arrivés vivants à l'hôpital. Ces situations correspondaient à des patients déjà très graves initialement et ne bénéficiant pas des traitements habituels.

Conclusion. — La majorité des décès surviennent à la phase pré-hospitalière. De plus, la majorité des décès à un an est associée à un tableau déjà grave avant la médicalisation. Cela démontre l'importance de la prévention, de l'éducation de la population et d'une amélioration de la prise en charge pré-hospitalière.

Introduction

Management of acute coronary syndromes (ACS) has improved greatly over the past few decades, with important consequences in terms of the epidemiology of coronary heart disease. Mortality is determined by incidence (incident events or recurrences) and by lethality (at the acute phase and over the long term). The mortality rate after an ACS has been in decline for more than 50 years throughout the world, but some geographic differences have been reported [1—4]. In the United States, the rate of death from coronary heart disease decreased by 59% between 1950 and 1999 [5]. This improvement was associated primarily with a decrease in the case-fatality of acute events, and in a more inconsistent way with a decrease in incidence of ACS [6—12]. However, recent data from France suggest that overall mortality has decreased slowly, mainly due to a decrease in incidence of coronary heart disease, whereas short-term case-fatality

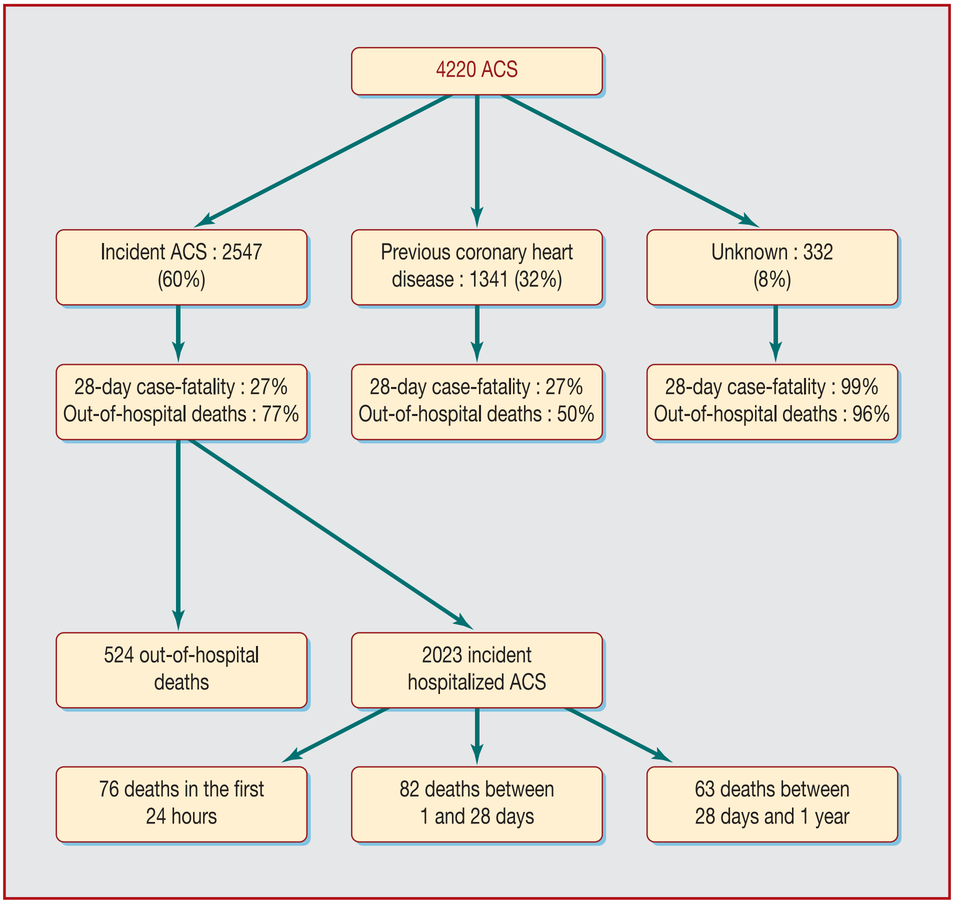

Figure 1. Distribution of deaths in the entire cohort (4220 ACS). ACS: acute coronary syndrome.

appears to have plateaued [13]. This pattern may reflect the impact of deaths occurring outside of hospital [6,14—16], which appear to be almost non-modifiable.

The aim of our study was first to estimate and describe the distribution of in-hospital and out-of hospital deaths following ACS in a population-based registry, and then to identify the main predictors of mortality occurring during the out-of-hospital phase, and post-discharge up to 1 year.

Methods

Population and registry

Our work was based on 2006 data from the French MONICA registries, in which information was collected in all cases of ACS occurring in people aged 35—74 years in three areas in North, North-East and South-West France. These exhaustive, population-based registries collected data from the case files of all patients hospitalized for an ACS (multiple sources were cross-checked), but also from all patients who died out-of-hospital from a suspected ACS, in which case the general practitioner or the physician who notified the death was interviewed [1—4]. Out-of-hospital deaths corresponded to patients dying after an out-of-hospital ACS diagnosis (five of the incident events), those dying after symptoms suggestive of an ACS (67 of the incident events), sudden deaths occurring within 24 hours of the index event (422 of the incident events), and other deaths with insufficient data but without any other suspected cause or medical history (30 of the incident events).

We first analysed the data collected over 1 year from 4220 ACS patients to estimate and describe the distribution of in-hospital and out-of hospital mortality. We then conducted an analysis to identify predictors of 1-year mortality using data from the 2023 patients with an incident event who reached hospital alive (Fig. 1). The rate of complete follow-up (follow-up to ≥ 1 year or death during follow-up) among these 2023 patients was 95.9%.

Determinants and outcomes

The main outcome was mortality at 1 year after the index event. Out-of-hospital deaths were recorded from the patient's medical history, but only age, gender and previous coronary heart disease were recorded for those who died before reaching the hospital.

More data were collected for hospitalized patients, including age, gender and chronic treatments for cardiovascular diseases (anticoagulants, medications for diabetes, antihypertensive drugs, lipid-lowering drugs, antiarrhythmic drugs and antiplatelets).

The type of ACS was determined by troponin concentration and electrocardiographic data, and was categorized as unstable angina or non-ST-elevation myocardial infarction (UA/NSTEMI), ST-elevation myocardial infarction (STEMI) and unclassified (non-interpretable electrocardiogram; corresponding to 4% of cases). Early complications were described as acute heart failure (dyspnoea, acute pulmonary oedema and out-of-hospital diuretic use) and life-threatening complications (resuscitated cardiac arrests, shocks and out-of-hospital use of amines). Life-threatening complications were divided into those occurring out-of-hospital (associated with out-of-hospital explicit treatments for cardiac arrest or shock: xylocaine, amines, sodium bicarbonate or external electrical defibrillation) and those occurring in hospital (all others; defined only for patients reaching the hospital alive). Coronary anatomical status was categorized as one-vessel disease, multivessel disease, left main coronary artery lesion and unknown.

Out-of-hospital management was described in terms of delays between symptom onset and hospitalization (patients already hospitalized before the event were considered as a specific category), management in a mobile intensive care unit and out-of-hospital specific treatment (e.g. aspirin, clopidogrel or anticoagulant).

In-hospital management was described in terms of prescription of recommended treatments (these were combined into a single variable corresponding to the prescription of dual antiplatelet therapy, anticoagulants, beta-blockers, statins and angiotensin-converting enzyme [ACE] inhibitors), and by revascularization strategy (no invasive exploration, coronary angiography without revascularization, percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG]).

Statistical analyses

The overall population was described according to case-fatality, corresponding to the proportion of deaths in the study groups (4220 incident and recurrent cases of ACS; 2547 incident ACS and 2023 incident hospitalized ACS). Cox modelling was then use to identify predictors of 1-year mortality. Before introducing covariates in the model, the assumption of proportional risk was checked for all variables and log-linearity was assessed for quantitative variables. Missing data for both the type of ACS and the delay to hospitalization were analysed as a specific category because they were more frequent, but for all other missing data were switched to a negative response. Sensitivity analyses were performed, replacing missing data with positive responses. Predictors of 1-year mortality were identified by creating a model of causation in which explanatory covariates were introduced successively and considered in the model according to their distance from the outcome variable (1-year mortality). More precisely, variables considered as the most distant from the outcome were first analysed (age, gender and previous medical treatments). Then, intermediate and proximal explanatory variables were added to the model in the following order: hospitalization before ACS occurrence, type of ACS, early complications, out-of-hospital management and in-hospital management and complications. This approach is more appropriate than stepwise regression to study determinants that are not equally distant to the outcome in the causal chain. This process was inspired by that used more frequently in social epidemiology [17]. Variables interpreted as clinically significant markers of severity of initial presentation and with a strong statistical weight were analysed in greater detail.

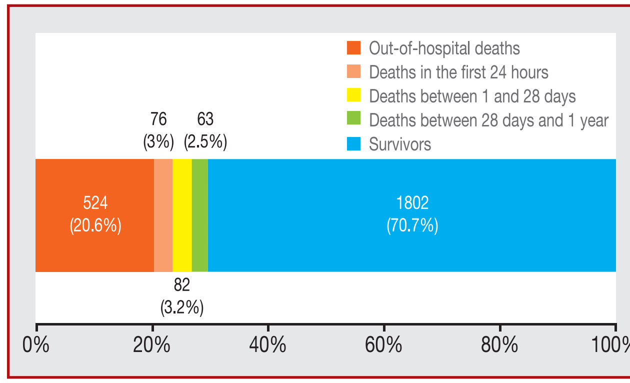

Figure 2. Chronological distribution of deaths (2547 incident ACS). ACS: acute coronary syndrome.

The different subgroups are described using counts and percentages or as medians. The χ^2 test or Fisher's exact test were used to test for differences in qualitative variables and Student's *t* test or the Mann-Whitney test for differences in quantitative variables.

We calculated the number of attributable deaths for each variable of interest with a similar method used for estimating attributable risk [18]. Variables of interest were considered as the 'exposure', and death was considered as the 'disease'. The population-attributable fraction for each exposure was estimated as:

$$[p \times (adjusted\ \ Hazard\ \ ratio - 1)\,/adjusted\ \ Hazard\ \ ratio]$$

where *p* was the proportion of patients with the exposure among death cases and where the adjusted hazard ratio was derived from the Cox-adjusted estimate related to the variable of interest [19]. The number of attributable deaths was then calculated by multiplying the population-attributable fraction by the total number of deaths. Confidence intervals (95% CI) for population-attributable fractions were calculated using the Greenland formula [20]. An overall population-attributable fraction was also estimated, representing the joint impact of the variables of interest. For calculating the overall population-attributable fraction, a single exposed level was considered and was defined as exposure to at least one variable of interest. The reference level was defined as exposure to none of the variables of interest.

Results

Out-of-hospital and in-hospital case-fatality

The different episodes of mortality are presented in Figs. 1 and 2. Among the total population, the overall 28-day case-fatality was 32.7% (1381/4220). Of the 1028 out-of-hospital deaths (accounting for 74.4% of 28-day case-fatality), 51.0% were incident events, 17.9% had a coronary history and 31.1% had missing data for medical history. Most (84.3%) out-of-hospital deaths occurred at home.

Among the 2547 patients with incident ACS, 524 (20.6%) died before reaching the hospital, 158 (6.2%) died in the first 28 days, and 63 (2.5%) died between 28 days and 1 year after the event. Total 1-year mortality was 29.3%, the proportion of out-of-hospital deaths was 70.3%, and 91.5% of deaths occurred in the 28 days following the ACS.

Among the 2023 hospitalized patients with incident ACS, 221 (10.9%) died in the first year: 76 in the first 24 hours, 82 between 24 hours and 28 days, and 63 between 28 days and 1 year (the 28-day case-fatality rate was 7.8% for people reaching the hospital alive).

Among the 1157 hospitalized ACS patients with previous coronary heart disease (184 out-of-hospital deaths were excluded), 96 died in the first 24 hours and 89 between 24 hours and 28 days (28-day case-fatality was 16.0% for people reaching the hospital alive).

Survival analyses in incident ACS patients reaching the hospital alive

The characteristics of the 2023 patients with an incident ACS who reached the hospital alive, along with univariate associations with 1-year mortality, are shown in Table 1. Factors associated with 1-year mortality in this population are shown in Table 2.

Variables of interest: initial severity of ACS

Three variables of interest (out-of-hospital life-and-death emergency, hospitalization before ACS occurrence, and lack of coronary angiography) were interpreted as determinants or proxy variables of the initial severity of the ACS. Among the 2023 patients, 99 (4.9%) presented with an out-of-hospital life-and-death emergency, 56 of who died (case-fatality 56.6%); 120 subjects were already hospitalized (5.9%), of which 56 died (case-fatality 46.7%); and 187 subjects (9.2%) did not have invasive coronary explorations, of which 119 died (case-fatality 63.6%). Among these 187 subjects, 95 were not associated with an out-of-hospital emergency and were not already hospitalized, 43 of who died. The description of these variables is presented in Table 3.

Number of attributable deaths

The number of deaths attributable to each variable of interest was estimated for the 2023 incident ACS who reached the hospital alive (Table 4). While none of the patients could belong simultaneously to the group already hospitalized and to those with an out-of-hospital life-and-death emergency, some patients who had not had a coronary exploration could be included in these two subgroups; consequently, only patients who did not belong to both groups were analysed (95 patients, 43 deaths), which would probably underestimate the number of attributable deaths.

The total number of deaths attributable to the three variables of interest was 130 (95% CI 86—170) after adjustment for potential confounding factors, corresponding to 59% (95% CI 39—77) of 1-year mortality (221 deaths) after exclusion of out-of-hospital deaths. The adjusted number of attributable deaths was 135 (95% CI 113—152) when considering the three groups as one variable, confirming good stability of the estimation (adjusted hazard ratio 7.68; population-attributable fraction 0.61, 95% CI 0.51—0.69).

The same analyses were performed through logistic regression for 28-day mortality. Of the 158 deaths over this period, 115 (95% CI 73—152) of the 127 with an exposure were attributable to the three categories (73% of deaths, 95% CI 46—96).

Sensitivity analyses

The number of attributable deaths was estimated after replacing missing data with the positive response. The results did not differ significantly but the number of attributable deaths increased slightly. Stratified analyses on hospitalization before ACS occurrence or adjustment for hospital discharge treatments (through a similar composite variable as that described for in-hospital treatments) did not modify the results significantly.

Discussion

The exhaustiveness of this population-based registry, including description of the out-of-hospital period and long-term follow-up, allows a complete evaluation of the current epidemiology of ACS. Coronary heart disease remains a serious condition, with an overall 28-day case-fatality rate of 32.7% and with three-quarters of people dying before reaching hospital. Patients who died out-of-hospital were younger than those who died in the 28 days after reaching the hospital (61 and 68 years, respectively, $P < 0.0001$), but were the same age as survivors at 28 days (61 years). A large percentage of out-of-hospital deaths (51%) occurred with incident events. Among individuals with incident ACS, 76.8% of the deaths occurring within 28 days happened out of hospital, and 70.3% of deaths at 1 year were out of hospital. These data are similar to those reported previously in other countries [6,14—16].

While our registry is exhaustive, with standardized methods used for patient inclusion, the study of out-of-hospital deaths is difficult [21,22] because of uncertain diagnoses. Our registry encompasses a relatively young population, with a limited number of very old patients and/or individuals with severe co-morbidities. Indeed, the majority of sudden deaths are of cardiac origin, with most being coronary deaths in young people [23,24]. Authors also separate sudden deaths that are genuinely related to an ACS from 'electrical' coronary deaths promoted by a former myocardial ischaemic scar, which occur frequently without any previous alerting symptom [25—28]. This is one reason why we studied only incident events for most of the analyses. Indeed, even if a death is associated with an 'electrical' sudden death without real ACS, it remains the first clinical manifestation of coronary heart disease. 'Electrical' sudden deaths occurring in people with previous known coronary heart diseases depend more on secondary prevention.

The rate of 1-year mortality with hospitalized incident events was 10.9%, which is lower than that described in other French ACS registries such as FAST-MI 2005 (11.3% for NSTEMI and 15.2% for STEMI) (FAST-MI Investigators. Personal communication). This is easily explained by differences in the populations (less than 75 years of age, inclusion

Table 1 Characteristics of the cohort and univariate associations with 1-year mortality (2023 hospitalized incident acute coronary syndromes).

	Proportion (%)	Hazard ratio[a]	95% CI	*P*
Centre				
Toulouse	31.1	1.00		
Strasbourg	36.8	1.82	1.25—2.66	0.002
Lille	32.1	2.47	1.71—3.58	< 0.0001
Age	58 (17)[b]	1.05[c]	1.03—1.06	< 0.0001
Female gender	23.7	1.19	0.88—1.60	0.25
Previous treatments				
Anticoagulants	4.1	3.50	2.32—5.26	< 0.0001
Antidiabetic medication	15.0	1.66	1.21—2.28	0.002
Antihypertensive drugs	37.6	1.46	1.12—1.90	0.005
Lipid-lowering agents	22.3	0.79	0.56—1.11	0.17
Antiplatelet therapy	13.1	1.69	1.21—2.35	0.002
Antiarrhythmic drugs	2.4	2.28	1.24—4.18	0.008
Type of ACS				
STEMI (without thrombolysis)	42.0	1.00		
STEMI (with thrombolysis)	9.3	0.35	0.16—0.75	0.007
UA/NSTEMI	44.7	0.83	0.61—1.13	0.24
Unclassifiable	4.0	8.55	5.98—12.23	< 0.0001
Out-of-hospital life-and-death emergency	4.9	9.55	7.03—12.98	< 0.0001
Acute heart failure	15.5	3.09	2.34—4.07	< 0.0001
Delay until hospitalization				
≥ 2 hours	65.6	1.00		
< 2 hours	21.6	2.44	1.75—3.39	< 0.0001
Already hospitalized	5.9	9.80	6.96—13.80	< 0.0001
Unknown	6.9	2.73	1.70—4.37	< 0.0001
Transfer with medical mobile unit	42.5	1.15	0.88—1.50	0.30
Out-of-hospital specific treatment	32.6	0.32	0.22—0.47	< 0.0001
In-hospital life-and-death emergency	4.8	8.97	6.58—12.22	< 0.0001
In-hospital recommended treatments	50.1	0.17	0.12—0.25	< 0.0001
Revascularization				
PCI	66.6	1.00		
No exploration	9.2	18.81	13.98—25.31	< 0.0001
Angiography without PCI	20.2	1.20	0.77—1.89	0.42
CABG	4.0	0.92	0.34—2.52	0.88
Coronary status				
One-vessel disease	48.8	1.00		
Multivessel disease	40.1	1.39	0.93—2.08	0.11
Left main coronary artery	1.7	4.29	1.83—10.06	0.001
Unknown/No exploration	9.4	21.19	14.98—29.95	< 0.0001

95% CI: 95% confidence interval; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; UA/NSTEMI: non-ST-elevation myocardial infarction.
[a] Hazard ratio for 1-year mortality, estimated by Cox modelling.
[b] Median in years (interquartile range).
[c] For a 1-year increase.

of unstable angina, exclusion of recurrences). Indeed, our population was relatively young, with ages ranging from 35 to 74 years (median 58), and with a majority of men as is usually described for patients with coronary heart disease. Age was associated with an increased mortality but no significant relationship was observed for gender in this young population. In hospitalized incident events, 15.0% were already on treatments for diabetes, 4.1% on anticoagulant treatments and 37.6% on antihypertensive drugs. Previous chronic use of anticoagulant treatments was associated with a significantly higher mortality (and there was a trend associated with the use of medications for diabetes). On the other hand, previous use of lipid-lowering drugs was associated with a significantly decreased mortality after adjustment for age. Subjects already hospitalized before the event (5.9%) had a poor prognosis (adjusted hazard ratio for 1-year case-fatality 4.66, $P < 0.0001$).

There was no significant impact of the type of ACS on 1-year mortality, but unclassifiable events were associated with an increased mortality, probably corresponding

Table 2 Multivariable analysis assessing predictive factors for 1-year-mortality (2023 hospitalized incident acute coronary syndromes).

	Hazard ratio[a]	95% CI	*P*
Age[b]	1.04	1.03–1.06	< 0.0001
Female gender[b]	0.92	0.68–1.25	0.59
Previous treatments[b]			
Anticoagulants	2.56	1.64–4.02	< 0.0001
Antidiabetic medication	1.36	0.97–1.89	0.073
Antihypertensive drugs	0.98	0.72–1.33	0.89
Lipid-lowering agents	0.57	0.40–0.82	0.002
Antiplatelet therapy	1.25	0.88–1.77	0.22
Antiarrhythmic drugs	1.08	0.56–2.06	0.83
Hospitalization before ACS occurrence[b]	4.66	3.31–6.56	< 0.0001
Type of ACS[c]			
STEMI	1.00		
UA/NSTEMI	0.84	0.62–1.14	0.27
Unclassifiable	5.13	3.44–7.63	< 0.0001
Out-of-hospital life-and-death emergency[d]	13.68	9.77–19.15	< 0.0001
Acute heart failure[e]	1.87	1.40–2.52	< 0.0001
Delay until hospitalization[f]			
≥ 2 h	1.00		
< 2 h	1.53	1.07–2.20	0.020
Unknown	2.01	1.22–3.33	0.006
Transfer with medical mobile unit[f]	1.15	0.79–1.68	0.47
STEMI with/without thrombolytic[g]	0.64	0.28–1.42	0.27
Out-of-hospital specific treatment[g]	0.29	0.18–0.45	< 0.0001
In-hospital life-and-death emergency[g]	5.92	4.07–8.59	< 0.0001
In-hospital recommended treatments[h]	0.28	0.19–0.42	< 0.0001
Revascularization [i]			
PCI	1.00		
No exploration	3.63	2.36–5.59	< 0.0001
Angiography alone	0.90	0.56–1.45	0.66
CABG	0.95	0.34–2.64	0.92

95% CI: 95% confidence interval; ACS: acute coronary syndrome; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; UA/NSTEMI: non-ST-elevation myocardial infarction.

[a] Hazard ratio for 1-year mortality, estimated by Cox modelling.
[b] Adjusted for centre, age, gender and previous treatments.
[c] Adjusted for [b] and hospitalization before ACS occurrence.
[d] Adjusted for [c] and type of ACS.
[e] Adjusted for [d] and out-of-hospital life-and-death emergency.
[f] Adjusted for [e], acute heart failure, delay until hospitalization and transfer with medical mobile unit.
[g] Adjusted for [f] and out-of-hospital specific treatments and thrombolytic therapy.
[h] Adjusted for [g] and in-hospital life-and-death emergency.
[i] Adjusted for [h] and in-hospital recommended treatments.

to early deaths. The majority of subjects (51.3%) had STEMI, although recent data [29] have shown a greater proportion of UA/NSTEMI versus STEMI in ACS. This discrepancy could be explained by the young age of the population and the restriction to incident events. Out-of-hospital life-and-death emergencies were associated with an important increase in mortality (adjusted hazard ratio 13.68, $P < 0.0001$), while acute heart failure seemed to have a less strong impact but was still significant. In-hospital life-and-death emergencies were associated with a significant but less important increase in mortality.

Concerning the out-of-hospital and in-hospital management, delays to hospitalization were mainly greater than 2 hours and less than the half of the cases were managed by a mobile intensive care unit. Surprisingly, a shorter delay between symptom onset and hospitalization was associated with a poorer prognosis and there was no impact of mobile intensive care units on mortality rates. This can probably be explained by confounding biases, with the most critical patients being managed earlier and being more medicalized. Out-of-hospital and in-hospital specific treatments were associated with decreased mortality.

More than 90% of patients had a coronary angiography, 66.6% with PCI and 4.0% with CABG. We did not detect any effect of revascularization (PCI or CABG) on mortality in our analyses, probably because most of the subjects underwent revascularization, leading to a very homogeneous population. However, people who did not benefit from a coronary

Table 3 Description of three selected variables of interest (2023 incident hospitalized ACS population).

	Out-of-hospital life-and-death emergency ($n = 99$)			Hospitalization before ACS occurrence ($n = 120$)			No coronary angiography ($n = 187$)		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
Age (median in years)	57.0	58.0	0.55	66.0	58.0	< 0.0001	66.0	58.0	< 0.0001
Female gender	24.2	23.7	0.90	40.8	22.6	< 0.0001	31.0	23.0	0.014
Previous treatments									
Anticoagulants	4.0	4.1	1.00	18.3	3.2	< 0.0001	14.4	3.1	< 0.0001
Antidiabetic	10.1	15.2	0.16	24.2	14.4	0.004	20.3	14.4	0.032
Antihypertensive drugs	36.4	37.6	0.80	53.3	36.6	< 0.0001	46.0	36.7	0.013
Lipid-lowering agents	19.2	22.5	0.45	15.0	22.8	0.048	19.8	22.5	0.39
Antiplatelet therapy	12.1	13.1	0.77	26.7	12.2	< 0.0001	23.0	12.1	< 0.0001
Antiarrhythmic drugs	5.1	2.3	0.088	5.8	2.2	0.023	4.8	2.2	0.040
Type of ACS									
STEMI	62.6	50.7	< 0.0001	32.5	52.5	< 0.0001	26.2	53.9	<0.0001
UA/NSTEMI	28.3	45.6		44.2	44.8		49.7	44.2	
Unclassifiable	9.1	3.7		23.3	2.7		24.1	1.9	
Resuscitated cardiac arrest	79.8	2.3	< 0.0001	10.8	5.8	0.027	24.6	4.2	< 0.0001
Shock	22.2	3.6	< 0.0001	21.7	3.5	< 0.0001	25.7	2.4	< 0.0001
Premature heart failure	29.3	14.8	< 0.0001	26.7	14.8	< 0.0001	35.8	13.4	< 0.0001
Delay until hospitalization									
≥ 2 h	42.4	66.8	< 0.0001	0.0	69.7	< 0.0001	31.6	69.1	< 0.0001
< 2 h	53.5	20.0		0.0	23.0		26.2	21.1	
Already hospitalized	0.0	6.2		100.0	0.0		30.5	3.4	
Unknown	4.0	7.0		0.0	7.3		11.8	6.4	
Transfer with medical mobile unit	97.0	39.7	< 0.0001	0.0	45.2	< 0.0001	38.5	42.9	0.24
Out-of-hospital specific treatment	41.4	32.2	0.056	0.0	34.7	< 0.0001	8.0	35.1	< 0.0001
In-hospital recommended treatments	26.3	51.3	< 0.0001	24.2	51.7	< 0.0001	9.6	54.2	<0.0001
Revascularization									
PCI	52.5	67.3	< 0.0001	25.0	69.2	< 0.0001	0.0	73.4	< 0.0001
No exploration	35.4	7.9		47.5	6.8		100.0	0.0	
Angiography without PCI	9.1	20.7		26.7	19.8		0.0	22.2	
CABG	3.0	4.1		0.8	4.2		0.0	4.4	

Data given as number (%) unless otherwise stated.
CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; UA/NSTEMI: non-ST-elevation myocardial infarction.

angiography had a significant increased mortality (adjusted hazard ratio 3.63, $P < 0.0001$); this appears largely due to the fact that people who were not explored were those with a more severe clinical presentation. Left main coronary artery lesion was also associated with a poor prognosis.

Predictors of outcome

After multivariable analysis, three situations were identified that were strongly associated with poor outcome: hospitalization before ACS occurrence (120 patients, 56 deaths); presence of an out-of-hospital life-and-death emergency (99 patients, 56 deaths); and lack coronary exploration following the ACS (187 patients, 119 deaths). These three situations represented less than one-sixth of the 2023 incident hospitalized ACS events, but 60% of 1-year deaths (130 deaths attributable to these three situations). When analysing 28-day mortality, 115 deaths (72.8%) were attributable to these three situations.

There were no differences in age, gender or medical history associated with out-of-hospital life-and-death emergency, but a significantly higher rate of STEMI was observed among emergent patients. These situations mainly included

Table 4 Estimation of the number of deaths attributable to selected variables of interest, during the 1-year follow-up (2023 hospitalized incident acute coronary syndromes).

	Hazard ratio [95% CI]	Number of exposed deaths	Population-attributable fraction	Number of attributable deaths
Hospitalization before the ACS occurrence (n = 120)[a]				
Unadjusted	6.79 [5.01–9.21]	56	0.22 [0.15–0.27]	48 [34–61]
Adjusted[b]	4.66 [3.31–6.56]	56	0.20 [0.13–0.26]	44 [29–58]
Out-of-hospital life-and-death emergency (n = 99)[a]				
Unadjusted	9.55 [7.03–12.98]	56	0.23 [0.17–0.28]	50 [36–63]
Adjusted[c]	13.68 [9.77–19.15]	56	0.24 [0.17–0.29]	52 [38–65]
No coronary angiography (n = 95)[a]				
Unadjusted	5.96 [4.27–8.33]	43	0.16 [0.11–0.21]	36 [23–47]
Adjusted[d]	4.87 [3.13–7.58]	43	0.16 [0.09–0.22]	34 [20–48]
Total (n = 314)[a]				
Unadjusted		155	0.61 [0.42–0.77]	134 [94–171]
Adjusted		155	0.59 [0.39–0.77]	130 [86–170]

95% CI: 95% confidence interval; ACS: acute coronary syndrome.
[a] Number of subjects in each category.
[b] Adjusted for centre, age, gender and previous medical treatments.
[c] Adjusted for centre, age, gender and previous medical treatments, type of ACS and hospitalization before ACS occurrence.
[d] Adjusted for centre, age, gender and previous medical treatments, type of ACS, out-of-hospital and in-hospital life-and-death emergency, acute heart failure, delay until hospitalization and hospitalization before ACS occurrence, transfer with a medical mobile unit, out-of-hospital use of specific treatments and thrombolytic drugs, in-hospital recommended treatments.

resuscitated cardiac arrests (79.8%) and several shocks. Out-of-hospital management was faster and more medicalized in the case of life-and-death emergency, but patients were less likely to receive specific treatments or undergo coronary exploration or revascularization.

Subjects already hospitalized before the ACS event were older, more frequently women and presented more often with co-morbidities. The type of ACS was more frequently unclassifiable and patients seldom received specific treatments and revascularization (25.8%), thus indicating complicated clinical situations in patients with multiple diseases. Patients with very low rates of exploration and revascularization are likely to have a poor initial prognosis. Indeed, these patients were also those presenting more frequently with acute heart failure, resuscitated cardiac arrest and overall shocks, and had a high rate of early death (51.8% in the first 24 hours and 78.6% in the first 28 days).

Patients who did not have coronary angiography were also older, more frequently women, more prone to be receiving chronic treatments and to have unclassifiable ACS compared to those who did have angiography. Rates of complications were also higher among these patients; although they were managed faster and were more medicalized, they had very low rates of out-of-hospital and in-hospital treatments (9.6%). Shorter delays to hospitalization and high rates of out-of-hospital medicalization are in accordance with a severe initial presentation. These patients appeared to have a very poor initial prognosis, with treatments and revascularization of no benefit as most of them died during the acute phase of the event (52.9% in the first 24 hours and 84.9% in the first 28 days). The lack of coronary angiography was not interpreted as a variable of management, but as a proxy variable of initial severity of presentation. This perception was strengthened by the fact that there was no difference in outcome among patients who had a coronary angiography alone and those who had angiography with PCI.

Finally, these three selected variables were interpreted as proxy variables corresponding to the same negative prognosis. Indeed, they probably corresponded to a poor prognosis even before the subjects received treatments for ACS, and despite rapid management, and were not modified by classic acute care.

Limitations

This study is based on observational data and is therefore subject to potential confounding. For example, the

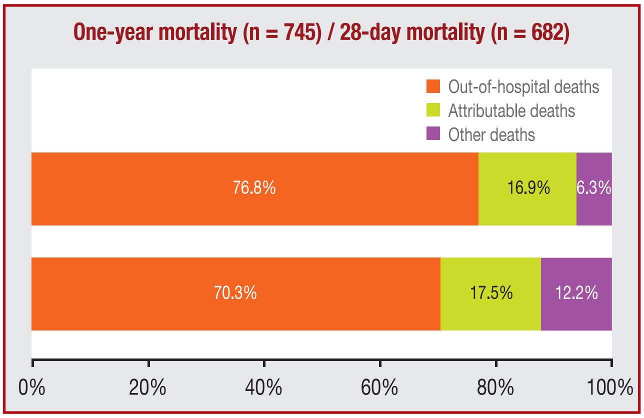

Figure 3. Distribution of 28-day and 1-year mortality among the 2547 incident ACS. ACS: acute coronary syndrome.

effect of bias is clear in relation to delays to hospitalization, as we observed increased mortality with shorter delays. Similarly, variables related to the management of the acute event should be interpreted with caution despite extensive adjustment for the severity of the event. Our analyses also suffer from a lack of information on renal function and co-morbidities given that recommended treatments may have been avoided because of contraindications linked to the patient's medical history. Several factors were not collected, such as renal insufficiency, peripheral artery disease or cancer, which are important predictors of mortality. There were also insufficient data on delays to reperfusion, which is a significant predictor of death in STEMI. However, we evaluated the initial management through delays to hospitalization. Concerning missing data, they were generally limited (1—3%) and were analysed as a specific category when they were more frequent. Sensitivity analyses for missing data did not show any significant differences in the results.

Conclusions

Despite a 1-year follow-up, the majority of deaths recorded occurred during the out-of-hospital period (70.3%), or in the days following hospitalization (34.4% in the first 24 hours, 71.5% in the first 28 days in patients who reached the hospital alive). Moreover, almost 60% of out-of-hospital phase survivors who died during 1-year follow-up were attributable to three situations, corresponding to patients with a very high mortality (72.8% of attributable deaths after analysis of 28-day mortality). These situations were characterized by an initial severe clinical presentation and very low rates of use of specific treatments and invasive procedures. It seems that the prognosis for these patients was already compromised at the initial phase because of irreversible damage, making any intervention inefficient. These situations are very close to out-of-hospital deaths on these points and the combination of both (out-of-hospital and attributable) corresponded to 87.8% of deaths after 1 year of follow-up and to 93.7% of deaths after 28 days (Fig. 3).

Reducing further the case-fatality of ACS appears to be very difficult despite the availability of new treatments; current therapies are already very efficient, and further improvements appear to benefit only those who have a low probability of dying. After the exclusion of out-of-hospital deaths and deaths attributable to the three situations described above, 1-year case-fatality would have decreased from 29.3% to 4.8%, which is close to the rate described in current randomized trials.

Our results highlight the importance of prevention in decreasing the incidence—and consequently mortality—of ACS, given that case-fatality seems difficult to reduce. Educating the general public about cardiac arrest and the importance of early management and prevention (e.g. prompt medical contact in case of suspected chest pain, telephoning the emergency services in the case of suspected cardiac arrest, and primary management of cardiac arrest), and making available semiautomatic defibrillators in public places, are measures that have been promoted in France and elsewhere in order to decrease case-fatality related to ACS, but these measures still have limitations. Indeed, more than 84% of out-of-hospital deaths occur at home. Furthermore, out-of-hospital deaths often occur in relatively young people who have no prior alerting symptoms, making potential victims difficult to identify.

Disclosure of interest

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

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