Modes and timing of death in 66 252 patients with non-ST-segment elevation acute coronary syndromes enrolled in 14 TIMI trials

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Aims

Although presenting features and early sequelae of non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) are well described, less is known about longer-term risks and modes of death. The purpose of this study was to characterize modes of death following NSTEMI-ACS in clinical trial populations.

Methods and results

We evaluated 66 252 patients with NSTEMI-ACS enrolled in 14 Thrombolysis in Myocardial Infarction (TIMI) trials, examining baseline characteristics and modes and timing of death. Of the 66 252 patients followed for a median of 372 (interquartile range 218–521) days, 3147 (4.8%) died by the time of last follow-up. Of the 2606 patients (82.8%) with known modes of death, 75.1% were related to a cardiovascular (CV) event, 3.0% were related to a bleeding event (including intracranial haemorrhage), and 21.8% were related to a non-CV/non-bleeding event. The most common modes of CV death were sudden death (SD) and recurrent myocardial infarction (MI) (36.4% and 23.4%, respectively, of CV deaths). The proportion of CV deaths related to recurrent MI was higher in the first 30 days than it was after 30 days following NSTEMI-ACS (30.6% vs. 18.7%), whereas the proportion of SD was lower in the first 30 days than after 30 days (21.6% vs. 46.2%).

Conclusion

Sudden death represents the largest proportion of CV deaths after 30 days among patients enrolled in CV clinical trials with NSTEMI-ACS. Further investigations aimed at defining the epidemiology of SD and developing specific therapies and management approaches to reduce SD following NSTEMI-ACS may be critical to reducing late mortality.

Keywords

Non-ST-segment elevation acute coronary syndromes • Cardiovascular death • Sudden death • Cardiovascular clinical trials

Introduction

Non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) now represent a greater proportion of acute coronary syndrome (ACS) events than ST-segment elevation myocardial infarctions

(STEMI).¹ This trend may be related to changes in preventive therapies (e.g. greater use of aspirin and statins), behaviours (e.g. lower rates of smoking),¹ and shifting underlying pathophysiology of ACS.²

Although early sequelae of NSTEMI-ACS have been well described, less is known about the longer-term risks. For example, the extent to

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which direct complications of myocardial necrosis (e.g. heart failure, arrhythmia, and thromboembolism) contribute to mortality at various time periods after a NSTEMI-ACS event is not clear. Moreover, some investigators have speculated that bleeding may contribute significantly to mortality in these patients.³ The objective of this analysis was to better characterize the modes and timing of death among patients enrolled in Thrombolysis in Myocardial Infarction (TIMI) trials with a diagnosis of NSTEMI-ACS.

Methods

Study design and population

The study population was derived from the TIMI Study Group clinical trials. The merged database developed for this analysis included subject level data from TIMI trials enrolling patients with a diagnosis of NSTEMI-ACS with trial initiation and completion between 1989 and 2014. No distinction was made between non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), since the advent of more sensitive troponin assays has increasingly led to reclassification of UA as NSTEMI over time.⁴ Data from nine trials each contributing <10 deaths and two trials with ≥10 deaths but with median follow-up duration <100 days ($n = 58$ deaths in total) were excluded. In total, 14 trials with ≥10 deaths and median follow-up duration ≥100 days were included (see [Supplementary material online, Appendix S1](#)).

Death classification

For all patients who died, the general class of death was characterized as cardiovascular (CV), bleeding, or non-CV/non-bleeding. Cardiovascular deaths were further subdivided into specific modes of death, including sudden death (SD), recurrent myocardial infarction (MI), heart failure (including cardiogenic shock), and other CV death (miscellaneous category including ischaemic stroke, pulmonary embolism, acute aortic syndromes, and cardiac rupture). Definitions were adapted from the American College of Cardiology/American Heart Association report on key data elements and definitions for CV endpoint events in clinical trials (see [Supplementary material online, Appendix S2](#)).⁵ Of note, SD, which is often referred to as sudden cardiac death in other analyses, was defined as death occurring unexpectedly and not following MI. Since this category was not limited to death due to an identified arrhythmia, and included unwitnessed death in a subject seen alive and clinically stable ≤24 h before being found dead without any evidence supporting a specific non-CV mode of death, we elected to use the more general term 'sudden death' in this analysis.

In 12 of the 14 trials, involving 2427 of the total 3147 deaths, an independent Clinical Events Committee (CEC) classified mode of death using predefined definitions.⁵ All adjudicated deaths were reviewed by two of the authors (D.D.B. and R.P.G.) and, as needed, reclassified according to the uniform prespecified definitions applied in this analysis based on the event terms reported on the CEC adjudication forms. For the two trials without a CEC (720 deaths, 23% of the total), death was classified based on review of the case record forms by the same authors (D.D.B. and R.P.G.) using the same uniform definitions.

Data analysis

The cumulative mortality rates of all NSTEMI-ACS patients in the merged database were calculated by the complement of Kaplan–Meier survival estimates. For initial analyses, the time origin was anchored at the date of randomization for each patient. For estimating risks of each general class and specific CV mode of death, a cumulative incidence function approach

was used due to the presence of competing risks.⁶ To describe survival experiences beyond 30 days from the onset of the *qualifying event* (index NSTEMI-ACS) rather than study enrolment (randomization date), an additional delayed entry analysis was performed, and accounted for competing risks of different modes of death.^{7–10} Mortality rates at 1 year based on Kaplan–Meier estimates were calculated for various baseline patient characteristics.

Both the general class and specific mode of death were stratified according to timing of death relative to the date of randomization, with prespecified time intervals of 0–30 days and >30 days. Differences in mode of death between these time intervals were evaluated using the χ^2 test.

We performed two subgroup analyses: (i) in patients with vs. without a history of heart failure at the time of trial enrolment and (ii) in patients enrolled in a trial with a start date prior to vs. after 31 December 2000. The relative risk of prior heart failure on overall mortality was calculated using a multivariable Cox model adjusted for differences in baseline characteristics. Two sensitivity analyses were also performed: one restricted to patients enrolled with NSTEMI (i.e. excluding patients with UA), and another restricted to deaths occurring *after* the index hospitalization to control for potential bias related to in-hospital monitoring, which could have affected mode of death classification in the 0–30-day period. Deaths from two trials (TIMI 51 and TIMI 52, see [Table 1](#)) were excluded from the second sensitivity analysis because index hospitalization discharge dates were not available. Results are reported in terms of adjusted hazard ratios and 95% confidence intervals (CIs).

Statistical significance was assessed at a nominal alpha level of 0.05. All reported *P*-values were two-sided. All statistical computations were done with SAS System V9.3 (SAS Institute Inc., Cary, NC, USA) and R software v3.01 (www.r-project.org).

Results

The primary cohort included 66 252 patients enrolled in 14 TIMI trials with a diagnosis of NSTEMI-ACS ([Table 1](#)). The median age of the overall population was 63 years and 30% were women ([Table 2](#)). Thirty percent of patients had a prior MI and 11% had a history of heart failure at the time of trial enrolment. Although exclusion criteria varied across trials, most trials excluded patients with cardiogenic shock, known bleeding diathesis or recent significant bleeding, severe renal dysfunction, or a severe comorbid condition with less than 1-year life expectancy.

The median time from onset of the index event to study enrolment was 1 day [interquartile range (IQR) 1–4 days]. The median follow-up time was 372 days (IQR 218–521 days). There were 3147 (4.8%) deaths through the last known follow-up. Death rates based on Kaplan–Meier estimates were 1.5% at 30 days (95% CI 1.4–1.6%), 3.0% at 6 months (95% CI 2.9–3.2%), 4.3% at 1 year (95% CI 4.2–4.5%), and 6.5% at 2 years (95% CI 6.3–6.8%) ([Figure 1](#)). Older patients and patients with a greater burden of atherosclerotic CV disease (including history of prior MI, history of angina, history of prior stroke, and known peripheral arterial disease) had an increased risk of death at 1 year following NSTEMI-ACS (each $P < 0.001$) ([Table 2](#)).

There was sufficient information available to classify mode of death in 2606 (82.8%) patients. Of these, 1958 (75.1%) died from a CV event, 79 (3.0%) had a fatal bleeding event, and 569 (21.8%) died from a non-CV event other than bleeding ([Table 3](#)). The crude cumulative incidence of CV death, fatal bleeding, and death from a non-CV/non-bleeding event was 2.69%, 0.11%, and 0.66%, respectively, at 1 year following trial enrolment for NSTEMI-ACS ([Take home figure](#)). In

Table 1 TIMI trials included in analysis

TIMI trial	Trial descriptions	Publication year	Number of NSTE-ACS patients	Median time from index event to randomization, days (25–75% IQR)	Median follow-up, days (25–75% IQR)	Number of deaths
TIMI 3B	Thrombolysis vs. placebo/invasive vs. conservative strategy in UA/NSTEMI	1994	1473	1 (0–1)	386 (371–743)	74
TIMI 11A	Enoxaparin dose ranging study in UA/NSTEMI	1997	630	1 (0–2)	376 (368–390)	36
TIMI 11B	Enoxaparin vs. heparin in UA/NSTEMI	1999	3759	0 (0–1)	368 (366–384)	292
OPUS-TIMI 16	Oral GP IIb/IIIa inhibitor vs. placebo in ACS	2000	6944	2 (1–2)	174 (113–253)	255
TACTICS-TIMI 18	Invasive vs. conservative therapy with tirofiban in UA/NSTEMI	2001	2220	0 (0–1)	190 (185–206)	79
A2Z-TIMI 21	Tirofiban + (enoxaparin vs. heparin)/simvastatin early vs. late in ACS	2004	2701	4 (3–5)	727 (606–743)	148
PROVE IT-TIMI 22	Pravastatin vs. atorvastatin/gatifloxacin vs. placebo post-ACS	2004	2722	6 (3–8)	773 (686–857)	85
MERLIN-TIMI 36	Ranolazine vs. placebo in UA/NSTEMI	2007	6560	1 (0–1)	348 (236–460)	348
TRITON-TIMI 38	Prasugrel vs. clopidogrel in PCI in ACS	2007	10 074	1 (1–2)	439 (274–458)	251
EARLY ACS-TIMI 39	Early eptifibatide vs. delayed provisional eptifibatide at PCI in UA/NSTEMI	2009	9406	0 (0–1)	372 (367–387)	646
SEPIA-ACS1-TIMI 42	Dose-ranging study of otamixaban in UA/NSTEMI	2009	3241	1 (0–1)	184 (181–190)	110
ATLAS ACS-TIMI 46	Dose-ranging study of rivaroxaban vs. placebo post-ACS	2009	1670	4 (3–5)	211 (209–214)	24
ATLAS ACS2-TIMI 51	Rivaroxaban (oral Xa inhibitor) vs. placebo post-ACS	2012	7709	5 (3–6)	487 (297–658)	297
SOLID-TIMI 52	Darapladib (selective Lp-PLA2 inhibitor) vs. placebo post-ACS	2014	7143	15 (7–23)	908 (804–1011)	502
All 14 trials		1994–2014	66 252	1 (1–4)	372 (218–521)	3147

ACS, acute coronary syndrome; GP IIb/IIIa, glycoprotein IIb/IIIa; IQR, interquartile range; IV, intravenous; Lp-PLA2, lipoprotein-associated phospholipase A2; NSTEMI, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; UFH, unfractionated heparin.

a landmark analysis starting at 30 days after the *qualifying* NSTEMI-ACS event, there were 1703 deaths with known mode of death, and the cumulative incidence of CV death, fatal bleeding, and death from a non-CV/non-bleeding event at 1 year was 1.52%, 0.06%, 0.50%, respectively (Figure 2A). The most common modes of the 1958 CV deaths in the primary analysis were SD and recurrent MI, which represented 36.4% ($n=713$) and 23.4% ($n=458$) of these deaths, respectively. Heart failure accounted for 19.1% ($n=374$) of CV deaths, and 21.1% ($n=413$) of CV deaths were classified as 'other', which included ischaemic stroke, pulmonary embolism, and acute aortic syndromes, among other modes (Table 3). The cumulative rates of SD, recurrent MI, heart failure, and other CV death were 0.90%, 0.67%, 0.54%, and 0.55%, respectively, at 1 year following trial enrolment for NSTEMI-ACS (Take home figure). From a landmark of 30 days

following the *qualifying* NSTEMI-ACS event, the cumulative incidence of SD, recurrent MI, heart failure, and other CV death at 1 year was 0.67%, 0.32%, 0.26%, and 0.28%, respectively (Figure 2B).

Of the 79 fatal bleeding events, 34 (43.0%) were due to intracranial haemorrhage. Malignancy accounted for 188 (33.0%) of the 569 total non-CV/non-bleeding deaths.

Relationships of modes and timing of death

Cardiovascular deaths represented the majority of deaths during both the first 30 days following randomization and after 30 days but were relatively more common during the 0–30-day period (84.5% vs. 70.0%; $P<0.001$) (Table 3). Among CV deaths, the proportion of deaths related to recurrent MI was greater in the first 30 days than

Table 2 Baseline characteristics

Variables	All patients ^a	Kaplan–Meier mortality rate (%) at 1 year	Unadjusted hazard ratio (95% CI)
Demographics			
Age (years), median (IQR)	63 (55–71) (66 203)		1.07 (1.07–1.08) (per 10 years)
Female sex	30.1 (19 955/66 252)	5.1	1.24 (1.15–1.33)
Male sex	69.9 (46 297/66 252)	4.0	
Caucasian	79.7 (52 657/66 075)	4.4	1.05 (0.97–1.15)
Non-Caucasian	20.3 (13 418/66 075)	3.9	
Admission diagnosis			
Non-ST-segment elevation MI	61.4 (40 667/66 252)	4.7	1.26 (1.17–1.36)
Unstable angina	38.6 (25 585/66 252)	3.7	
Timing of trial enrolment			
Time from index NSTEMI-ACS event to randomization (days), median (IQR)	1.0 (1.0–4.0) (66 181)		0.98 (0.97–0.98) (per 1 day)
Enrolled prior to hospital discharge	95.8 (48 757/50 904)	4.3	1.82 (1.44–2.31)
Enrolled after hospital discharge	4.2 (2147/50 904)	2.0	
Prior history			
Hypertension	66.4 (43 865/66 049)	4.8	1.49 (1.38–1.62)
No hypertension	33.6 (22 184/66 049)	3.3	
Diabetes mellitus	28.2 (18 432/65 425)	6.2	1.67 (1.56–1.80)
No diabetes mellitus	71.8 (46 993/65 425)	3.6	
Hypercholesterolaemia	57.1 (35 711/62 590)	3.9	0.82 (0.76–0.88)
No hypercholesterolaemia	42.9 (26 979/62 590)	4.9	
Active smoking	31.3 (20 692/66 066)	3.2	0.70 (0.65–0.76)
No active smoking	68.7 (45 374/66 066)	4.8	
Myocardial infarction	30.4 (20 042/66 021)	6.0	1.71 (1.59–1.83)
No myocardial infarction	69.9 (45 979/66 021)	3.6	
Stroke	4.2 (2684/64 111)	9.2	2.17 (1.91–2.46)
No stroke	95.8 (61 427/64 111)	4.1	
Peripheral arterial disease	7.8 (4570/58 277)	9.7	2.40 (2.17–2.65)
No peripheral arterial disease	92.2 (53 707/58 277)	4.0	
Angina	52.5 (34 673/66 011)	5.4	1.75 (1.63–1.89)
No angina	47.5 (31 338/66 011)	3.1	
Heart failure	10.5 (6812/64 638)	10.9	3.16 (2.92–3.42)
No heart failure	89.5 (57 826/64 638)	3.5	
Renal insufficiency or CrCl <60	11.0 (7301/66 240)	9.5	2.71 (2.50–2.94)
No renal insufficiency or CrCl <60	89.0 (58 939/66 240)	3.7	
Prior medications			
Beta-blocker	56.3 (37 277/66 180)	4.3	1.01 (0.94–1.09)
No beta-blocker	43.7 (28 903/66 180)	4.4	
Calcium channel blocker	27.6 (11 563/41 976)	5.2	1.43 (1.30–1.58)
No calcium channel blocker	72.4 (30 413/41 976)	3.8	
ACE-I or ARB	49.0 (32 401/66 103)	4.5	1.14 (1.06–1.23)
No ACE-I or ARB	51.0 (33 702/66 103)	4.1	
Nitrates	48.3 (23 961/49 577)	5.3	1.28 (1.18–1.39)
No nitrates	51.7 (25 616/49 577)	4.2	
Aspirin	71.7 (47 450/66 217)	4.4	1.10 (1.02–1.20)
No aspirin	28.3 (18 767/66 217)	4.0	
Lipid-lowering agent	44.2 (28 072/63 525)	3.3	0.67 (0.62–0.72)
No lipid-lowering agent	55.8 (35 453/63 525)	5.2	
Examination, median (IQR)			
Weight (kg)	80 (70–91) (64 416)		0.98 (0.98–0.99) (per 10 kg)
BMI (kg/m ²)	27.7 (25.0–31.0) (63 193)		0.97 (0.96–0.97) (per kg/m ²)

Continued

Table 2 Continued

Variables	All patients ^a	Kaplan–Meier mortality rate (%) at 1 year	Unadjusted hazard ratio (95% CI)
HR (b.p.m.)	70 (62–80) (53 999)		1.02 (1.02–1.02) (per 10 b.p.m.)
SBP (mm of mercury)	130 (120–147) (55 533)		1.00 (1.00–1.00) (per 10 mmHg)
DBP (mm of mercury)	77 (70–85) (55 525)		0.99 (0.99–0.99) (per 10 mmHg)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CrCl, creatinine clearance; DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; SBP, systolic blood pressure.

^aCategorical variables are shown as percent of patients; continuous variables as median (IQR). The absolute numbers are included in parentheses for categorical (*n/N*) and continuous variables (*N*). Kaplan–Meier mortality estimates and unadjusted hazard ratios are provided for each variable.

Figure 1 Cumulative mortality of non-ST-segment elevation acute coronary syndrome patients in the merged clinical trial database. Cumulative mortality rates were calculated using the complement of Kaplan–Meier survival estimates. The numbers below the x-axis indicate the number of patients alive and still being followed at the corresponding time. The 95% confidence interval is indicated with dashed lines.

later (30.6% vs. 18.7%; $P < 0.001$), whereas the proportion of deaths related to SD was lower in the first 30 days (21.6% vs. 46.2%; $P < 0.001$). The proportion of heart failure deaths was greater before than after 30 days (24.3% to 15.7%; $P < 0.001$) (Table 3). The cumulative incidence of SD increased steadily and more rapidly than other modes of CV death after 30 days, and by day 119 exceeded the rate of death due to recurrent MI (Take home figure).

The proportion of deaths directly related to bleeding was similarly low in the 0–30 and >30-day periods (3.4% and 2.9%, $P = 0.48$, respectively, of all deaths with known mode) (Table 3). Non-CV/non-bleeding deaths accounted for a smaller proportion of overall deaths before 30 days (12.2% in the 0–30-day period vs. 27.1% in the >30-day period, $P < 0.001$). Not surprisingly, within the group of non-CV/non-bleeding deaths, malignancy was responsible for a substantially larger proportion of these deaths beyond 30 days (40.7%) when compared with those occurring during the first 30 days (1.8%, $P < 0.001$).

Subgroup analyses

Patients with prior heart failure had significantly higher overall mortality rates than patients without a history of heart failure (2-year

Kaplan–Meier mortality rates 15.8% vs. 5.2%, respectively, with adjusted hazard ratio 2.2, 95% CI 2.0–2.4). The proportion of deaths related to a CV mode was higher (80.8% vs. 72.4%, excluding unknown deaths) and the proportion of deaths related to a non-CV/non-bleeding mode was lower (17.3% vs. 24.0%) in this group compared with those without prior heart failure ($P < 0.001$ for both) (see Supplementary material online, Appendix S3). The proportion of SD as a mode of CV death was similar between patients with and without prior heart failure in both the 0–30-day period (20.0% vs. 22.8%; $P = 0.44$) and after day 30 (48.1% vs. 46.2%; $P = 0.53$).

In an analysis of deaths occurring in patients enrolled in trials with start dates prior to ($n = 856$) vs. after 31 December 2000 ($n = 1750$), the mortality rates at 1 month (1.9% vs. 1.3%), 6 months (3.5 vs. 2.8%), and 12 months (4.8% vs. 4.1%) were higher among the pre-2001 trials (log-rank test $P = 0.028$). There were no significant differences in the distribution of the general classes of death (CV, bleeding, non-CV/non-bleeding) ($P = 0.87$) between these two periods (see Supplementary material online, Appendix S4a). Among CV deaths, however, the proportion of SD (24.9% vs. 42.1%) was significantly lower and the proportions of deaths due to recurrent MI (30.3% vs. 20.0%) and heart failure (24.3% vs. 16.6%) were significantly higher among patients enrolled in trials with start dates before 31 December 2000 ($P < 0.001$ for each, Supplementary material online, Appendix S4a). These results were qualitatively similar even after exclusion of five trials that enrolled patients who had been stabilized post-ACS (see Supplementary material online, Appendix S4b).

Sensitivity analyses

We performed two sensitivity analyses: one restricted to the 1737 deaths with known mode occurring in the 40 667 patients enrolled with NSTEMI (i.e. excluding patients with UA), and another restricted to the 1388 deaths with known mode occurring in the 50 965 patients who survived the index hospitalization (see Supplementary material online, Appendix S5) to control for potential bias related to in-hospital monitoring. In both analyses, the differences in the proportions of each general class and specific CV mode of death between the 0–30 and >30-day periods seen in the overall cohort and described above remained significant ($P < 0.001$). Specifically, the proportion of CV deaths related to recurrent MI was higher and the proportion of deaths related to SD lower during the 0–30-day period compared with the >30-day period, consistent with the findings of the overall cohort.

Figure 2 Landmark analysis of the cumulative incidence of modes of death starting at 30 days following the index non-ST-segment elevation acute coronary syndrome event. The cumulative incidence of each (A) general class of death and (B) specific cardiovascular mode of death starting at 30 days following non-ST-segment elevation acute coronary syndrome is shown through 12 months. Point estimates are provided at 12 months.

Discussion

In this analysis of 66 252 patients with NSTEMI-ACS enrolled in TIMI trials, we found that three-fourths of deaths were related to CV modes, although the relative proportion of CV deaths decreased with time following the event. Recurrent MI represented the largest proportion of CV deaths in the first 30 days following trial enrolment for NSTEMI-ACS, whereas SD was a proportionately greater mode of CV death after 30 days.

Outcomes following non-ST-segment elevation acute coronary syndromes

Defining the modes of death following NSTEMI-ACS is essential to identifying the optimal therapies and improving survival. Much of what we understand about outcomes following MI is based on studies in patients with STEMI.^{11,12} In contrast, relatively less is known about patients with NSTEMI-ACS, even though they are now more frequent. Only in the last decade has it been widely appreciated that patient characteristics and outcomes are different between these groups. Patients with NSTEMI-ACS (when compared with patients with STEMI)

Table 3 Modes of death following NSTEMI-ACS

	All patients (N = 66 252)
All deaths (all follow-up)	N = 3147
Cardiovascular	75.1 (1958/2606)
Bleeding	3.0 (79/2606)
Non-CV/non-bleeding	21.8 (569/2606)
Unknown	— (541)
CV deaths (all follow-up)	N = 1958
Sudden death	36.4 (713/1958)
Recurrent MI	23.4 (458/1958)
Heart failure	19.1 (374/1958)
Other CV death	21.1 (413/1958)
Deaths in the first 30 days	N = 975
Cardiovascular	84.5 (779/922)
Bleeding	3.4 (31/922)
Non-CV/non-bleeding	12.2 (112/922)
Unknown	— (53)
Deaths after day 30	N = 2172
Cardiovascular	70.0 (1179/1684)
Bleeding	2.9 (49/1684)
Non-CV/non-bleeding	27.1 (456/1684)
Unknown	— (488)
CV deaths in the first 30 days	N = 779
Sudden death	21.6 (168/799)
Recurrent MI	30.6 (238/799)
Heart failure	24.3 (189/799)
Other CV death	23.6 (184/799)
CV deaths after day 30	N = 1179
Sudden death	46.2 (545/1179)
Recurrent MI	18.7 (220/1179)
Heart failure	15.7 (185/1179)
Other CV death	19.4 (229/1179)

Deaths were grouped into one of three mutually exclusive classes—cardiovascular, bleeding, and non-CV/non-bleeding. CV deaths were subclassified into one of four specific modes—sudden death, recurrent MI, heart failure, and other CV death (includes ischaemic stroke, pulmonary embolism, acute aortic syndromes, cardiac rupture, and peripheral arterial disease). The proportions of each general class and specific CV mode of death occurring 0–30 days and >30 days following NSTEMI-ACS are shown. Percent of deaths in each category are shown with absolute numbers in parentheses. Deaths of unknown mode were excluded from the percent calculations.

CV, cardiovascular; MI, myocardial infarction.

tend to be older, are more likely to be female, have more medical comorbidities including hypertension, diabetes, obesity, and renal dysfunction and have a greater burden of heart disease, including higher baseline rates of previous MI, heart failure, stroke, and prior revascularization.^{13,14} While short-term outcomes are worse following STEMI due to higher in-hospital mortality rates, multiple studies have shown that post-discharge mortality is actually higher among patients with NSTEMI-ACS,^{13–15} perhaps related to older age and greater burden of these comorbidities. Regardless, the high risk of death in the mid- to longer-term following NSTEMI-ACS underscores the importance of understanding modes of death in this population.

Take home figure Cumulative incidence of modes of death. The cumulative incidence of each (A) general class of death and (B) specific cardiovascular mode of death is shown over the first year following trial enrollment for non-ST-segment elevation acute coronary syndrome. The number of patients at-risk is shown below the x-axis and accounts for the presence of competing risks. Point estimates are provided at 12 months.

Sudden death following non-ST-segment elevation acute coronary syndromes

The distinct pattern of CV mortality between patients who died during the time periods of up to and beyond 30 days following trial enrollment for NSTEMI-ACS suggests that SD may be an important mode of late mortality in this patient group. In addition, while the absolute rate of SD was higher in patients with a history of heart failure due to the higher overall mortality rate, the comparable proportion of SD among CV deaths observed in patients with and without a history of heart failure implies that this finding may be independent of pre-

existing heart failure. Importantly, although SD is often attributed to an arrhythmic event, and therapies designed to prevent SD generally target ventricular tachyarrhythmia (e.g. implantable cardioverter-defibrillators), it can be difficult to distinguish whether recurrent MI is the underlying mode of SD. In addition, autopsy series of patients who died from SD often describe other modes of death (e.g. acute pulmonary embolism, aortic rupture) that were not clinically evident prior to death.^{16,17} In our analysis, the increasing proportion of SD over time was significant even when deaths occurring during the index hospitalization were excluded, suggesting that the temporal

shift was not predominantly due to bias associated with in-hospital monitoring.

Although many studies have explored the risk and timing of SD following acute MI,^{18–21} very few studies have investigated SD specifically in patients who have experienced a NSTEMI-ACS. In an analysis of the MERLIN-TIMI 36 trial (included in this analysis), Scirica *et al.*²² highlighted a risk of SD that extended throughout the first year following NSTEMI-ACS in a population generally thought to be at low risk for SD. In a pooled cohort analysis of NSTEMI-ACS patients enrolled in four large clinical trials, Hess *et al.*²³ reported that SD occurred at a rate of approximately 1% per year following NSTEMI-ACS and accounted for about one-third of CV deaths. Our analysis extends these findings to a larger cohort, provides additional granularity regarding other modes of CV death and demonstrates that SD is more common than other modes of CV death beyond the first month following NSTEMI-ACS. Our analysis also highlights the SD risk following NSTEMI-ACS in patients without pre-existing heart failure.

The implications of our findings are several-fold. First, since the pathophysiology of SD can be variable, further investigations are needed to better define the specific causes of SD in patients who have had NSTEMI-ACS. For example, studies that leverage the electrocardiographic data obtained from wearable cardioverter-defibrillators or existing cardiac implantable electronic devices may offer mechanistic insights.²⁴ Second, it appears that while efforts to reduce re-infarction are still needed to reduce early mortality post-NSTEMI-ACS, interventions to reduce SD after 30 days may have a greater potential to reduce later deaths. Specific management approaches designed to modify the risk of SD in patients with NSTEMI-ACS merit further investigation through prospective studies. For example, closer monitoring (e.g. with implantable loop recorders) or testing (e.g. with electrophysiological studies) of patients at increased risk of SD following NSTEMI-ACS might identify patients who could benefit from a wearable or implantable cardioverter-defibrillator.

Fatal bleeding

Fatal bleeding was uncommon in this clinical trial population, accounting for only 3.0% of all deaths, despite the introduction of increasingly more potent antithrombotic therapies. Importantly, this may be a function of the selected populations enrolled in clinical trials and may not reflect the number of fatal bleeding events that occur in clinical practice. In addition, while bleeding may contribute to death indirectly (e.g. by resulting in interruption of important antithrombotic therapies), our analysis only accounts for fatal bleeding events, which underestimates the overall impact of bleeding.

Non-cardiovascular/non-bleeding death

Non-CV/non-bleeding deaths, especially malignancy-related deaths, accounted for a larger proportion of later deaths following NSTEMI-ACS in this clinical trial population. The lesser early contribution is likely related to clinical trial entry criteria, which exclude patients with active cancer and other life-threatening non-cardiac comorbid conditions. Importantly, these data highlight the increasing contribution of non-CV modes of death over time. This is especially relevant to clinical trials with long follow-up periods, which may require competing risk models to appropriately compare late survival rates between therapies.

Strengths

To our knowledge, this is the largest patient-level analysis of mortality from an NSTEMI-ACS clinical trial population followed long-term. Since our study population is taken exclusively from clinical trials, the fidelity of the outcomes data is generally greater than it is in large observational studies. Mortality analyses of CV disease have traditionally relied on large public registries, which often report discrepant data and lack the granularity to reliably classify CV outcomes.^{25,26} For example, many of these registries rely on ICD coding, which may not be accurate in the context of CV disease.²⁷ While prospective CV registries have been designed to capture outcomes following ACS,^{13,28,29} detailed descriptions of the subcategories of CV death are generally not available, and the outcomes have not been formally adjudicated.²⁸ In contrast, 77% of deaths in our analysis were adjudicated by an independent CEC as part of a clinical trial, and all deaths were reviewed by two independent physician-investigators using a uniform set of prespecified criteria. In addition, our analysis includes important subgroup analyses of modes of death in patients with and without a history of heart failure and in patients enrolled prior to and after 31 December 2000, as well as valuable sensitivity analyses restricted to deaths occurring in patients with NSTEMI and deaths occurring after the index hospitalization to control for potential bias related to in-hospital monitoring.

Limitations

Lack of generalizability is an often-cited limitation of using a clinical trial database since clinical trial populations are usually healthier and more likely to receive appropriate therapy. Selection bias is an especially important consideration in this mortality analysis, since patients with cancer, end-stage renal disease, severe bleeding disorders, and other life-threatening comorbidities were excluded from most of the trials. The results reported in this analysis should therefore be interpreted in that context and are not intended to provide a precise estimate of the prevalence of CV death for a general population with NSTEMI-ACS. Nevertheless, our study population had similar rates of prior MI, peripheral arterial disease, heart failure, and renal dysfunction when compared with cohorts derived from the Global Registry of Acute Coronary Events (GRACE).²⁹ The large number of CV deaths in our cohort allowed us to explore the specific CV modes of death. Our findings are most directly relevant to designing future CV trials and developing novel therapies to reduce mortality (both early and later) following NSTEMI-ACS.

Other limitations of our analysis deserve attention. There was variability in the duration of follow-up across the TIMI trials, so late outcomes were not available for some of the shorter and generally smaller trials, and only 25% of patients were followed for more than 17 months. In addition, there was variability between trials in the timing of trial enrolment following NSTEMI-ACS since some enrolled patients at the time of initial presentation and others enrolled patients who had been stabilized post-ACS. Because of the delayed timing of trial enrolment for some trials, the number of early deaths is likely to be underestimated in our cohort, and there is potential bias in the distribution of specific CV modes of death in the 0–30-day period. Nevertheless, the median time from onset of the index event to study enrolment was 1 day for the merged cohort. Furthermore, the landmark analyses of general class and specific CV mode of death

starting at 30 days following the *qualifying* NSTE-ACS event closely parallel the results of the primary analysis.

Finally, accurately classifying mode of death is complicated for many reasons. First, mode of death is often multifactorial, especially for patients with NSTE-ACS who are elderly and often have multiple comorbidities. Second, assigning mode of death to a single (or the most proximate) event may not adequately describe the clinical nuances involved in a patient's death. For example, bleeding may prompt a healthcare provider to discontinue antithrombotic or other therapies, thereby increasing the risk of recurrent ischaemic events.³⁰ Third, CV death classifications often have overlapping pathophysiologies and may not fit cleanly into one category, as in the case of SD. To this end, there have been efforts to standardize definitions for end-point events in CV trials and to provide greater granularity regarding potential causal relationships that may be implicated in a patient's death,⁵ which are important but remain imperfect. These challenges in analysing mortality data are not unique to the present analysis, and highlight the importance of using validated methods to assess modes of death (e.g. postmortem examination).

Conclusion

Cardiovascular events are responsible for the majority of deaths following NSTE-ACS in a population derived from CV clinical trials over a 25-year period. Modifying CV risk following NSTE-ACS is paramount to improving survival in this population. Recurrent MI represents the largest proportion of CV deaths in the first 30 days following NSTE-ACS, whereas SD is a proportionately greater mode of death beyond 30 days in a CV clinical trial population. Further investigations aimed at defining the epidemiology of SD and developing specific therapies and management approaches to reduce SD following NSTE-ACS may be critical to reducing late mortality.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 2010; **362**:2155–2165.
2. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. *Eur Heart J* 2015; **36**: 2984–2987.
3. Budaj A, Eikelboom JW, Mehta SR, Afzal R, Chrolavicius S, Bassand JP, Fox KA, Wallentin L, Peters RJ, Granger CB, Joyner CD, Yusuf S; OASIS 5 Investigators. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. *Eur Heart J* 2008; **30**:655–661.
4. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? *Circulation* 2013; **127**:2452–2457.
5. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL; American College of Cardiology, American Heart Association. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation* 2015; **132**:302–361.
6. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16**:1141–1154.
7. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. *Biometrics* 2011; **67**: 39–49.
8. Cnaan A, Ryan L. Survival analysis in natural history studies of disease. *Stat Med* 1989; **8**:1255–1268.
9. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. *Stat Med* 2007; **26**: 1343–1359.
10. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**:496–509.
11. Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Recent changes in attack and survival rates of acute myocardial infarction (1975 through 1981). The Worcester Heart Attack Study. *JAMA* 1986; **255**:2774–2779.
12. McGovern PG, Jacobs DR Jr, Shahar E, Arnett DK, Folsom AR, Blackburn H, Luepker RV. Trends in acute coronary heart disease mortality, morbidity, and medical care from 1985 through 1997: the Minnesota heart survey. *Circulation* 2001; **104**:19–24.
13. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, Flather MD, Sadiq I, Kasper R, Rushton-Mellor SK, Anderson FA; GRACE Investigators. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol* 2002; **90**:358–363.
14. Polonski L, Gasior M, Gierlotka M, Osadnik T, Kalarus Z, Trusz-Gluza M, Zembala M, Wilczek K, Lekston A, Zdrojewski T, Tendera M; PL-ACS Registry Pilot Group. A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: are non-ST myocardial infarctions associated with worse long-term prognoses? *Int J Cardiol* 2011; **152**:70–77.
15. Allen LA, O'Donnell CJ, Camargo CA Jr, Giugliano RP, Lloyd-Jones DM. Comparison of long-term mortality across the spectrum of acute coronary syndromes. *Am Heart J* 2006; **151**:1065–1071.
16. Pouleur AC, Barkoudah E, Uno H, Skali H, Finn PV, Zelenkofske SL, Belenkov YN, Mareev V, Velazquez EJ, Rouleau JL, Maggioni AP, Kober L, Califf RM, McMurray JJ, Pfeffer MA, Solomon SD; VALIANT Investigators. Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *Circulation* 2010; **122**: 597–602.
17. Papadakis M, Raju H, Behr ER, De Noronha SV, Spath N, Kouloubinis A, Sheppard MN, Sharma S. Sudden cardiac death with autopsy findings of uncertain significance: potential for erroneous interpretation. *Circ Arrhythm Electrophysiol* 2013; **6**:588–596.
18. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; **335**:1933–1940.
19. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; **341**:1882–1890.
20. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial III. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877–883.
21. Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, Harsanyi A, Rouleau JL, Maggioni A, Kober L, White H, Van de Werf F, Pieper K, Califf RM, Pfeffer MA; Valsartan in Acute Myocardial Infarction Trial Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005; **352**:2581–2588.
22. Scirica BM, Braunwald E, Belardinelli L, Hedgepeth CM, Spinar J, Wang W, Qin J, Karwowska-Prokopczuk E, Verheugt FW, Morrow DA. Relationship between nonsustained ventricular tachycardia after non-ST-elevation acute coronary syndrome and sudden cardiac death: observations from the metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndrome-thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation* 2010; **122**:455–462.
23. Hess PL, Wojdyla DM, Al-Khatib SM, Lokhnygina Y, Wallentin L, Armstrong PW, Roe MT, Ohman EM, Harrington RA, Alexander JH, White HD, Van de Werf F, Piccini JP, Held C, Aylward PE, Moliterno DJ, Mahaffey KW, Tricoci P. Sudden cardiac death after non-ST-segment elevation acute coronary syndrome. *JAMA Cardiol* 2016; **1**:73–79.
24. Kandzari DE, Perumal R, Bhatt DL. Frequency and implications of ischemia prior to ventricular tachyarrhythmia in patients treated with a wearable cardioverter defibrillator following myocardial infarction. *Clin Cardiol* 2016; **39**:399–405.
25. Erdem G, Bakhai A, Taneja AK, Collinson J, Banya W, Flather MD. Rates and causes of death from non-ST elevation acute coronary syndromes: ten year follow-up of the PRAIS-UK registry. *Int J Cardiol* 2013; **168**:490–494.
26. Normand ST, Glickman ME, Sharma RG, McNeil BJ. Using admission characteristics to predict short-term mortality from myocardial infarction in elderly patients. Results from the Cooperative Cardiovascular Project. *JAMA* 1996; **275**: 1322–1328.
27. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of myocardial infarction diagnoses in administrative databases: a systematic review. *PLoS One* 2014; **9**:e92286.
28. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buyschaert I, Lambrechts D, Van de Werf F. Underestimated and unrecognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J* 2010; **31**:2755–2764.

29. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;**163**:2345–2353.

30. Wang TY, Xiao L, Alexander KP, Rao SV, Kosiborod MN, Rumsfeld JS, Spertus JA, Peterson ED. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. *Circulation* 2008;**118**: 2139–2145.

CARDIOVASCULAR FLASHLIGHT

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Residual shunt diagnosed with 4D flow after reparation of post-infarct ventricular septal defect

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We present the case of a medium age male patient with acute myocardial infarction and secondary ventricular septal defect (VSD). He underwent emergency surgery to repair of post-infarction VSD by David infarct exclusion technique.

A pericardial patch was attached to the endocardium of the left ventricle (LV) all around the necrotic myocardium to exclude the VSD and the infarct from the left ventricular cavity.

A week after the procedure, the patient clinical condition was good but there was a typical murmur of a VSD. By Doppler ultrasound a small flow with apparently no communication with the LV was assessed through the VSD.

A cardiac MRI was performed, with a protocol that included 4D flow sequence (a tridimensional flow sequence with temporal resolution).

In the anatomic sequences, the pericardial patch showed no defect. Because of the technique of David exclusion, the right ventricle (RV) remained communicated through the VSD with a thin false cavity between the residual interventricular septum and the pericardial patch. Four-dimensional flow images showed a small defect between the left ventricular apex and the pericardial patch. Through this defect, there was a small flow from LV passing towards the previously described false cavity between pericardial patch and residual septum. This flow presented posterior and superior direction to finally communicate with the RV through the VSD.

Besides direct visualization of the flow, with 4D flow sequence we could measure the shunt flow (4 L/min) and obtain indirect sign of left-right shunt (Q_p/Q_s ratio: 3:2). As the ventricular function and the clinical evolution of the patient were good and there were no symptoms of left ventricular overload, follow-up was decided, monitoring with US and MRI. Doppler ultrasound 6 months after showed no changes.

Four-dimensional flow imaging where colour depends on velocity magnitude and vectors show flow direction. *Panel A* shows coronal MIP reconstruction. *Panel B* shows four chambers image. *Panel C* shows oblique short-axis image. Small flow through small defect in the LV apex between LV and the pericardial patch (arrow in *Panel C*) goes towards the false thin cavity (asterisk) between pericardial path and residual interventricular septum. It is shown the shunt between the false cavity and the RV (left-right shunt) through VSD (arrows in *Panels A and B*).

Supplementary material is available at *European Heart Journal* online.