

# Sudden cardiac death after acute ST elevation myocardial infarction: insight from a developing country

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## ABSTRACT

**Background** There is no data concerning sudden cardiac death (SCD) following acute ST elevation myocardial infarction (STEMI) in India. We assessed the incidence and factors influencing SCD following STEMI.

**Methods** Patients with STEMI admitted in our hospital from 2006 to 2009 were prospectively entered into a database. In the period 2010–2011, patients or their kin were periodically contacted and administered a questionnaire to ascertain their survival, and mode of death if applicable.

**Results** Study population comprised of 929 patients with STEMI (mean age  $55 \pm 17$  years) having a mean follow-up of  $41 \pm 16$  months. The total number of deaths was 159, of which 78 were SCD (mean age  $62.2 \pm 10$  years). The cumulative incidence of total deaths and SCD at 1 month, 1, 2, 3 years and at conclusion of the study was 10.1%, 13.2%, 14.6%, 15.8%, 17.3% and 4.9%, 6.5%, 8.0%, 8.9% and 9.7%, respectively. The temporal distribution of SCD was 53.9% at first month, 19.2% at 1 month to 1 year, 15.4% in 1–2 years, 7.6% in 2–3 years and 3.8% beyond 3 years. Comparison between SCD and survivor cohorts by multivariate analysis showed five variables were found to be associated with SCD (age  $p=0.0163$ , female gender  $p=0.0042$ , severe LV dysfunction  $p=0.0292$ , absence of both reperfusion and revascularisation  $p=0.0373$  and lack of compliance with medications  $p < 0.0001$ ).

**Conclusions** SCD following STEMI accounts for about half of the total deaths. It involves younger population and most of these occur within the first month. This data has relevance in prioritising healthcare strategies in India.

## INTRODUCTION

Sudden cardiac death (SCD) is a devastating and unpredictable cardiovascular outcome and there is in general a deficiency of data concerning this problem in India. The only focused study involving the general population found that sudden deaths constitute about 10% of the total mortality.<sup>1</sup> It is well established that patients who have suffered acute myocardial infarction constitute a high risk group for the occurrence of SCD and this population has not been systematically studied in this part of the world. In this study, we aimed to assess the incidence, distribution and factors predicting the occurrence of SCD following acute ST elevation myocardial infarction (STEMI) in patients from a large tertiary medical centre in India.

## Rationale for this study

It is well established that about 80% of deaths related to cardiovascular disease occur in the lower and middle income countries.<sup>2</sup> Despite the large

prevalence of coronary artery disease in countries like India, there is to date no reliable information available on sudden deaths. The twin problems of acute myocardial infarction and associated mortality in the younger and economically productive age groups magnify the acute need for systematic data in this area. A recently published registry has unravelled the prevalent heterogeneous patterns of management of acute coronary syndromes which are governed by a variety of socioeconomic factors. This study also showed that unlike the Western world, STEMI constitutes about 60% of patients diagnosed as acute coronary syndrome.<sup>3</sup>

The PURE study discovered large discrepancies from countries including India in adherence to evidence based secondary prophylaxis practices.<sup>4</sup> The logical implications of these studies are that the postmyocardial infarction mortality and SCD figures may not be in line with published data. The SCD statistics and trends from a country with over a billion population are likely to impact worldwide mortality figures and influence global strategies for reduction in the burden of sudden deaths.

## METHODS

This study was done in CARE Hospitals, Nampally, Hyderabad, India, which is a tertiary care multi-specialty private hospital situated in the capital city of the state of Andhra Pradesh. Facilities for round the clock care acute coronary syndromes including primary angioplasty are available. Patients admitted with ACS come to this hospital from nearby geographical areas as well as by referral from physicians in the nearby districts and are from heterogeneous socioeconomic strata.

Data of all patients admitted in this hospital from July 2006 to June 2009 with the diagnosis of STEMI was prospectively entered into a pre-designed database. This included detailed information on the demographic and clinical profiles, left ventricular ejection fraction (LVEF) assessed by echocardiography, management and outcomes in the hospital. Surviving patients following discharge from the hospital were followed up at outpatient clinics of our hospital, by their primary physicians or cardiologists as per their choice. Starting from 2010 January, the survival status of each of these patients was periodically ascertained at 6-monthly intervals and a questionnaire was administered to the patient or their kin in case of the patient's demise. Data were collected after obtaining verbal consent and was aimed at gathering information on physician follow-up, compliance with medications, hospitalisations and revascularisation procedures in

the intervening period. This questionnaire contained a series of structured questions that required the responder to choose from the given alternatives. In the event of death, they were also required to complete a narrative component to describe the medical condition of the deceased in the last 1–2 days. The questions were designed to ascertain the sequence of events leading to the terminal event in case of the patient's death. Patients or their kin were contacted during their visits to our hospital, by phone or at the home visit made by a trained coordinator. The study was terminated in October 2011 and data captured were analysed. Deaths were classified based on data obtained from the questionnaires and a review of in-hospital and outpatient medical records when feasible. Deaths were classified as cardiovascular deaths (CVDs), non-cardiovascular or unclassifiable. CVDs were further classified as sudden or non-sudden. Classification of deaths was done by two independent monitors and decided by an adjudicator in case of conflict. This study was approved by the institutional ethics committee.

### Statistics

Statistical analyses were performed using MedCalc for Windows, V.12 © 1993–2011 (MedCalc Software, Mariakerke, Belgium). Discrete variables were presented in per cent and continuous variables as mean  $\pm$  SD. Student t test was done to compare continuous variables. Cumulative event rates were calculated with the use of the Kaplan–Meier method. Event times for all patients were measured from the time of admission. Univariate analysis was done using logistic regression and multivariate analysis was done by using Cox proportional-hazards model where SCD was the end point and each factor served as a time dependent covariate. A p value  $<0.05$  was considered statistically significant.

### Definitions

For the purpose of this study we used the following definitions.

1. CVD: Deaths related to heart failure, ischaemia, recurrent infarction, arrhythmic and non-arrhythmic sudden deaths, and cerebrovascular accidents.
2. In-hospital death: Patients admitted with the diagnosis of STEMI and who died from any cause prior to discharge.
3. SCD<sup>5</sup>: CVD was defined as sudden if it was: (A) a witnessed death that occurred within 60 min from the onset of new

symptoms unless a cause other than cardiac was obvious; (B) an unwitnessed death ( $<24$  h) in the absence of pre-existing progressive circulatory failure or other causes of death; or (C) death during attempted resuscitation.

4. Survivors: Patients who are alive for a period of 3 years or more following the index STEMI.
5. Reperfusion therapy: Administration of thrombolytic therapy or subjecting the patient to primary angioplasty.
6. Revascularisation therapy: Patients were considered to have received revascularisation when they underwent coronary angioplasty or CABG.
7. Left ventricular function: Left ventricular function was categorised by the quantitative assessment of LVEF or qualitatively reported LVEF as follows: normal:  $\geq 50\%$ , mild left ventricular (LV) dysfunction: 40%–49%, moderate LV dysfunction: 31%–39% and severe LV dysfunction:  $\leq 30\%$ .
8. Compliance with medications: Patients who at least took  $\beta$ -blockers and antiplatelets.

### RESULTS

The population in this study comprised of 929 consecutive patients (765 male and 164 female subjects) who were admitted with the diagnosis of STEMI. The mean age of these patients was  $55 \pm 17$  years (male subjects:  $54 \pm 18$  years and female subjects  $60 \pm 11$  years,  $p < 0.001$ ). The demographics of the study population, the survivors and SCD and non-SCD mortality subsets are summarised in table 1. The mean follow-up of these patients was  $41 \pm 16$  months. In view of termination of the study at a point in time, the surviving patients had variable follow-up times. Thus, follow-up data were available for 881 patients at the end of 1 month, 777 patients at 1 year, 746 patients at 2 years and 545 patients at 3 years and beyond. Data of 67 patients were unavailable at different points in time; 48 after 1 month, 12 after 1 year and seven after 2 years and these patients were excluded from analysis. This resulted from patients not coming for follow-up, being non-traceable or not consenting to give any data. The 545 patients who had a follow-up of over 3 years after index admission were defined as survivors and this group had a mean follow-up of  $50 \pm 9$  months.

### Time course of mortality

Total deaths in this study were 159 (112 male and 47 female subjects), of which 78 were sudden deaths, 47 were non-sudden

**Table 1** Population characteristics

	STEMI	SCD	Non-sudden deaths	Survivors
Total number	929	78	81	545
Age in years	$55.5 \pm 17.5$	$62.2 \pm 10.4$	$59.9 \pm 10.7$	$53.8 \pm 11.4$
Male/female	765/164	58/20	54/27	464/81
AWMI	548 (59%)	56 (71.8%)	48 (59.4)	311 (57.1%)
Inferior $\pm$ posterior MI	339 (36.5%)	15 (19.2%)	23 (28.3)	216 (39.6%)
Other sites of MI	42 (4.5%)	7 (9%)	10 (12.3)	18 (3.3%)
Diabetes	403 (43.4%)	41 (52.6%)	44 (54.3)	228 (41.83%)
Hypertension	486 (52.3%)	45 (57.7%)	50 (61.7)	282 (51.74%)
Smoking	365 (39.2%)	22 (28.2%)	22 (27.2)	210 (28.53%)
Family history of CAD	196 (21.1%)	6 (7.69%)	10 (12.3)	136 (24.95%)
Window period (hours)	$4.04 \pm 3.17$	$5.0 \pm 3.0$	$5.1 \pm 3.8$	$3.83 \pm 3.0$
Thrombolysis	483 (52%)	39 (50%)	29 (35.8)	302 (55.41%)
Primary/rescue PCI	263 (28.21%)	12 (15.38%)	14 (17.3)	162 (29.72%)
Reperfusion therapy	657 (70.7%)	46 (60.25%)	41 (50.6%)	406 (74.5%)
LVEF (%)	$45.9 \pm 11$	$41.82 \pm 13.16$	$39.2 \pm 12.2$	$47.21 \pm 10.22$

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous intervention; SCD, sudden cardiac death; STEMI, ST elevation myocardial infarction; AWMI, anterior wall myocardial infarction.

CVD, 11 were non-cardiovascular and in 23 the cause of death was unclassifiable.

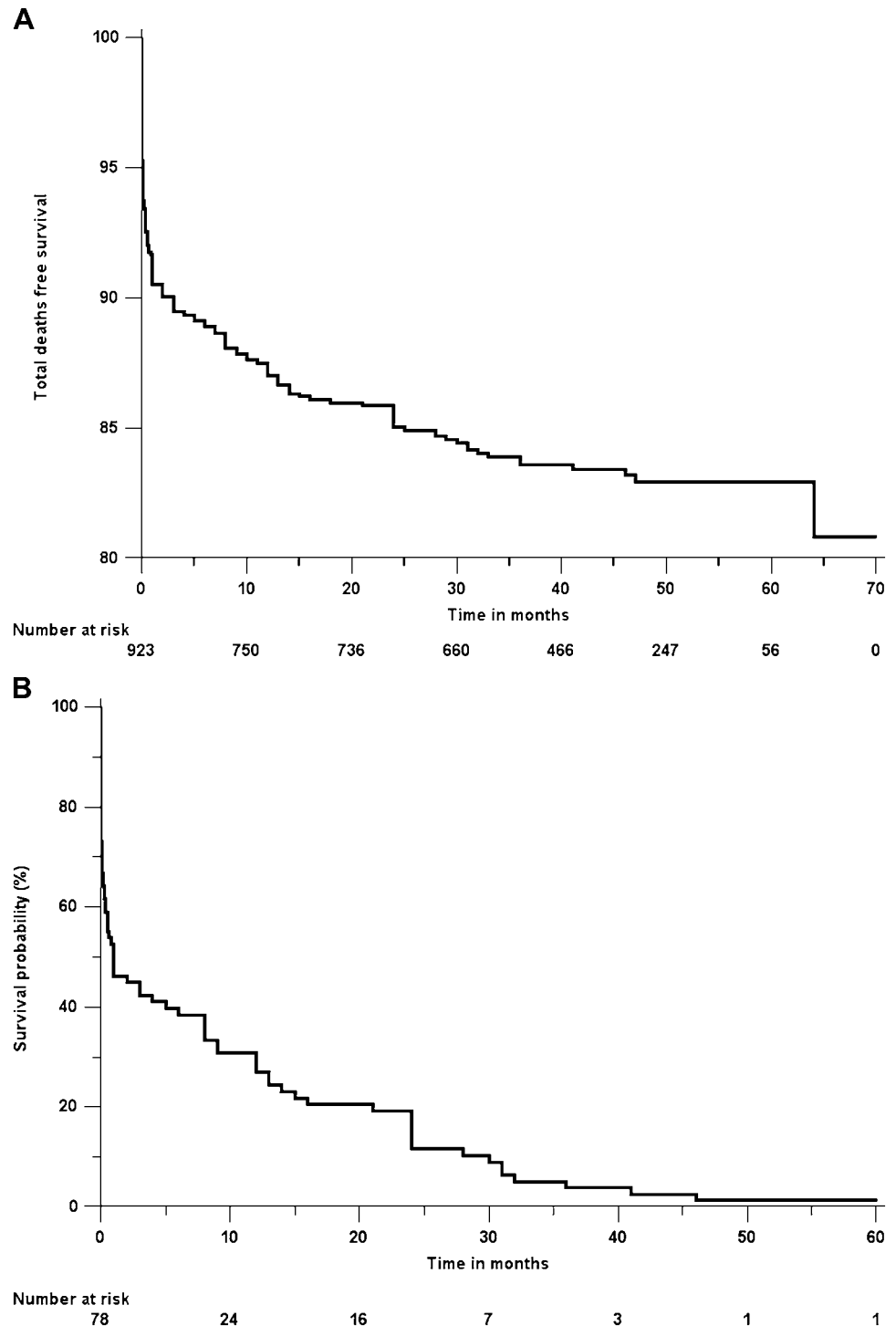
There were 73 (7.9%) deaths inhospital during the treatment of index STEMI, 30 were SCD and 22 were non-sudden CVD. The remaining 21 deaths were attributed to sepsis, renal failure and multi-organ failure. These inhospital deaths occurred after a mean duration of  $5 \pm 5$  days after admission. Total deaths at 1 month including inhospital mortality were 92; SCD accounted for 42 (45.6%) and non-sudden CVD for 34 (37%) of these deaths. This resulted in a cumulative total first month mortality of 10.1% and a cumulative incidence of SCD of 4.9% in this period. Of the 789 patients who survived the first month and whose follow-up is available, 31 (3.9%) died within the first year.

Of these, 15 were due to SCD (48.3%) and 10 (32.3%) due to non-sudden SCD. The incidence of total deaths in the second and third years was 2.5% ( $n=19$ ) and 1.6% ( $n=12$ ) while that of SCD was 1.6% ( $n=12$ ) and 0.8% ( $n=6$ ). Beyond 3 years, there were five deaths, three of which were classified as SCD. Cumulative total mortality at end of 1, 2, and 3 years and at culmination of the study was 13.2%, 14.6%, 15.8% and 17.3% (figure 1A).

#### The SCD cohort and the survivors

There were 78 deaths in total classified as SCD resulting in a cumulative sudden death mortality of 9.7% at a follow-up of  $41 \pm 16$  months. The cumulative incidence of SCD at the end

**Figure 1** (A) Cumulative survival curve for the entire ST elevation myocardial infarction (STEMI) population is shown. (B) The temporal distribution of the mortality due to sudden cardiac deaths shows that the majority of these deaths occur in the first year, particularly in the first month following the STEMI.



**Table 2** Univariate analysis of SCD and survivor cohorts

Variables	SCD	Survivors	OR Est (CI)	p Value
Total number	78	545		
Age in years (mean±SD)	62.2±10.4	53.8±11.4	1.004 (1.000 to 1.009)	0.01
Female gender	20 (25.6%)	81 (14.9%)	0.506 (0.289 to 0.887)	0.0173
Diabetes	41 (25.94%)	228 (41.83%)	1.541 (0.957 to 2.48)	0.075
Time to presentation (h) (mean±SD)	5.0±3.0	3.83±3.0	1.116 (1.039 to 1.198)	0.0026
Reperfusion therapy	46 (60.25%)	406 (74.5%)	0.492 (0.301 to 0.804)	0.0046
Severe LV dysfunction	8 (10.25%)	23 (4.22%)	0.955 (0.934 to 0.977)	<0.0001
Revascularisation	16 (21.8%)	232 (42.6%)	0.348 (0.196 to 0.619)	0.0003
Either reperfusion or revascularisation	48 (61.5%)	430 (78.9%)	0.433 (0.262 to 0.713)	0.001
Compliance to medications	8 (23.1%)	520 (95.41%)	0.006 (0.002 to 0.017)	<0.0001

LV, left ventricular; SCD, sudden cardiac death; Est, estimated.

of first, second and third years was 6.5%, 8.0% and 8.9%, respectively. The mean age of the SCD cohort was 62.2±10 years which was higher than that of STEMI population (55±17 years). The temporal distribution of the SCD showed that 42 (53.9%) occurred within the first month, 15 (19.2%) beyond first month and within the first year, 12 (15.4%) in 1–2 years, six (7.7%) in 2–3 years and three (3.8%) beyond 3 years (figure 1B). Various characteristics of the SCD cohort, along with those of the whole population, are shown in table 1. Different variables characterising the SCD and survivor cohorts were compared using univariate and multivariate analyses. The overall prevalence of coronary risk factors did not differ between the two groups as 78% of the survivors had at least one coronary risk factor compared with 81% of the SCD cohort (p=NS). Univariate analysis found eight of the nine variables tested significantly differing among the two cohorts; multivariate analysis, however, showed only age, female gender, severe LV dysfunction, reperfusion or revascularisation, and compliance to medications being independently associated with SCD (tables 2 and 3). The SCD cohort was older than the survivors and STEMI overall population, but the mean age of males and female subjects in this group was similar (male subjects 63.3±10.4 years and female subjects 63.7±9.9 years, p=NS). The proportion of women in the population was small, but their proportion among the SCD cohort was larger (17.7% vs 25.6%). The mean LVEF was lower in the SCD group (42±13% vs 47±10%) and the percentage of patients in this cohort with severe LV dysfunction was 10.2% compared with 4.2% in the survivors. Importantly, 43.1% of patients in SCD cohort had mild or no significant impairment of LV function showing that using LV function criteria alone would not have adequately risk stratified these patients. Major differences were seen between the two cohorts in reperfusion and revascularisation therapies. In all, 41% of the SCD cohort did not get reperfusion therapy compared with 25.5% in the survivors, and the percentage of patients who were treated by primary angioplasty was 15.5% and 29.7% in the 2 groups respectively. Revascularisation rates were also lower in the SCD group (20.5% vs 37.5%). Though each of these was found to be significant on univariate analysis none of them individually reached statistical significance on multivariate analysis probably in view of the small numbers. However, when the variable with patients who had either reperfusion or revascularisation was introduced in the analysis, the difference was found to be significant. Striking differences were seen in the groups with respect to adherence to prescription medications as shown by the fact that 95.4% of the survivors and 43.6% in the SCD group demonstrated compliance (figure 2).

## DISCUSSION

This report gives an insight into the pattern of SCD following acute myocardial infarction in a Third World country and highlights the geographically relevant discriminating factors that influence survival in this population. The data clearly suggests that the patterns of SCD in this part of the world do not follow global trends. We found that SCD is the major contributor to the total mortality following STEMI accounting for about half of the total deaths in this population at different points in time. The SCD cohort was about 7 years older than the STEMI population yet it is pertinent to note that both the groups encompass much younger population compared with the data from the developed nations.

### Temporal distribution of sudden deaths

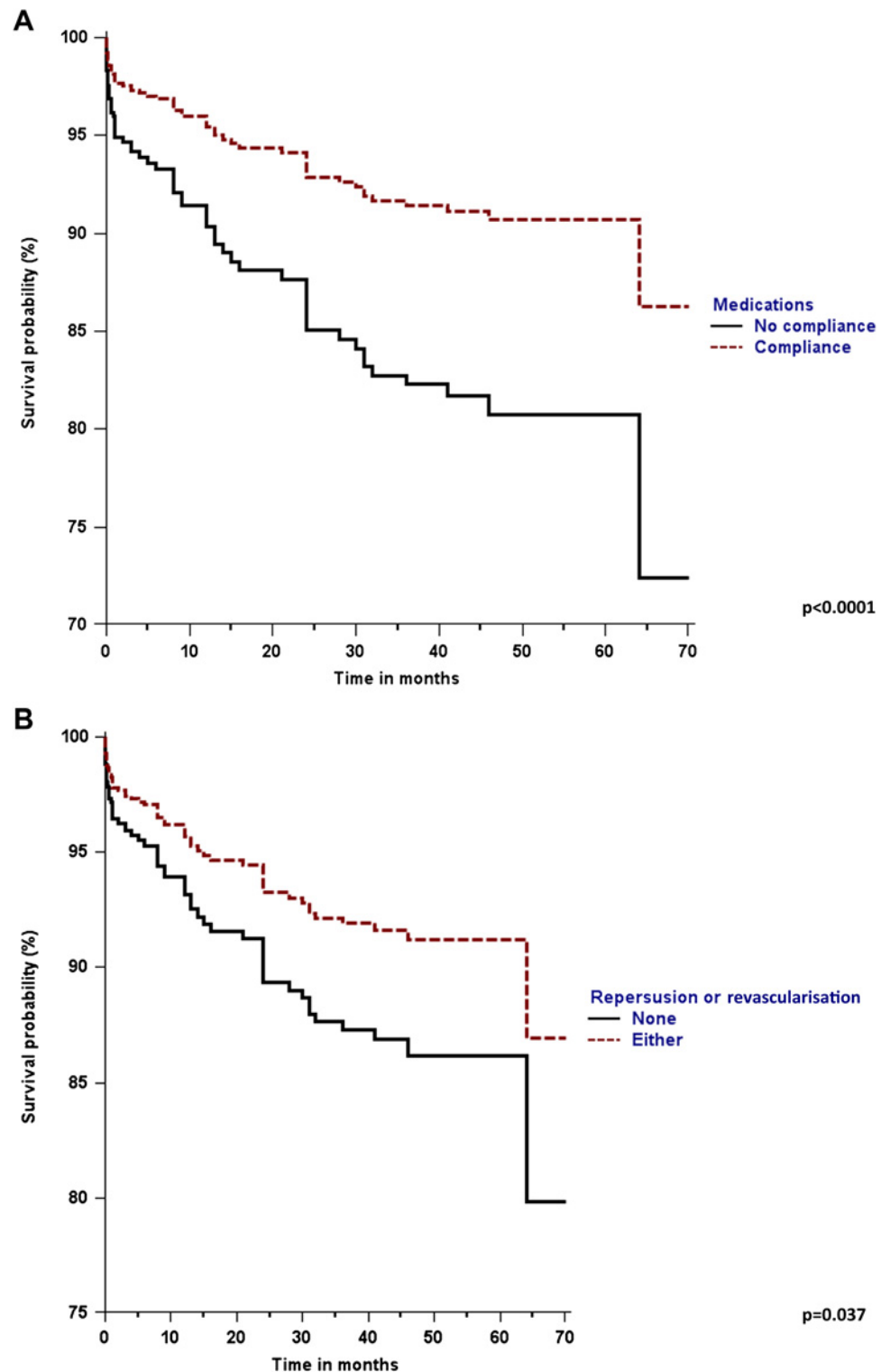
In the last few decades, there has been a progressive decline in the burden of SCD in the postmyocardial infarction population owing to increasing incorporation of evidence based medicine in the management of acute coronary syndromes. The reported annual incidence of SCD was 5%–7% in the Framingham study and 3.6% in a multicentre postinfarction programme which decreased to 1.5%–1.9% in the thrombolytic era.<sup>6–8</sup> With the use of optimal medical therapy and revascularisation, occurrence of SCD has been reported to be as low as <1%.<sup>9</sup> This global positive trend on the declining sudden and non-sudden cardiovascular mortality is not reflected in our study. The incidence of SCD in the initial period following STEMI continues to be high (4.5% at 1 month and 6.5% at 1 year) and the temporal distribution of these deaths is highly skewed with 54% occurring within the first month and nearly three-fourths in the first year. Further, at different points in time SCD accounts for about 50% of the total deaths while globally it has been reported to have decreased to 20%–30%.<sup>7–9</sup> Factors that distinguished our STEMI population from those included in the published literature from developed countries were delayed presentation to hospital (4.04±3.17 h), low incidence of use of thrombolysis (52%) and paucity of use of primary percutaneous interventions procedures (28.2%). These variables are likely to have influenced

**Table 3** Multivariate analysis of SCD and survivor cohorts

Covariate	Exp(b)	95% CI of Exp(b)	p Value
Age	1.0250	1.0047 to 1.0457	0.0163
Female gender	1.7803	1.0229 to 2.8530	0.0042
Compliance with medications	0.0336	0.0170 to 0.0665	<0.0001
Severe LV dysfunction	2.3451	1.0943 to 5.0254	0.0292
Either reperfusion or revascularisation	0.5977	0.3692 to 0.9678	0.0373

LV, left ventricular; SCD, sudden cardiac death.

**Figure 2** (A and B) Survival curves showing that compliance with medications and patients getting either reperfusion or revascularisation were important independent factors influencing freedom from sudden cardiac death in post-ST elevation myocardial infarction patients.



the temporal distribution of mortality in our study. Subgroup analysis of autopsy data of the VALIENT study showed that 12.4% of the deaths classified as sudden on clinical grounds were caused by cardiac rupture and their occurrence along with recurrent myocardial infarction was the highest in the first month after AMI.<sup>10</sup> In absence of autopsy data, our study was unable to conclusively identify different aetiologies of SCD, but it may be logically inferred that a percentage of early deaths in our SCD cohort may have been caused by cardiac rupture.

#### Predictors of SCD

LVEF in the SCD cohort differed significantly from the survivors and predictably severe LV dysfunction was a strong univariate and multivariate predictor of SCD. It is reasonable to infer that delayed hospital presentations and low reperfusion rates contributed to LV impairment in the SCD cohort. It is to be nevertheless reiterated that a significant number in the SCD group had only a minor impairment in LV function showing that factors beyond LVEF influence the occurrence of sudden



deaths. It is well recognised that early reperfusion therapy and optimal revascularisation have effectively contributed to decline in the rates of SCD by myocardial salvage and preservation of LV function.<sup>9–11</sup> In this study, fewer (61%) in the SCD group had either reperfusion or revascularisation compared with the survivors (79%).

Adherence to medications and follow-up with doctors were important factors determining the occurrence of SCD. This factor is a matter of concern as more than half the patients in the SCD group discontinued medications ( $\beta$ -blockers and antiplatelets) following discharge. This fact reproduces the observation in the PURE study where it was shown that there was a gross underusage of proven medications for secondary prophylaxis in low income compared with high income countries.<sup>3</sup> This partly accounts for the geographical variations in predictors of SCD as in the VALIENT trial where among the various temporal predictors of SCD, medication usage was not found to influence SCD.<sup>12</sup> Limitations in patient education, awareness and socioeconomic issues contribute to the problem of non-compliance with medications. It was shown earlier that in a population based study that women have lower rates of CAD but a larger proportion of them have SCD.<sup>13</sup> Women constituted 17.6% of our STEMI population but contributed to a third of in-hospital mortality and 25.6% of the sudden deaths. One explanation was that women were older than their male counterparts (60 years vs 55 years); the second being due to socioeconomic reasons women are less likely to undergo revascularisation procedures, make physician visits or take medications regularly; and the third is possible increased propensity of women for SCD that needs focused study.

### Relevance of the study to public health management

In the last few decades, there has been a perceptible reduction in the sudden and non-sudden cardiovascular mortality following acute myocardial infarction both in-hospital and in the community. This trend has been achieved in developed countries by increased efforts at effective use of emergency care services, timely administration of reperfusion therapies, better revascularisation rates, optimal medical therapy and use of implantable devices (ICD).<sup>11–14–17</sup> The data from this study clearly point to the fact that these therapeutic advances and the resulting favourable outcomes are yet to percolate to large populations of the world. It is imperative to systematically focus on integrating these proven instruments influencing survival into the healthcare system to be able to follow the positive global trends. The mean time of presentation to hospital following chest pain is concerning high, precluding the benefits of timely thrombolytic therapy. As a large proportion of patients pay for their medical expenses out of their pocket, financial constraints limit the use of primary percutaneous interventions and optimal revascularisation therapy. Our data show that 3-year survival free SCD is strongly influenced by adherence to standard medications. Ensuring proper administration of medications to these patients presents a very cost effective public health intervention to counter the devastating outcomes of AMI. In the SCD cohort 42 of the 78 deaths occurred in the first month, limiting the ability of ICDs to prevent the majority of sudden deaths. None of the patients received an ICD though overall as per guidelines only 51 patients among our entire STEMI population qualified for primary prophylaxis indication of ICD and theoretically may have prevented seven out of 30 SCDs that occurred in this subgroup as assessed by the follow-up data. The focus of SCD prevention programs in this country should be on addressing issues relating to recognition, and prevention of early

mortality following STEMI. Another important observation is that the gender balance of SCD is adversely tilted towards women. This necessitates systematic investigation of factors influencing gender bias in distribution of medical resources.

The data strongly argue for prioritising cardiovascular healthcare resources to increase accessibility of patients to reperfusion and revascularisation therapies and to improve secondary prevention measures. These measures are the most cost effective strategies to prevent SCD in India. It is also important to emphasise that lifestyle including diet and exercise influence occurrence of SCD after STEMI and these factors should also form an important part of secondary prevention strategies.

### Limitations of the study

This is a single centre study with relatively small number of SCD where the follow-up management was not governed by a structured protocol. In view of the small cohort, to increase the strength of the multivariate analysis the number of variables used to differentiate SCD from survivors was by design limited to nine. The absence of regulated follow-up allowed this study to assess the true scenario of patient follow-up in practice. The limitations of recall bias inherent in any questionnaire based study also exist; however, data were crosschecked with medical records and treating physicians. Further, in case of deaths, when feasible, more than one of the kin of the deceased was interviewed to corroborate the data.

### CONCLUSIONS

SCD is the commonest cause of post-STEMI mortality. It involves younger population and most of these deaths occur within the first year, particularly in the first month. Factors predicting occurrence of SCD were age, female gender, severe LV dysfunction, absence of reperfusion or revascularisation, and poor compliance with medications. This data has relevance in prioritising healthcare strategies in India.

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**Contributors** All the authors have significantly contributed to the work done in this study. Following is the contribution. HBR: principal investigator for the study, protocol writing, data analysis, manuscript writing. BKSS and PKR: protocol preparation, manuscript writing. RK: data collection, data analysis.

**Competing interests** None.

**Patient consent** By protocol verbal consent was obtained from all patients.

**Ethics approval** Ethics approval was provided by the Institutional Ethics committee, CARE Hospitals, Hyderabad, India.

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