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# Predictors of Early Cardiac Morbidity and Mortality After Ischemic Stroke

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**Background and Purpose**—In the first 3 months after acute ischemic stroke, 2% to 6% of patients die from cardiac causes. This may reflect preexisting cardiac disease, cardiac dysfunction related to the acute neurohumoral and autonomic stress response to stroke, or both. Delineation of a high-risk group could facilitate prevention strategies. We aimed to describe the temporal profile of cardiac risk after stroke and develop a predictive model of serious cardiac adverse events (SCAEs) using baseline variables.

**Methods**—We used data from the one trial in the Virtual International Stroke Trials Archive that matched prespecified criteria. Survival analysis was used to describe the temporal profile of cardiac events after stroke. Prognostic determinants were assessed with multivariable logistic regression, and a risk score was derived from the key predictor variables.

**Results**—Of 846 ischemic stroke patients, 35 (4.1%) died from cardiac causes and 161 (19.0%) suffered at least one SCAE. The hazard of cardiac death was highest (0.001/d) in the second week. Hazard of a first SCAE peaked at 0.02/d between day 2 and 3. The 5 factors most predictive of SCAEs were a history of heart failure (OR 3.33 [2.28, 4.89],  $P < 0.001$ ), diabetes (OR 2.11 [1.39, 3.21],  $P < 0.001$ ), baseline creatinine  $> 115 \mu\text{mol/L}$  (OR 1.77 [1.16, 2.70],  $P = 0.008$ ), severe stroke (OR 1.98 [1.34, 2.91],  $P = 0.001$ ), and a long QTc or ventricular extrasystoles on ECG (OR 1.93 [1.31, 2.85],  $P = 0.001$ ). Risk of SCAEs ranged from 6.3% (no predictors) to 62.2% ( $\geq 4$  predictors).

**Conclusion**—Serious cardiac events are common in the acute period after stroke. Patients at highest risk are identifiable and may benefit from more aggressive strategies to improve survival. (*Stroke*. 2007;38:2295-2302.)

**Key Words:** cardiovascular disease ■ electrocardiography ■ ischemic ■ prognosis ■ risk factors ■ stroke

Most deaths after ischemic stroke can be directly attributed to the initial neurologic injury. However, approximately 2 to 6% of all stroke patients die from cardiac causes in the first 3 months after ischemic stroke.<sup>1,2</sup> After the acute period, cardiac risk declines but remains higher than for age-matched controls. A recent meta-analysis estimated an annual rate of myocardial infarction (MI) and nonstroke vascular death in stroke patients of 2.2% and 2.1%, respectively.<sup>3</sup> Despite these relatively high risks, many patients will not have cardiac events. An approach to identifying patients at high risk of cardiac events is required to assess potential preemptive strategies, including monitoring, investigation, and treatment. Such strategies have received scant attention to date.

Cardiac risk in acute stroke populations is likely to be linked to the prevalence of ischemic heart disease (IHD) and other comorbidities. More recently evidence has emerged that cerebrogenic autonomic and neurohumoral dysregulation af-

ter stroke may contribute to cardiac morbidity and mortality, but the relative importance of this to overall cardiovascular risk is uncertain.<sup>4</sup>

The aims of this study were first to describe the temporal profile of cardiac mortality and morbidity within the first 3 months after stroke to determine the magnitude and time course of the risk. Secondly we sought to identify patient characteristics associated with an increased risk of cardiac events during this period using simple demographic and clinical variables available at the time of admission. We aimed to use these predictive characteristics to derive a simple score which could be used in a clinical setting to stratify patients according to risk.

## Materials and Methods

### Subjects

The Virtual International Stroke Trials Archive (VISTA) is a collaborative venture undertaking the collation and standardization

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of data from multiple clinical trials (21 as of July 2006) in an academic database.<sup>5</sup> VISTA aims to facilitate analysis of the natural history of subgroups of stroke patients with the ultimate aim of improving clinical trial design. We searched VISTA for any trials which met the following prespecified criteria: (1) comprehensive data on patient demographics, history, and baseline physiology, (2) quantitative and qualitative ECG data at baseline, (3) documentation of cardiac adverse events (including death), and (4) complete follow-up. Only 1 trial (conducted in Europe and North America in 1996 to 1997) fulfilled these criteria.<sup>6</sup> We used patients from the placebo group only (n=846), because of the potential cardiac effects of the study drug.

Inclusion criteria were a clinical diagnosis of ischemic stroke (supported by CT brain scan), stroke severity measured by the European Stroke Scale (ESS) of <70 at baseline (range 0 to 100, the lower the score, the worse the neurologic deficit),<sup>7</sup> and commencement of drug/placebo within 8 hours of stroke onset. Significant relevant exclusions included serious ventricular arrhythmia at baseline, 2<sup>nd</sup>/3<sup>rd</sup> degree atrioventricular block, (uncorrected) baseline QT interval >450ms, acute or uncompensated heart failure, or acute myocardial infarction within the preceding 6 weeks. All patients were followed until death or the end of week 12.

Detailed demographic and historical information was collected at enrolment, including medication use and preexisting conditions (including diabetes, hypertension, hyperlipidemia, congestive heart failure (CHF), ischemic heart disease (IHD), previous acute myocardial infarction (AMI), and previous stroke or transient ischemic attack). Designation of comorbidities was at the discretion of local investigators. Baseline clinical measures included blood pressure, heart rate, stroke severity, and routine biochemistry (including electrolytes, total cholesterol, and creatinine). ECGs were performed at baseline, baseline +1 hour, and day five, and were centrally analyzed according to predetermined quantitative and qualitative parameters (Table 2). Bazett's formula was used to correct the QT interval for heart rate.

The (placebo) patients received a continuous infusion of normal saline solution of 120 mL (total) over 5 days, in addition to usual fluids.

### Definition of Outcomes

For this study we were interested in 2 outcome variables (which were determined by local investigators).

#### Cardiac Mortality

Cause of death was divided into 4 categories: neurologic (deaths attributable to stroke progression, hemorrhagic transformation, brain edema, raised intracranial pressure, herniation), cardiac (acute myocardial infarction [AMI], congestive heart failure [CH], ventricular tachycardia/fibrillation [VT/VF] or other arrhythmia, and cardiac arrest), pneumonia/infection and other (a heterogeneous group including recurrent stroke, pulmonary embolism, systemic hemorrhage, and other miscellaneous causes).

#### Serious Cardiac Adverse Events

This was a composite end point defined as a nonfatal episode of VT, VF, AMI, pulmonary edema/moderate-severe cardiac failure, or cardiac death, as defined above (to include all the patients who died from cardiac causes). For the purposes of survival analysis, the time to the first event was analyzed if a patient experienced more than one.

### Statistical Analysis

Statistical analysis was performed with Stata 8.0 (Stata Corp). Survival analysis techniques were used to model time to death for each cause of death. All patients who did not die were followed-up for the entire 12-week study period. Mortality from each cause was compared using a competing risk 'marginal probability'<sup>8</sup> model and the data represented graphically in terms of the hazard function. A marginal probability approach was used, given that death from one cause could not be presumed independent of factors that were also prognostic of death from other causes. However, results and conclu-

**TABLE 1. Patient Characteristics**

	n/846	%
Male	414	48.9
Caucasian	774	91.5
Age in years (median, range)	73 (22, 96)	
Right handed	801	95.8
Right hemisphere stroke	434	51.3
ESS score (median, range)	42 (8,76)	
Dead at day 84	180	21.3
Atrial fibrillation	267	31.5
Ischemic heart disease	388	44.7
Congestive heart failure	250	28.5
Diabetes mellitus	195	23.1

sions were similar when the data were analyzed using either a conditional probability or Kaplan–Meier function ie, where patients dying from other causes were treated as 'censored'.

### Definition of Predictor Variables

To explore factors associated with nonfatal and fatal cardiac events, each patient was allocated a binary code for 'serious cardiac adverse event' (SCAE, if they experienced a serious cardiac adverse event at any time during the study period). The data were analyzed using a multivariable binary logistic regression model. We elected to model events as a binary rather than time-to-event measure, for 2 reasons: (1) because of the potential difficulty of handling competing risks in the context of Cox regression, as described above, and (2) to simplify the development of a risk score to identify high- and low-risk patients.

Initial exploratory analysis was performed to check modeling assumptions and select variables for a multivariable model. Only factors (demographic, historic, and clinical) which have been demonstrated to affect cardiac or stroke outcomes (or could reasonably be expected to, based on current knowledge) were tested, to limit the likelihood of chance associations. The factors included age, sex, preexisting comorbidities, stroke severity, affected hemisphere, baseline systolic blood pressure, creatinine, total cholesterol, baseline ECG parameters, and treatment at the time of enrolment with beta blockers or lipid lowering agents (Table 2).

Cardiac risk appeared to increase above age 75, but remained constant below that. Hence, age was dichotomized at 75 for the purpose of subsequent analysis. Baseline systolic blood pressure (sBP) was also dichotomized at 110 mm Hg, as lower values were associated with progressively greater risk but higher values were not. Stroke severity (ESS) was examined as a continuous variable for the initial regression analysis as risk of SCAEs appeared to increase progressively over the range of ESS values. Plasma creatinine and QTc interval were dichotomised about conventionally accepted upper limits of the normal range for each.

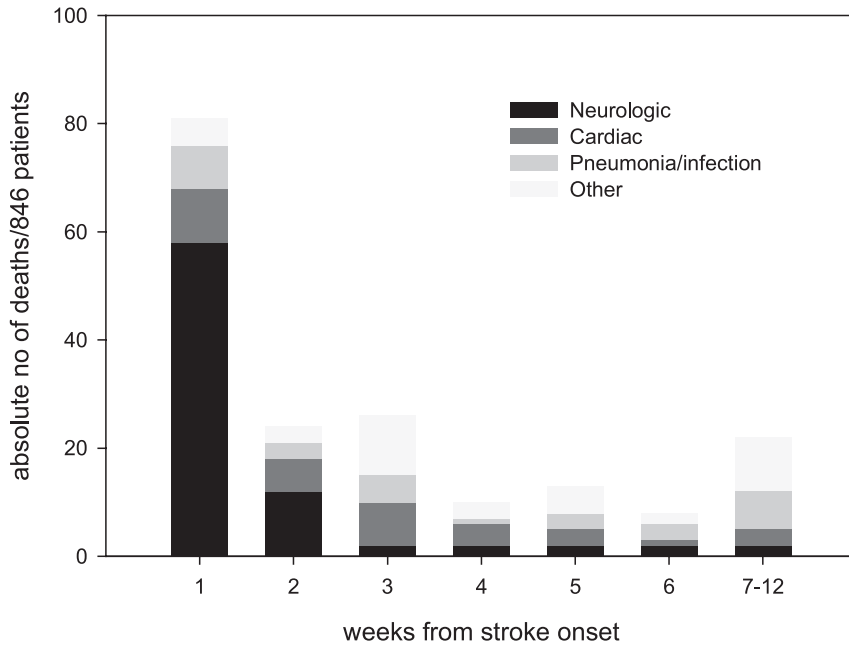
The risk of a first SCAE was determined in relation to each variable by univariate logistic regression. Variables with a probability value <0.2 were included in a multivariable regression model using forward and backward stepwise selection. Modeling assumptions and fit were checked and found to be adequate. Associations are presented as odds ratios (ORs) with 95% confidence intervals.

The variables found to be most highly predictive of SCAEs were then incorporated into a risk score. Patients were allocated 1 point for each predictor variable present, the overall predictive score being the sum. The test performance of the risk score to predict SCAEs and cardiac death was summarized in terms of sensitivity and specificity.

## Results

### Patient Characteristics

The 846 patients were largely caucasian. Despite the cardiac exclusion criteria, many patients had preexisting cardiac comorbidities. 180 (21.3%) were dead at 12 weeks (Table 1).



**Figure 1.** Frequency distribution of numbers of deaths and cause of death per week from stroke onset; weeks 7 to 12 have been compressed because of low absolute numbers.

**Temporal Profile of Cardiac Mortality and Morbidity**

**Cardiac Death**

Neurologic deaths (79/180, 43.9% of all deaths) predominated overall and were clustered in the first 2 weeks (Figure 1). However, cardiac deaths made up the second largest group (35/180, 19.4% of all deaths), with deaths from pneumonia/infection third (29/180, 16.1%), and other miscellaneous causes making up the last group (37/180, 20.6%).

The temporal profile of the hazard of cardiac death in relationship to the other causes of death is shown in Figure 2a. The rate of cardiac deaths was maximal around day 14. At that time, the hazard was 0.001 (ie, 1/1000 patients per day).

**Serious Cardiac Adverse Events**

161 patients (19.0%) experienced at least one SCAE. This group comprised 7 cardiac deaths not preceded by a nonfatal SCAE and 154 nonfatal SCAEs. Of these 154 patients, 28 subsequently died from a cardiac cause. Most SCAEs (128/161, 79.5%) occurred in patients with a history of IHD and/or CHF. The rate of first SCAEs peaked between day 2 and 3 (Figure 2b). At that time the hazard of a first SCAE was 0.02 (20/1000 patients per day), a rate 20 times higher than the peak rate of cardiac death. Thereafter the rate of first events declined.

Twelve-week mortality in the SCAE group was 74/161 (46.0%), compared with 21.3% mortality overall. In the SCAE group (apart from the 35 who died from cardiac causes), 18 died from neurologic causes and 20 from other causes.

**Predictive Model**

As the variables which predict cardiac death should be similar to those that predict SCAEs, we chose to build a predictive model based on the latter because of a larger n (161 versus 35), enabling the fitting of a multivariable model, and reduced dependence on potentially erroneous cause-of-death

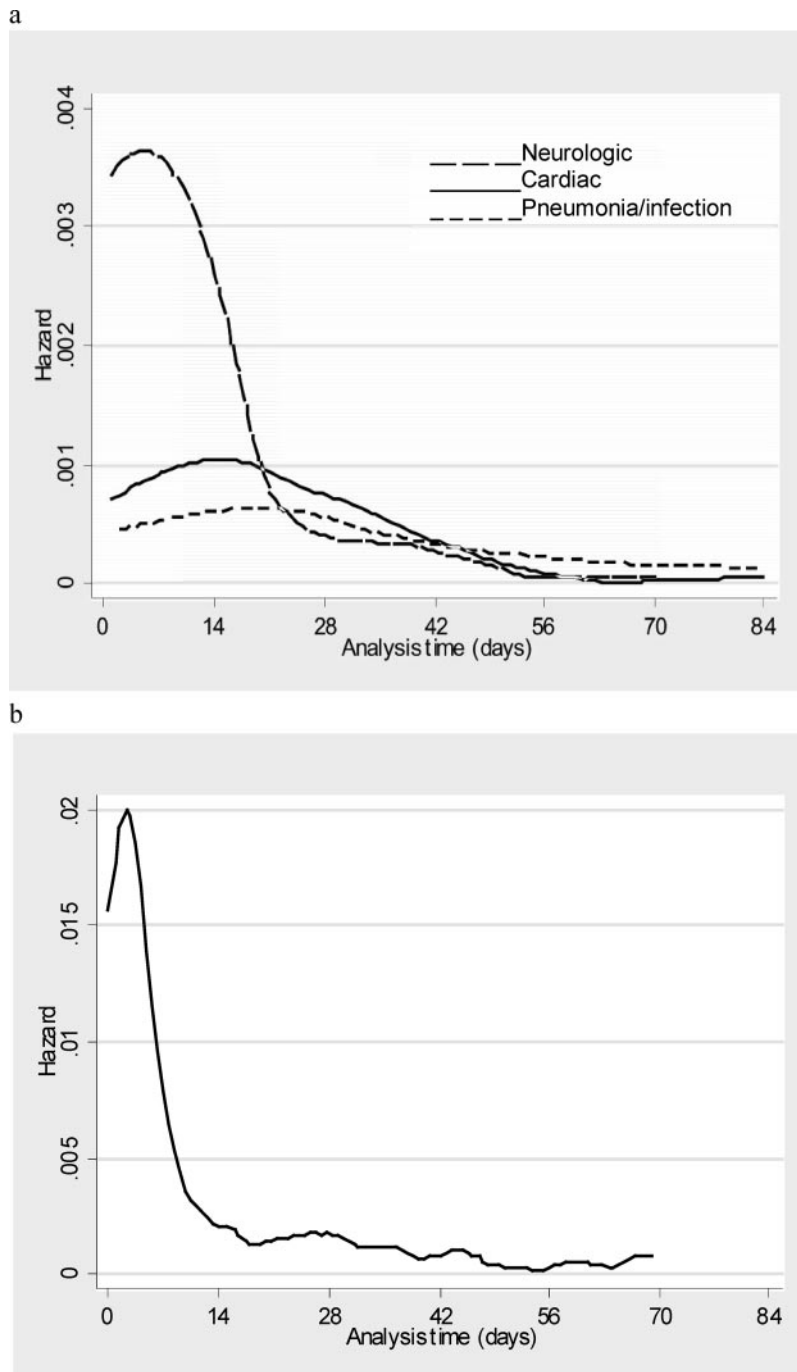
coding. The unadjusted ORs for each predictor variable are presented in Table 2. Increasing serum cholesterol was associated with a reduced risk of SCAEs. Given lack of biological plausibility for this finding, and the possibility of confounding by an unmeasured variable, we chose not to include it in the multivariable model.

The 9 variables in the final model included age >75 years, preexisting diabetes, CHF and hypertension, increasing stroke severity, baseline creatinine  $\geq 115\mu\text{mol/L}$ , baseline systolic BP  $\leq 110$  mm Hg, prolonged baseline QTc (>450ms for males, >470ms for females), and presence of ventricular premature beats on baseline ECG. An ROC curve derived directly from the 9 variable logistic regression equation is shown in Figure 3a. Atrial fibrillation, prior stroke, and IHD were significant univariate predictors of SCAEs, as were ECG parameters of increasing heart rate, prolonged QRS, and left ventricular hypertrophy, but they failed to add any additional explanatory power to the predictive model. Sex, affected hemisphere, treatment with lipid lowering agents and beta blockers at the time of stroke, and other ECG parameters were not predictive.

In an exploratory analysis, we also tested the influence of hemispheric lateralization on the baseline ECG parameters. Prolonged QTc interval was the only ECG parameter associated with any hemispheric lateralization. Prolonged QTc interval was associated with left hemisphere stroke (OR 1.58 [1.14, 2.17]  $P=0.005$ ), independent of age, sex, and history of IHD or CHF.

**Risk Score for Prediction of SCAEs**

To devise a simple risk score for prediction of cardiac events, we needed to refine the predictive model down to a handful of key variables, allocate a score for each, and assess test performance with sensitivity and specificity. For simplicity, the 2 ECG parameters were collapsed to a single category ('high risk ECG' = prolonged QTc or presence of VPBs). As the ESS is no longer in widespread use, stroke severity was



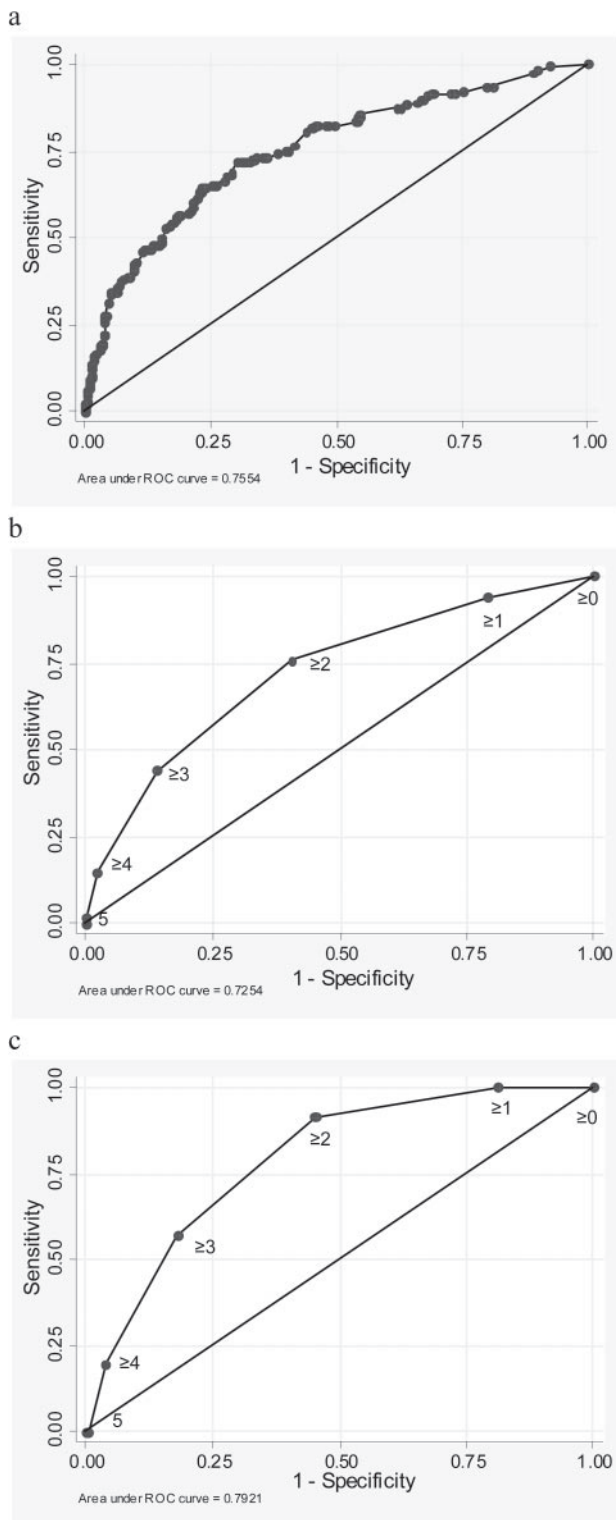
**Figure 2.** a, Hazard (or hazard rate) per day (marginal probability approach) for each cause of death category. The hazard here corresponds to the observed instantaneous rate of death, from each cause, at any given time. b, Hazard (or hazard rate) per day (marginal probability approach) for first serious cardiac adverse event (SCAE).

simply dichotomised about the median ESS score, dividing the cohort arbitrarily into 'moderate' and 'severe' strokes (mild strokes (ESS >70) were excluded at the outset).

We then repeated the multivariable analysis but restricted the final model (by backward stepwise selection) to variables with adjusted probability values of <0.01. The 5 remaining key predictor variables were CHF (OR 3.33 [2.28, 4.89]  $P<0.001$ ), creatinine  $>115\mu\text{mol/L}$  (OR 1.77 [1.16, 2.70]  $P=0.008$ ), diabetes (OR 2.11 [1.39, 3.21]  $P<0.001$ ), severe stroke/ESS <42 (OR 1.98 [1.34, 2.91]  $P=0.001$ ), and a high risk ECG (OR 1.93 [1.31, 2.85]  $P=0.001$ ). Each factor was allocated a value of 0 (absent) or 1 (present), giving each patient a total cardiac risk score between 0 and 5.

Table 3 shows the risk of SCAE and cardiac death stratified according to the score. Risk of at least 1 SCAE ranged from 6.3% (no predictors) to 62.2% ( $\geq 4$  predictors). Risk of cardiac death ranged from 0% (no predictors) to 18.9% ( $\geq 4$  predictors).

Sensitivity and specificity data are summarized in ROC curves (Figure 3, b and c). The area under the ROC curve (AUC) for the simplified 5 variable model was 0.73 for prediction of at least 1 SCAE and 0.79 for prediction of cardiac death, compared with 0.76 for the ROC curve derived directly from the full model. This indicates very similar predictive power despite considerable simplification of the model. At higher cutoffs, the score was very specific but not sensitive. For example, a score of  $\geq 3$  predicted at least 1



**Figure 3.** ROC curves. a, ROC curve for prediction of SCAEs derived from the full 9 variable logistic regression model. AUC 0.76 [0.71 to 0.80]. b, ROC curve for prediction of SCAEs derived from the simplified 5 variable risk score; score cut points are marked on the curve. AUC 0.73 [0.68 to 0.77]. c, ROC curve for prediction of cardiac death derived from the simplified 5 variable risk score; score cut points are marked on the curve. AUC 0.79 [0.73 to 0.85].

SCAE with a specificity of 86.0% and sensitivity of 44.1%, and cardiac death with a specificity of 82.0% and sensitivity of 57.1%.

## Discussion

This is the first large scale study to examine the temporal profile and predictive factors for cardiac mortality and morbidity in the acute phase after ischemic stroke. The main points that emerge from our study are that serious cardiac adverse events are common and begin to occur very early after stroke onset. Furthermore, cardiac risk can be stratified with a 5 point risk score derived from simple clinical and demographic variables available at the time of admission.

We found that cardiac mortality is the second commonest cause of death in this acute stroke population, second only to neurologic deaths as a direct result of the incident stroke. The cardiac death rate is higher in the first 4 weeks after stroke, then gradually declines. Most cardiac deaths were preceded by at least 1 nonfatal SCAE, which are very common, with a peak in the rate of first SCAE between day 2 and day 3. This temporal peak may reflect the physiological consequences of an acute stress response. It is consistent with published studies of biomarkers of the acute stress response, such as elevation of serum catecholamines, pathological elevation of nocturnal blood pressure, and cardiac enzymes.<sup>9,10</sup> We cannot however rule out that some of the cardiac events were iatrogenic, or sequelae of the (cardiac) cause of the incident stroke, or chance occurrences in patients with established heart disease. The occurrence of an SCAE was nonetheless a poor overall prognostic indicator, with a case fatality rate in these patients more than twice as high as the general study population (46% versus 21%).

None of the variables found to be predictive of SCAEs in the final model were unexpected. Both diabetes and elevated creatinine have been shown to predict recurrent coronary events and stroke in populations with established IHD.<sup>11</sup> Regarding stroke severity, patients with preexisting heart disease (in particular, atrial fibrillation) have been shown to have larger, more severe strokes.<sup>12</sup> Severe strokes are also associated with a more pronounced inflammatory and metabolic stress response, with potentially more severe cardiac and autonomic derangement.<sup>13</sup>

It is not surprising that the prevalence of preexisting cardiac disease in acute stroke patients influences the risk of cardiac events. Typically the prevalence of symptomatic IHD in acute stroke studies is 20% to 30%.<sup>2</sup> Asymptomatic IHD is also common, with small studies suggesting that up to 40% of stroke patients without overt IHD may have evidence of silent myocardial ischemia.<sup>14</sup> A history of ischemic heart disease and heart failure were strong univariate predictor of SCAEs, but IHD failed to independently predict SCAEs in the multivariable model (an effect partially explained by some correlation between CHF and IHD). This suggests that in the acute stroke setting left ventricular dysfunction is a critical determinant of early cardiac risk. It is also possible that the burden of risk from IHD is underestimated if only patients with symptomatic IHD are considered. The lack of effect of atrial fibrillation in the multivariable model was almost entirely explained by correlation with CHF.

**TABLE 2. Predictors of SCAEs**

Covariate	Prev (%) or mean, SD	Univariate Analysis		Multivariable Analysis (n=800)	
		OR [95%CI]	P	OR [95%CI]	P
<b>Demographic variables</b>					
Age >75 years	41.5	1.61 [1.14, 2.27]	0.007	1.51 [1.02, 2.25]	0.040
Male sex	48.9	1.14 [0.81, 1.60]	0.461		
<b>Preexisting comorbidities</b>					
Diabetes	23.1	1.95 [1.34, 2.84]	0.001	2.13 [1.39, 3.27]	0.001
CHF	28.5	3.77 [2.64, 5.38]	<0.001	3.07 [2.08, 4.53]	<0.001
Hypertension	63.5	1.74 [1.19, 2.55]	0.004	1.60 [1.04, 2.46]	0.033
IHD	44.7	2.33 [1.64, 3.32]	<0.001		
Prior stroke	35.9	1.48 [1.05, 2.10]	0.023		
Atrial fibrillation	31.5	1.97 [1.38, 2.80]	<0.001		
<b>Stroke characteristics</b>					
Stroke severity	42.2, 16.8	1.19 [1.07, 1.32]*	0.001	1.16 [1.03, 1.30]*	0.014
Left hemisphere (vs right)	48.7	1.12 [0.79, 1.57]	0.529		
<b>Physiologic parameters</b>					
Sys BP $\leq$ 110mmHg	3.3	2.88 [1.32, 6.29]	0.008	3.22 [1.31, 7.95]	0.011
Creatinine >115 $\mu$ mol/L	21.3	2.07 [1.40, 3.07]	<0.001	1.67 [1.09, 2.57]	0.019
Cholesterol, mmol/L	5.5, 1.3	0.79 [0.69, 0.91]	0.001		
<b>Baseline ECG characteristics</b>					
Heart rate, bpm	81.2, 17.8	1.14 [1.04, 1.25]†	0.005		
PR duration, ms	173.7, 38.5	1.01 [0.96, 1.07]‡	0.613		
QRS duration, ms	94.9, 24.1	1.14 [1.06, 1.21]‡	<0.001		
QT duration, ms	377.1, 45.4	1.00 [0.97, 1.04]‡	0.24		
Long QTc duration§	23.5	1.88 [1.29, 2.73]	0.001	1.64 [1.07, 2.51]	0.023
L bundle branch block	6.0	1.85 [0.99, 3.47]	0.055		
R bundle branch block	7.2	1.29 [0.69, 2.41]	0.419		
Atrial fibrillation	22.8	1.41 [0.95, 2.08]	0.085		
Ventricular premature beats	6.3	3.06 [1.71, 5.47]	<0.001	3.05 [1.60, 5.81]	0.001
Supraventricular premature beats	3.2	1.22 [0.49, 3.08]	0.668		
Abnormal repolarization	4.4	0.99 [0.43, 2.30]	0.986		
Left ventricular hypertrophy	13.8	1.52 [1.02, 2.26]	0.038		
Old myocardial infarction	16.1	1.40 [0.90, 2.18]	0.133		
<b>Medications at baseline</b>					
Beta blockers	15.0	0.82 [0.50, 1.36]	0.438		
Lipid lowering agents	4.9	0.87 [0.38, 2.00]	0.744		

\*per 10 units decrease; †per 10 bpm; ‡per 10 ms; §&gt;450 ms for males, &gt;470 ms for females.

Early hypertension (sBP >220 mm Hg) and hypotension (sBP <150 mm Hg) have been identified as predictors of death within 90 days in previous studies of acute ischemic stroke.<sup>15</sup> We found a history of treated hypertension and low baseline sBP (<110 mm Hg) predisposed to SCAEs, but there was no relationship between baseline elevated sBP and SCAEs. The effect of acute hypotension on all-cause mortality has been suggested to reflect impaired cerebral autoregulation and consequent poor perfusion of the ischemic brain.<sup>15</sup> We propose that at least part of the relationship between early hypotension and mortality is explained by its association with cardiac adverse events, and may reflect underlying left ventricular dysfunction.

The ECG variables most highly predictive of SCAEs were a prolonged QTc and presence of VPBs on baseline ECG. Both VPBs and prolonged QTc are potential substrates for lethal ventricular arrhythmias. QTc prolongation (measured 12 months after stroke) has been shown to predict cardiac death in stroke survivors<sup>16</sup> and correlates with left ventricular mass index and cardiac disease burden.<sup>17</sup> QTc interval may also be influenced by changes in autonomic tone brought about by cerebral infarction. We found a relationship between QTc prolongation and left hemisphere infarction, consistent with previous evidence linking left insular damage with increased basal sympathetic tone.<sup>18</sup> There was no evidence of lateralized hemispheric influence on the occurrence of



**TABLE 3. Twelve-Week Risk of a First SCAE and Cardiac Death According to Cardiac Risk Score (n is Reduced Due to Missing Data for Some Variables)**

Cardiac Risk Score	Patients (n=800)	SCAEs (n=152)	% Risk of SCAE	Cardiac Deaths (n=35)	% Risk of Cardiac Death
0	144	9	6.3	0	0
1	278	28	10.1	3	1.1
2	220	48	21.8	12	5.5
3	121	44	36.4	13	10.7
4 or 5	37	23	62.2	7	18.9

SCAEs, though we could not examine insular involvement directly. It has been suggested that stroke populations with IHD might be protected from the effect of (left) insular cortical ischemia because of 'ischemic preconditioning' of the heart or concomitant administration of cardioprotective drugs.<sup>4</sup>

We acknowledge some potential limitations of our data and its interpretation. We had no data on smoking status or baseline serum glucose and cannot assess their contributions as predictors or potential confounders. Stroke etiological subtype was also unavailable, and has been suggested as a predictor of cardiac outcomes after stroke by inference.<sup>19</sup> Definition and ascertainment of some predictor variables (specifically comorbidities) were left to the discretion of local investigators. Similarly, determination of outcomes for the current study (cardiac death and SCAEs) was based on local investigator opinion, and was not subject to review by an independent Endpoints Committee. Classification of cause of death after stroke is important but subject to great variability between investigators.<sup>20</sup> We anticipated this problem and built the multivariable model principally around the nonfatal SCAEs. However, inconsistencies in the measurement of these variables may have introduced bias.

As the model has been developed from a clinical trial population, it needs validation in a population-based cohort before it is incorporated into clinical practice. Our data may underestimate the risk of cardiac events, as in an unselected stroke population the underlying prevalence of heart disease and other comorbidities may be much higher. It is also probable that our risk model could be refined further. Short-term cardiac risk might be more directly assessed by measures of cardiac function in addition to the predictors we have identified. Insular cortical ischemia (and manifestations of the neurohumoral stress response such as elevated catecholamines and troponin) may predispose to cardiac events in acute stroke patients. Because of the large burden of cardiac disease in stroke patients (and as the vast majority of SCAEs in our cohort occurred in patients with a history of cardiac disease), it will be essential to assess the role of insular cortical ischemia in unselected stroke populations.

### Clinical Implications

Patients with a cardiac risk score of  $\geq 4$  were 10 times more likely to suffer an SCAE than those with a score of zero (62.2% versus 6.3%), whereas the risk of cardiac death ranged from zero (no risk factors) to 18.9% ( $\geq 4$  risk factors).

At higher cut points, the score was very specific but not sensitive, so using the score to divide patients accurately into one high and one low risk group is not possible. This provides a continuing rationale for pursuing general cardiac risk reduction strategies across the whole stroke population. However, because of its high specificity, the score could identify a patient group at very high cardiac risk who could be selected for trials of additional targeted prevention.

One potential preemptive strategy is cardiac monitoring to rapidly identify changes in cardiac rhythm before symptoms arise, though some authors have also suggested trials of beta blockers and even stellate ganglion blockade.<sup>21,22</sup> In published guidelines there is no consensus on which stroke patients most need cardiac monitoring and for how long it should be performed. The current AHA guidelines simply recommend "cardiac monitoring during the initial evaluation of patients with acute ischemic stroke" and the European Stroke Initiative guidelines suggest "on-line" ECG monitoring is desirable in stroke patients with a history of heart disease.<sup>23,24</sup> As we have demonstrated that the rate of first SCAEs continues to rise well into the third day after stroke, we argue that very high-risk patients should be monitored for at least 72 hours, and that the capability to provide continuous physiological monitoring should be offered in all stroke units.

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