Determinants of early case-fatality among stroke patients in Maputo, Mozambique and impact of in-hospital complications

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The burden of stroke is increasing in developing countries that struggle to manage it efficiently. We identified determinants of early case-fatality among stroke patients in Maputo, Mozambique, to assess the impact of in-hospital complications. Patients admitted to any hospital in Maputo with a new stroke event were prospectively registered ($n = 651$) according to the World Health Organization's STEPwise approach, in 2005–2006. We assessed the determinants of in-hospital and 28-day fatality, independently of age, gender and education, and computed population attributable fractions. In-hospital mortality was higher among patients with Glasgow score at admission ≤6 (more than fivefold) or needing cardiopulmonary resuscitation during hospitalization (approximately 2·5-fold). Pneumonia and deep vein thrombosis/other cardiovascular complications during hospitalization were responsible for 19·6% (95% confidence interval, 5·3 to 31·7) of ischaemic stroke and 15·9% (95% confidence interval, 5·8 to 24·9) of haemorrhagic stroke deaths until the 28th day. Ischaemic stroke patients with systolic blood pressure 160–200 mmHg had lower in-hospital mortality (relative risk = 0·32, 95% confidence interval, 0·13 to 0·78), and, for those with haemorrhagic events (haemorrhagic stroke), 28-day mortality was higher when systolic blood pressure was over 200 mmHg (hazard ratio = 3·42; 95% confidence interval, 1·02 to 11·51), compared with systolic blood pressure 121–140 mmHg. Regarding diastolic blood pressure, the risk was lowest at 121–150 mmHg for ischaemic stroke and at 61–90 mmHg for haemorrhagic stroke. Early case-fatality was mostly influenced by stroke severity and in-hospital complications. The allocation of resources to the latter may have a large impact on the reduction of the burden of stroke in this setting.

Key words: early case-fatality, in-hospital complications, Mozambique, stroke

This investigation was based on a STEPS Stroke study conducted in Mozambique. It included all patients living in town for more than 12 months, admitted to any governmental or private hospital in Maputo from 1 August 2005 to 31 July 2006, suspected of having an incident stroke event. The identification of stroke events and the evaluation of the participants were conducted following the STEPS Stroke protocol, Step 1, as previously described (1–3).

Stroke was defined according to the World Health Organization clinical definition: 'a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin' (4). During the study period, 651 cases of stroke were recorded, from which 531 (81·6%) were first events and 120 (18·4%) recurrent events. Confirmation by CT scan or autopsy was obtained for 92·3% of cases (601 stroke events). This allowed categorization in ischaemic events ($n = 351$, 58·4%), haemorrhagic events ($n = 242$, 40·3%), and sub-arachnoid haemorrhages ($n = 8$, 1·3%). The latter were not considered in the present analyses because they were in small number.

Patients' socio-demographic characteristics, date of symptoms onset, and date of admission were recorded. Smoking status and dyslipidaemia were self-reported. Disability before stroke was evaluated using the modified Rankin Scale (5). Hypertension and diabetes were considered present when reported by the patients or their next of kin or when pharmacological treatment was prescribed on an inpatient or post-discharge basis. Atrial fibrillation was assessed through an electrocardiogram. Blood pressure and Glasgow score at admission were later added to the protocol. Admission blood pressure was obtained for 437 patients and Glasgow score was calculated for 286 patients. The need for cardiopulmonary resuscitation (CPR) as well as the occurrence of pneumonia, deep vein thrombosis (DVT), and other cardiovascular complications (e.g. acute myocardial infarction, pulmonary embolism) during hospital stay were abstracted from clinical records.

All in-hospital deaths were registered. From the 434 patients discharged alive, follow-up at the 28th day was accomplished for 412 (94·9%).

Data analysis was conducted separately for ischaemic and haemorrhagic events. In-hospital case-fatality was calculated as the proportion of patients who died during hospital stay and 28-day case-fatality rate (CFR) was quantified using the Kaplan–Meier failure function.

To identify the socio-demographic, pre-stroke morbidity, and clinical determinants of early case-fatality, we computed relative risks (RR) of death during hospitalization and hazard ratios (HR) of death until the 28th day, using Poisson regression and Cox regression, respectively, adjusting for age (<44, 45–54,

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55–64, >65 years), sex, and education (0, 1–4, 5, ≥6 years of schooling).

To estimate the impact of in-hospital complications on early case-fatality, we computed population attributable fractions and the corresponding 95% confidence interval (95% CI) using the Stata's *punaf* command (6). All analyses were conducted using STATA, Version 11·2 (Stata Corporation, College Station, TX, USA).

The study protocol was approved by the National Mozambican Ethics Committee and written informed consent was obtained from all participants or their relatives.

Results

Two-fifths of the ischaemic events occurred in subjects aged above 64 years, while the haemorrhagic strokes (HS) were observed predominantly in the age group 45–54 years (35·7%). The distribution of major cardiovascular risk factors was similar in both stroke sub-types, with hypertension being the most frequently reported. Approximately 40% of ischaemic and 55% of HS patients had a Glasgow score at admission below 11. During hospitalization (median hospital stay: 6·0 days; interquartile range: 3·0–9·0), DVT or other cardiovascular complications and pneumonia affected approximately 5% of the ischaemic stroke (IS) patients and three times more subjects with an haemorrhagic event (Table S1).

From the 651 patients admitted, 217 died during hospital admission and 277 were dead 28 days after the event generating an overall in-hospital CFR of 33·3% (19·0% for ischaemic and 48·3% for HS events) and a 28-day CFR of 39·6% (26·6% for ischaemic and 52·6% for HS events).

Socio-demographic characteristics, pre-stroke morbidity, and pre-stroke disability were not significantly associated with in-hospital mortality, either among ischaemic or HS events. In-hospital mortality was higher among patients arriving at the hospital more than 15 days after an ischaemic event (RR = 4·56, 95% CI 1·05 to 19·74), having a Glasgow score at admission ≤6 (more than fivefold) or needing CPR during hospitalization (approximately 2·5-fold). Complications during hospitalization were associated with more than twofold higher in-hospital mortality, regardless of stroke sub-type (Table 1).

Table 2 depicts the results regarding the determinants of 28-day mortality. Among patients with an ischaemic event, the risk of death was nearly 60% lower in subjects with higher formal education than in the less educated. Patients with moderate disability prior to an ischaemic event had an approximately twofold higher risk of death when compared with those with minimal or no disability. The magnitude of the associations between the time until presentation in a hospital and markers of stroke severity and 28-day mortality were similar to the observed for in-hospital mortality. Complications during hospitalization were also significantly associated with higher mortality.

Regarding systolic blood pressure (SBP), the lowest risk of in-hospital death for ischaemic events was observed at 161–200 mmHg of SBP (RR = 0·32, 95% CI 0·13 to 0·78, in comparison with SBP 121–140 mmHg). For HS, the association between SBP and early case-fatality was *U*-shaped, with the lowest risk observed for 121–140 mmHg. Among haemorrhagic events, SBP over 200 mmHg was associated with a significantly higher 28-day mortality (HR = 3·42, 95% CI 1·02 to 11·51) (Figure 1).

For diastolic blood pressure (DBP), there was also a *U*-shaped relationship with early case-fatality, only among ischaemic events. When compared to DBP 61–90 mmHg, the lowest risk was observed for DBP 121–150 mmHg (in-hospital: RR = 0·48, 95% CI 0·16 to 1·44; 28-day: HR = 0·44, 95% CI 0·17 to 1·19); for HS events, the risk of in-hospital and 28-day mortality was higher when DBP was 121–150 mmHg, although not significantly (Figure 2).

Altogether, in-hospital complications were responsible for 12·0% and 14·1% of in-hospital deaths among ischaemic and HS patients, respectively. Regarding 28-day mortality, 19·5% of IS deaths and 16·3% of those observed among HS patients were attributable to in-hospital complications (Table 3).

Discussion

Early case-fatality among stroke patients in Maputo was mostly influenced by stroke severity, blood pressure at admission and complications during hospitalization. The latter were responsible for almost 20% of IS deaths and 16% of HS deaths at 28 days.

The data obtained in this study contributes to understand the burden of stroke in low-income settings, where there is little prospective information regarding stroke epidemiology, and scarce health resources are expected to contribute to poor stroke outcomes (7). Previous evidence from Mozambique suggests that this country is in an early stage of epidemiological transition with stroke occurring at early ages and with a high proportion of HS events, even when compared with other less developed countries (1). A systematic review conducted by Connor *et al.* (8) found six prospective studies addressing stroke case-fatality in Sub-Saharan Africa. We additionally identified four prospective studies [one in Nigeria (9), one in Tanzania (10), one in Congo (11), and one in Gambia (12)] that analyzed early CFR in the African context. Stroke diagnosis was based on verbal autopsies or clinical diagnosis with no distinction of stroke sub-type in many of the previous reports (8–10,12). These studies had a global stroke CFR one-month after the event ranging between 23·8% and 44% which encompasses our estimates for Maputo. In our study, because more than 90% of the stroke patients performed either CT scan or autopsy, we were able to accurately classify patients according to stroke sub-type which is an important determinant of stroke prognosis, adding robustness to previous information. Among the studies described earlier, only four addressed mortality determinants in the African setting (7,9,11,12). Also, we successfully followed the STEPS stroke methodology, analyzing a large number of events which contributes to good precision of the estimates and achieved a 28-day follow-up for 95% of the patients. However, some limitations need to be addressed regarding methodological constraints. Our study is based on step 1 of the STEPS stroke protocol which only comprises a 28-day follow-up, and, therefore, the results do not reflect longer-term prognosis. Nevertheless, early case-fatality is very high in low-income

Table 1 Determinants of in-hospital case-fatality, according to stroke sub-type

	Ischaemic stroke events		Haemorrhagic stroke events	
	CFR* (%)	Adjusted RR† (95% CI)	CFR* (%)	Adjusted RR† (95% CI)
Socio-demographic characteristics				
Age group (years)				
<44	18·9	1·49 (0·59 to 3·77)	47·5	1·11 (0·61 to 2·03)
45–54	14·0	1	42·2	1
55–64	24·3	1·78 (0·87 to 3·67)	52·3	1·24 (0·76 to 2·00)
≥65	19·7	1·38 (0·71 to 2·68)	50·0	1·19 (0·68 to 2·08)
Sex				
Female	17·5	1	48·6	1
Male	20·6	1·42 (0·83 to 2·43)	48·1	0·98 (0·65 to 1·48)
Education (years)				
None	21·2	1	48·4	1
1–4	14·9	0·62 (0·32 to 1·21)	46·8	0·97 (0·59 to 1·62)
5	13·8	0·51 (0·21 to 1·23)	50·0	1·04 (0·56 to 1·94)
≥6	13·9	0·48 (0·17 to 1·39)	48·6	1·03 (0·52 to 2·02)
Pre-stroke morbidity				
Diabetes	23·2	1·34 (0·72 to 2·50)	69·6	1·62 (0·94 to 2·78)
Hypertension	18·4	0·74 (0·36 to 1·51)	46·4	0·92 (0·37 to 2·31)
High serum cholesterol	22·9	1·45 (0·74 to 2·83)	51·8	1·16 (0·65 to 2·06)
Atrial fibrillation	20·7	1·05 (0·44 to 2·48)	100·0	2·16 (0·78 to 6·00)
Current smoking	6·4	0·35 (0·08 to 1·47)	52·4	1·10 (0·58 to 2·08)
Pre-stroke disability				
Modified Rankin scale score				
0–2 (minimal/no)	18·2	1	48·1	1
3 (moderate)	25·0	1·55 (0·55 to 4·31)	100·0	2·02 (0·49 to 8·38)
4 (moderate-severe)	42·9	2·31 (0·71 to 7·52)	33·3	0·72 (0·10 to 5·26)
5 (severe)	0·0	–	0·0	–
Time to presentation				
Day of symptoms onset	16·4	1	52·6	1
1 day after stroke	18·4	0·99 (0·51 to 1·89)	33·3	0·64 (0·38 to 1·07)
2–7 days after stroke	21·2	1·25 (0·68 to 2·30)	37·5	0·71 (0·31 to 1·64)
8–14 days after stroke	33·3	1·69 (0·64 to 4·45)	100·0	1·91 (0·70 to 5·26)
≥15 days after stroke	66·7	4·66 (1·08 to 20·16)	0·0	–
Clinical features at admission and during hospitalization				
Glasgow at admission				
11–15	9·6	1	10·0	1
6–10	47·9	4·94 (2·26 to 10·82)	69·1	7·19 (3·01 to 17·18)
3–5	63·6	5·82 (2·12 to 15·96)	100·0	11·18 (4·39 to 28·52)
CPR during hospitalization	40·3	2·39 (1·40 to 4·06)	74·3	2·58 (1·75 to 3·80)
Complications during hospitalization				
Pneumonia	71·4	3·62 (1·79 to 7·30)	85·7	2·02 (1·28 to 3·19)
DVT and other CV complications	80·0	2·96 (1·02 to 8·61)	100·0	2·28 (1·20 to 4·33)

*Case-fatality rate, expressed as % of deaths at discharge.
†Adjusted for age (<44, 45–54, 55–64, >65 years), sex, and education (0, 1–4, 5, ≥6 years of schooling).
CFR, case-fatality rate; CI, confidence interval; CV, cardiovascular; DVT, deep vein thrombosis; RR, relative risk.

countries, and our results generate information on stroke mortality that identifies the need for changes in the outcome of stroke through the implementation of measures to improve acute management and prevention of complications (12–14). Another limitation is the fact that information on the presence of risk factors, namely dyslipidaemia, diabetes, and hypertension, was mostly self-reported which could have led to information bias, with a magnitude and direction that are difficult to predict. The fact that hypertension and diabetes were assessed through a combination of self-report of a previous diagnosis, reporting by a next-of-kin, pharmacological treatment with anti-hypertensive or anti-diabetic drugs, and information collected during hospital admission may have minimized bias. Unfortunately, the information on dyslipidaemia was exclusively self-reported and misclassification may have occurred. Finally, blood pressure and Glasgow score at admission were only available for a sub-sample, but missing data are due to design constraints and were not determined by the characteristics of the participants or the events; therefore, this is not expected to induce bias and the sub-sample was large enough to yield precise estimates.

Our results are in accordance with a previous systematic review of 36 studies that showed no relation between sex and overall CFRs (15). However, the lower mortality observed in individuals aged over 65 years when compared to those aged 55–64 is in contrast with previous studies that consistently associated older age with higher case-fatality (15,16). We may hypothesize that this

Table 2 Determinants of 28-day mortality according to stroke sub-type

	Ischaemic stroke events		Haemorrhagic stroke events	
	CFR* (%)	Adjusted HR† (95% CI)	CFR* (%)	Adjusted HR† (95% CI)
Socio-demographic characteristics				
Age group (years)				
<44	19·1	0·97 (0·41 to 2·33)	53·6	1·39 (0·78 to 2·49)
45–54	20·8	1	44·5	1
55–64	28·4	1·52 (0·81 to 2·85)	56·0	1·41 (0·88 to 2·26)
>65	31·2	1·48 (0·86 to 2·56)	56·1	1·33 (0·78 to 2·28)
Sex				
Female	25·4	1	53·8	1
Male	27·7	1·54 (0·98 to 2·43)	51·6	1·01 (0·68 to 1·52)
Education (years)				
None	34·6	1	54·2	1
1–4	19·2	0·45 (0·26 to 0·79)	53·9	0·93 (0·57 to 1·53)
5	19·1	0·44 (0·21 to 0·90)	50·0	0·86 (0·46 to 1·60)
≥6	19·4	0·41 (0·17 to 0·97)	51·4	0·80 (0·41 to 1·58)
Pre-stroke morbidity				
Diabetes	40·1	1·89 (1·45 to 3·11)	70·2	1·59 (0·92 to 2·74)
Hypertension	27·0	1·04 (0·52 to 2·09)	51·0	1·09 (0·44 to 2·71)
High serum cholesterol	31·1	1·46 (0·83 to 2·59)	59·3	1·21 (0·70 to 2·10)
Atrial fibrillation	32·1	1·02 (0·50 to 2·08)	100·0	3·10 (1·12 to 8·59)
Current smoking	10·0	0·36 (0·11 to 1·45)	53·2	1·06 (0·56 to 2·00)
Pre-stroke disability				
Modified Rankin scale score				
0–2 (minimal/no)	24·9	1	52·0	1
3 (moderate)	50·0	2·20 (1·05 to 4·59)	100·0	3·00 (0·70 to 12·88)
4 (moderate-severe)	42·9	2·13 (0·66 to 6·89)	66·7	1·23 (0·30 to 5·08)
5 (severe)	0·0	–	–	–
Time to presentation				
Day of symptoms onset	23·0	1	56·6	1
1 day after stroke	27·8	1·03 (0·60 to 1·77)	40·0	0·60 (0·37 to 0·98)
2–7 days after stroke	30·5	1·38 (0·82 to 2·31)	37·5	0·53 (0·23 to 1·24)
8–14 days after stroke	33·3	1·18 (0·46 to 3·06)	100·0	2·34 (0·84 to 6·54)
≥15 days after stroke	66·7	5·72 (1·31 to 24·94)	–	–
Clinical features at admission and during hospitalization				
Glasgow at admission				
11–15	14·0	1	15·5	1
6–10	54·7	5·75 (2·91 to 11·37)	74·6	8·44 (4·03 to 17·67)
3–5	90·9	12·08 (4·97 to 29·37)	100·0	33·88 (14·58 to 78·73)
CPR during hospitalization	51·4	2·90 (1·82 to 4·62)	75·2	3·62 (2·50 to 5·24)
Complications during hospitalization				
Pneumonia	71·4	3·89 (1·98 to 7·66)	85·7	2·04 (1·29 to 3·22)
DVT and other CV complications	100·0	7·09 (2·67 to 18·81)	100·0	3·37 (1·75 to 6·49)

*Case-fatality rate, calculated through Kaplan–Meier failure function.
†Adjusted for age (<44, 45–54, 55–64, >65 years), sex, and education (0, 1–4, 5, ≥6 years of schooling).
CFR, case-fatality rate; CI, confidence interval; CV, cardiovascular; DVT, Deep vein thrombosis; HR, hazard ratio.

Table 3 Impact of in-hospital complications on early case-fatality in stroke patients (population attributable fractions), according to stroke sub-type

	Population attributable fractions, % (95% CI)			
	Ischaemic stroke events		Haemorrhagic stroke events	
	In-hospital case-fatality	28-day case-fatality	In-hospital case-fatality	28-day case-fatality
DVT and other CV complications	2·7 (–3·6 to 8·7)	11·5 (–1·4 to 22·8)	4·9 (–1·2 to 10·6)	8·1 (0·2 to 15·3)
Pneumonia	10·4 (0·8 to 19·0)	13·1 (1·2 to 23·5)	10·2 (0·9 to 18·5)	9·1 (0·4 to 18·0)
DVT, other CV complications, and pneumonia	12·0 (2·1 to 21·7)	19·5 (5·3 to 31·7)	14·1 (4·3 to 22·9)	16·3 (6·1 to 25·3)

CI, confidence interval; CV, cardiovascular; DVT, deep vein thrombosis.

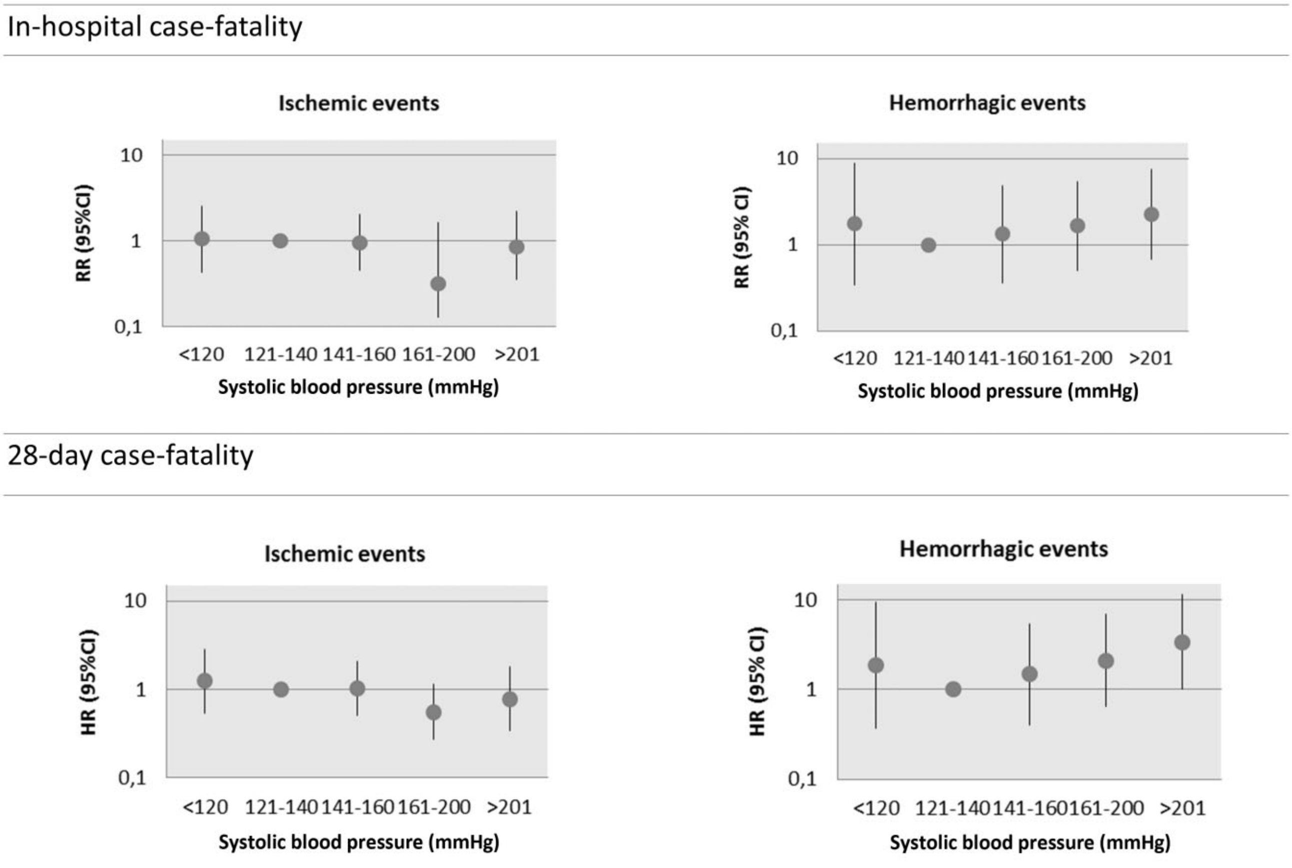

Fig. 1 Association between systolic blood pressure at admission and case-fatality, adjusted for age, sex, and education. Circles represent the point estimates of relative risk (RR) for in-hospital mortality and hazard ratio (HR) for 28-day mortality and vertical lines represent 95% confidence intervals (95% CI).

difference is due to higher resilience of older people in such a high mortality setting (17). Although medical care in public hospitals is free for people with scarce resources, post-discharge mortality depends on the availability of physical therapy and nursing homes, which are scarce in the public system (18). This may have accounted for lower 28-day mortality among the IS patients with higher formal education, which is a proxy for higher socio-economic status. Previous studies showed an increased mortality after stroke among patients with comorbidities such as diabetes, hypertension, or atrial fibrillation (16,19), which was not confirmed in our study, probably because patients with severe events were less likely to be able to report their comorbidities, thus erroneously diluting overall risk; also, stroke risk factors have more influence on longer-term CFR (19).

Delay in reaching a medical facility has proven to worsen the prognosis of stroke (20), although this evidence comes mostly from settings where thrombolysis is available. As in Mozambique many patients never reach a medical care facility (21), patients who present a relatively long time after symptom onset may have had stroke complications that led them to the hospital, therefore having a higher risk of death.

Both high and low blood pressures at hospital admission after a stroke event have been associated with a poorer outcome (22,23). The worse prognosis observed for extreme values of blood pressure is explained by the fact that elevated blood pressure increases early recurrence and death resulting from oedema and low blood pressure promotes ischaemia to the grey zones surrounding the affected areas by reduction of the blood flow to these areas (22). One study from Japan (23) has shown that, for ischaemic events, the relationship between SBP or DBP and stroke mortality was *U*-shaped, with the risk being higher for SBP below 120 mmHg. For haemorrhagic events, the relationship was *J*-shaped for SBP and *U*-shaped for DBP, with higher risk for higher blood pressure which is in accordance with our data. Results from the International Stroke Trial also showed a *U*-shaped relationship between SBP at baseline and early case-fatality (22).

Patients with lower Glasgow scores and needing CPR had more severe events and therefore higher CFRs, in accordance with previous evidence on the prognostic value of stroke severity markers (9,16).

Regarding the impact of in-hospital complications, a previous study, conducted in a well-equipped German hospital with a very low proportion of in-hospital deaths (4·9%), estimated an attributable fraction of death of 31·2% (95% CI, 30·9–31·5) for pneumonia (16). On the other hand, in one study conducted in Gambia (7), all in-hospital deaths were due to neurological complications of stroke itself, probably reflecting the fact that, in poor-resource countries, the lack of immediate specialized care has great impact on the outcome, leading to death before infec-

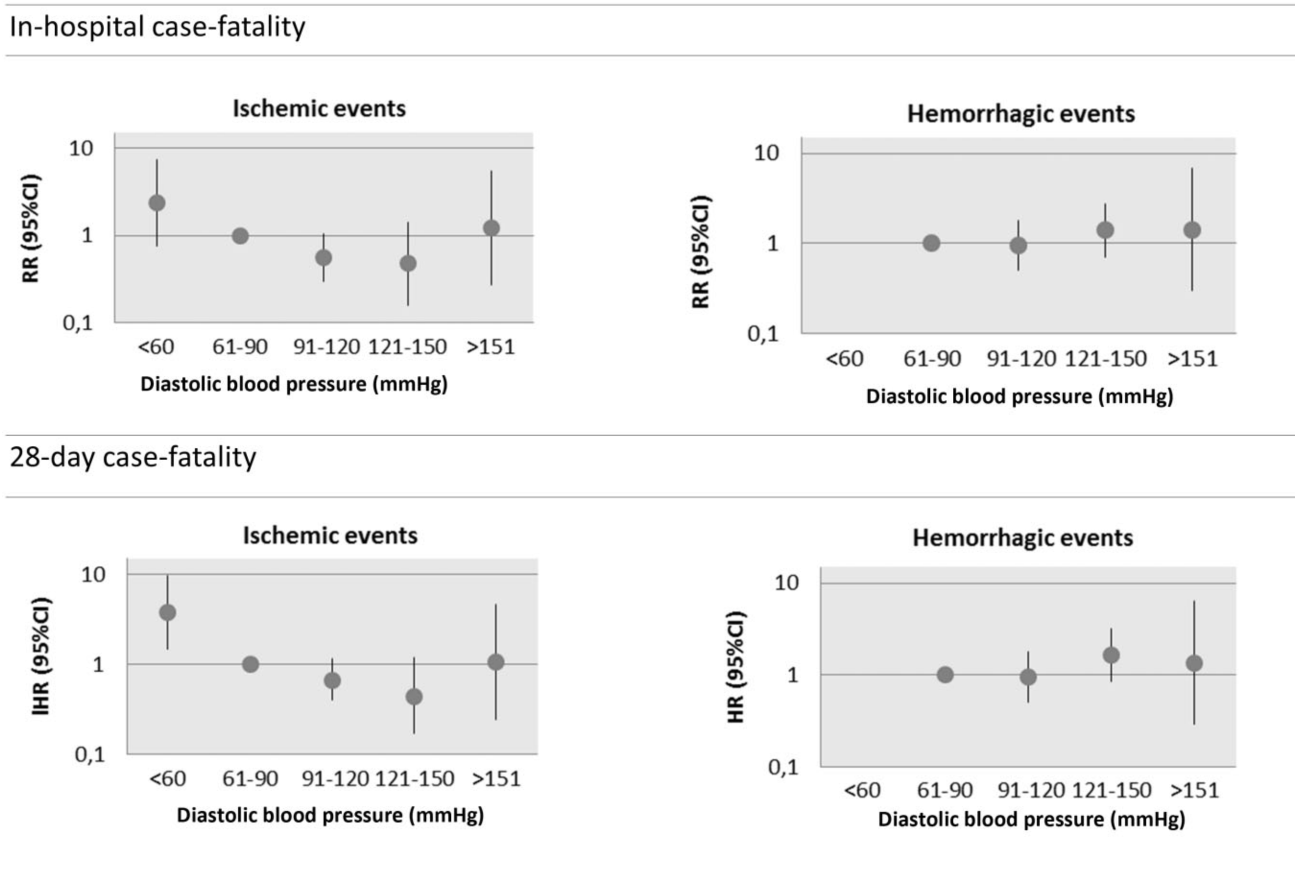

Fig. 2 Association between diastolic blood pressure at admission and case-fatality, adjusted for age, sex, and education. Circles represent the point estimates of relative risk (RR) for in-hospital mortality and hazard ratio (HR) for 28-day mortality and vertical lines represent 95% confidence intervals (95% CI).

tious complications occur. In Maputo, there are no stroke units and stroke patients receive care in a non-specialized medical ward with a very high patient/nurse ratio, although there is consistent evidence that acute stroke care in specialized stroke units diminishes mortality and reduces the incidence of medical complications (24).

Stroke risk factors tend to become more frequent as urbanization increases. High incidence and CFRs suggest that Maputo may strongly benefit from having an organized strategy for the management of acute stroke. Measures such as performing CT scans to all patients at admission, management of all cases in a stroke dedicated ward, early administration of aspirin to the confirmed ISs, effective management of blood pressure and treatment of infectious complications, and adequate prevention of DVT may lead to a decrease in stroke CFRs in this setting.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Pre-hospital profile, time to presentation, clinical features, and in-hospital complications, according to stroke sub-type.