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Heart failure on admission and the risk of stroke following acute myocardial infarction: the VALIANT registry

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KEYWORDS
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Aims We sought to assess the relative contribution of heart failure (HF) on admission for an acute myocardial infarction (MI) to the subsequent in-hospital stroke risk.
Methods and results The VALsartan In Acute myocardial iNfarcTion (VALIANT) registry enrolled 5573 consecutive MI patients at 84 international sites from 1999 to 2001. We calculated odds ratios (ORs) for stroke and adjusted for baseline characteristics, Killip Class, and risk factors for stroke, such as diabetes and prior HF.
In-hospital stroke occurred in 81 (1.5%) patients. HF was present on admission in 38% of patients who developed a stroke and in 24% who did not ($P = 0.001$). Older age (OR 1.03 increase/year, 95% confidence interval (CI) 1.01–1.04), Killip Class III (OR 1.66, CI 0.86–3.19) or IV (OR 4.85, CI 1.69–13.93), history of hypertension (OR 1.73, CI 1.06–2.82), and history of stroke (OR 1.89, CI 1.06–3.37) were more common in patients who had in-hospital stroke. In-hospital mortality in patients with and without stroke was 27.2 and 6.5%, respectively ($P < 0.001$).
Conclusion Patients with stroke after MI have a dismal prognosis. The presence of HF on admission for an acute MI increases in-hospital stroke risk. HF treatments may modify the risk of stroke.

Introduction

Stroke is an uncommon but devastating complication in patients with acute myocardial infarction (MI). Within the first month following an MI, between 1 and 2% of patients have a stroke,[1,2] and half of these post-MI strokes occur within the first week.[3] Stroke following an MI is associated with an early mortality approaching 50%.[4,5] The incidence of stroke varies with individual factors as well as the type and size of the MI. Generally, patients with larger and anterior MIs and patients with higher heart rate on admission have been shown to have a higher stroke risk following MI,[3,5,6] probably due to larger wall motion abnormalities pre-disposing to left ventricular thrombi formation and embolic strokes. Reduced left ventricular function is associated with long-term stroke risk following MI.[7]

Higher Killip Class assessed on admission for an MI is a predictor of post-MI mortality.[8] In contrast, the association of heart failure (HF) on presentation for an MI and the subsequent stroke risk in a broad MI population has not been systematically examined. A worse haemodynamic state with more HF symptoms has been reported more frequently in patients who experience a stroke following MI, both in patients enrolled in thrombolytic trials as well as in general MI populations.[3,9] Killip Class was shown to increase the risk of stroke (one-third of strokes were haemorrhagic) in one thrombolytic trial,[5] although it has not been shown to be an independent predictor of stroke following MI.[3] Reperfusion therapy increases the risk of haemorrhagic stroke, but at the same time decreases embolic stroke. Overall stroke rates are not altered by thrombolytic therapy. Even though stroke rates are lower in patients with non-ST-elevation acute coronary syndromes, stroke occurs nearly twice as often in those patients who also have in-hospital congestive HF.[6]

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In this study, we assessed the relative contribution of HF status on admission to the subsequent in-hospital stroke risk following an MI in a general MI-population that comprised patients with both ST- and non-ST-elevation MI treated with contemporary therapies.

Methods

Study population: the VALIANT registry

The VALIANT (VALsartan In Acute myocardial iNfarcTion) registry was an ancillary study to the VALIANT trial.[10] The VALIANT trial was designed to assess the efficacy of the angiotensin receptor blocker valsartan, the angiotensin-converting enzyme inhibitor captopril, and their combination in patients with an acute MI complicated by either clinical HF (Killip Class $\geq$II), left ventricular systolic dysfunction, or both.[10] The VALIANT registry was much more encompassing in that it was created to estimate the proportion of the general MI population to whom the VALIANT trial results would apply. In total, 5573 consecutive MI patients from 84 participating hospitals in nine countries (Argentina, Australia, Canada, Czech Republic, Germany, Italy, the Netherlands, New Zealand, and the United States) were included in the VALIANT registry between November 1999 and June 2001.

The MI diagnosis for inclusion into the VALIANT registry was based on the individual hospital's MI criteria, although the use of VALIANT trial MI inclusion criteria (elevated biochemical markers of myocardial necrosis combined with symptoms and/or electrocardiogram changes consistent with MI) was recommended.[10] Both ST- and non-ST elevation could be consistent with MI diagnosis. Baseline characteristics, medication prior to admission, electrocardiogram on admission, therapy given on the initial day of MI diagnosis, clinical events, in-hospital procedures, discharge medication, and disposition were prospectively recorded. There were no follow-up appointments after discharge.

HF status was assessed on admission and graded according to Killip Class. Worsening HF was defined as the unplanned use of intravenous inotropes, vasodilators, and/or diuretics.

Dyslipidaemia refers to any abnormality of cholesterol, triglycerides, or other blood lipids. Chronic renal insufficiency was defined as a serum creatinine $>$2.0 mg/dL ($>$177 μmol/L) before the qualifying MI. Peripheral arterial disease (PAD) was defined as having claudication or prior arterial surgery.

Stroke classification

Stroke was defined as an acute focal neurological deficit consistent with the diagnosis and lasting more than 24 h or resulting in death. Stroke was identified by the treating physician and reported prospectively as one of the clinical in-hospital events on the case report form. The exact timing of the stroke was not recorded. Imaging was not required for the diagnosis of stroke and was performed as deemed appropriate by the treating physician. No classification into haemorrhagic or ischaemic stroke types was made.

Statistical analysis

Continuous baseline characteristics and clinical outcomes were reported as medians with interquartile ranges. The Wilcoxon rank–sum test was used to assess the differences in the distributions between the stroke groups (stroke vs. non-stroke). Categorical variables were analysed using the likelihood ratio χ^2 test. Simple unadjusted mortality rates were generated to explore the distribution of deaths across stroke groups. Patients with missing values were included in the relevant denominator to calculate per cent by stroke group.

Model building using selection algorithms was not possible because of the low stroke event rate; hence statistically significant and clinically relevant variables were used in multivariable logistic regression to predict in-hospital survival along with stroke. A second multivariable logistic regression using the same variables was used to predict both stroke and in-hospital death. Adjustments were made for the following variables: age, history of stroke, PAD, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, prior HF, and Killip Class at presentation. Relationship between age (a continuous variable) and in-hospital survival was examined using spline functions with inflection points. The independent splines were incorporated into the model.

For all analyses, a two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using SAS statistical software (SAS Institute, Cary, NC, USA).

Results

A total of 81 (1.5%) patients suffered in-hospital strokes out of the 5573 patients with MI enrolled in the VALIANT registry. *Table 1* shows baseline characteristics and medications on

Table 1 Baseline characteristics and medications for patients with and without stroke on admission

Variable	With stroke ($n = 81$)	Without stroke ($n = 5492$)	*P*-value
Age (years)	76 (65, 80)	66 (55, 76)	<0.001
Male	48 (59)	3669 (67)	0.318
Ethnicity			
Caucasian	77 (95)	3669 (91)	0.628
Black	1 (1)	207 (4)	—
Asian	0 (0)	70 (1)	—
Other/unknown	2 (2)	155 (3)	—
Weight (kg)	79 (74, 87)	80 (70, 91)	0.077
Prior angina	14 (17)	1001 (18)	0.827
Prior MI	17 (21)	1317 (24)	0.531
Prior PCI	9 (11)	683 (12)	0.720
Prior coronary artery bypass graft surgery	12 (15)	581 (11)	0.220
History of HF	8 (10)	539 (10)	0.985
History of stroke	16 (20)	450 (8)	<0.001
Prior PAD	13 (16)	454 (8)	0.012
Known dyslipidemia	23 (28)	1942 (35)	0.193
Prior COPD	15 (19)	546 (10)	0.011
Prior chronic renal insufficiency	7 (9)	326 (6)	0.308
Prior hypertension	54 (67)	2782 (51)	0.004
Prior diabetes	23 (28)	1382 (25)	0.506
Current smoker	16 (20)	1557 (28)	0.088
Medications			
Aspirin	27 (33)	2053 (37)	0.455
Ticlopidine	2 (2)	32 (1)	0.031
Clopidogrel	2 (2)	165 (3)	0.779
Warfarin	8 (10)	167 (5)	0.039
Statin	15 (19)	1190 (22)	0.494
β-blocker	26 (32)	1476 (27)	0.293
Calcium channel blocker	19 (23)	991 (18)	0.209
Loop diuretic	19 (23)	886 (16)	0.076
Spironolactone	1 (1)	96 (2)	0.726
Digoxin	6 (7)	371 (7)	0.817
Amiodarone	1 (1)	48 (1)	0.730
Other antiarrhythmic	3 (4)	42 (1)	0.003
ACE inhibitor	19 (23)	1306 (24)	0.946
Angiotensin II receptor blocker	3 (4)	255 (5)	0.690

ACE, angiotensin-converting enzyme. Values indicate median (25th, 75th) or *n* (%).

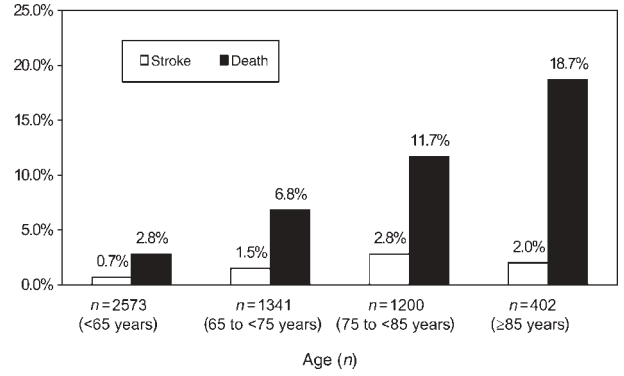

Figure 1 Incidence (%) of stroke and death per age group in patients following MI.

hospital admission for patients with and without stroke. The patients who had a stroke during the acute MI were significantly older, and the incidence increased up to 84 years of age (*Figure 1*). Prior stroke, known PAD, and hypertension were more common in patients who experienced a stroke. Initial blood pressures and heart rates were similar on admission (*Table 2*). When analysed as a cut-off value, a borderline significant number of patients with stroke had a heart rate $\geq$100 b.p.m. compared with patients without stroke (27.2 vs. 19.3%, $P = 0.06$). History of atrial fibrillation was not documented on admission, but this arrhythmia was reported almost twice as often, after admission, in patients who experienced a stroke than in those who did not (*Table 3*).

The frequency of ST-elevation or ST-depression on the admission electrocardiogram was similar in both groups (*Table 2*). The frequency of initial therapy with either a thrombolytic agent (21% in patients with stroke vs. 20% in those without, $P = 0.947$) or primary percutaneous coronary intervention (PCI) (10 vs. 13%, $P = 0.347$) was also similar in both groups. Reperfusion therapy did not significantly alter the incidence of stroke compared with not receiving thrombolytics or undergoing PCI (*Table 4*). There was no difference in the use of unfractionated heparin (67 vs. 64%, $P = 0.587$) or low molecular weight heparin (15 vs. 23%, $P = 0.098$) in the two groups within the first day of admission, although patients with stroke were less likely to receive aspirin on admission (67 vs. 78%, $P = 0.013$). Pre-admission and discharge medications are shown in *Tables 1* and *5*.

HF signs were present in 31 (38%) patients with stroke and 1292 (24%) patients without stroke (*Table 2, Figure 2A*). Patients presenting with Killip Class II had a stroke risk similar to that of patients with no HF signs on admission (OR 1.0, 95% CI 0.65–1.83) (*Figure 2B*). Patients with Killip Class III had a 1.5 times increased OR for stroke compared with Killip Class I (OR 1.66, 95% CI 0.86–3.19), whereas Killip Class IV patients had more than four times higher OR (OR 4.85, 95% CI 1.69–13.93). In-hospital worsening of HF and hypotension requiring therapy occurred more frequently in patients who experienced a stroke (*Table 3*). Approximately 54% of patients with stroke and 44% without stroke had echocardiography during the hospital stay. There was a trend for the left ventricular ejection fraction to be lower in patients with stroke (*Table 3*).

After adjusting for all significant baseline characteristics and a limited number of previously described factors associated with an increased stroke risk (Killip Class on admission, diabetes, and prior HF),[4,5,7] we found that age (OR 1.03 increase/year, 95% CI 1.01–1.04), history of stroke (OR 1.89, 95% CI 1.06–3.37), prior hypertension (OR 1.73,

Table 2 Haemodynamic status and electrocardiographic changes on admission in patients with and without stroke

	With stroke ($n = 81$)	Without stroke ($n = 5492$)	*P*-value
Killip class			
I	47 (58)	4066 (74)	0.001
II	14 (17)	810 (15)	0.523
III	12 (15)	417 (8)	0.016
IV	5 (6)	65 (1)	<0.001
Systolic blood pressure (mmHg)	138 (117, 160)	138 (120, 158)	0.935
Diastolic blood pressure (mmHg)	76 (66, 90)	80 (67, 90)	0.850
Heart rate (b.p.m)	78 (65, 102)	79 (66, 94)	0.567
ECG on admission			
ST-elevation	40 (49)	2688 (49)	0.938
ST-depression	23 (28)	1649 (30)	0.751
Non-specific ST/T-wave abnormalities	21 (26)	1400 (26)	0.929
Q-wave	8 (10)	667 (12)	0.535
Left bundle branch block	5 (6)	270 (5)	0.604
Other	11 (14)	673 (12)	0.718
Infarct location on ECG			
Anterior location	24 (30)	1774 (32)	0.610
Inferior location	23 (28)	1964 (36)	0.169
Other location	31 (38)	1688 (31)	0.145

ECG, electrocardiogram. Values indicate medians (25th, 75th) or *n* (%).

Table 3 In-hospital events in patients with and without stroke

	With stroke ($n = 81$)	Without stroke ($n = 5492$)	*P*-value
Atrial fibrillation	16 (20)	594 (11)	0.011
Sustained ventricular tachycardia/fibrillation	10 (12)	307 (6)	0.009
Worsening HF	10 (12)	378 (7)	0.055
Cardiogenic shock	11 (13)	245 (4)	<0.001
Hypotension requiring intervention	16 (20)	551 (10)	0.004
Intra-aortic balloon pump	6 (7)	235 (4)	0.169
Echocardiography	44 (54)	2435 (44)	0.073
Ejection fraction (%)	45 (35, 50)	49 (38, 56)	0.081
Recurrent ischaemia	6 (7)	540 (10)	0.466
Recurrent MI	2 (2)	101 (2)	0.676
Pacemaker implantation	7 (8)	119 (2)	<0.001
Defibrillator implantation	1 (1)	29 (0.5)	0.388
Length of hospital stay (days)	9 (6, 16)	6 (3, 9)	<0.001
Discharge to home	31 (38)	4193 (76)	<0.001
Death	22 (27.2)	358 (6.5)	<0.001

Values indicate *n* (%) and median (25th, 75th).

Table 4 Reperfusion therapy and risk of stroke

	Incidence of stroke *n*
Thrombolytic therapy	17/1100 (1.5)
Primary PCI	8/747 (1.1)
Both thrombolytic therapy and PCI	2/190 (1.1)
Thrombolytic therapy and/or PCI	27/2037 (1.3)
No reperfusion therapy	54/3536 (1.5)
Total	81/5573 (1.5)

Primary PCI performed on the day of admission. Thrombolytic therapy was given within 24 h of admission. Values indicate *n*(%).

Table 5 Discharge medications in patients with and without stroke

	With stroke ($n = 59$)	Without stroke ($n = 5134$)	*P*-value
Aspirin	43 (73)	4392 (86)	0.006
Ticlopidine	2 (3)	87 (2)	0.318
Clopidogrel	15 (25)	2171 (42)	0.009
Warfarin	19 (32)	535 (10)	<0.001
Statin	21 (36)	2745 (53)	0.006
β-blocker	40 (68)	3882 (76)	0.165
Calcium channel blocker	11 (19)	770 (15)	0.436
Loop diuretic	23 (39)	1179 (23)	0.004
Spironolactone	7 (12)	161 (3)	<0.001
Digoxin	19 (32)	553 (11)	<0.001
Amiodarone	7 (12)	258 (5)	0.018
Other antiarrhythmic	2 (3)	60 (1)	0.118
ACE inhibitor	37 (63)	2701 (53)	0.122
Angiotensin II receptor blocker	5 (8)	208 (4)	0.089

Values indicate *n* (%).

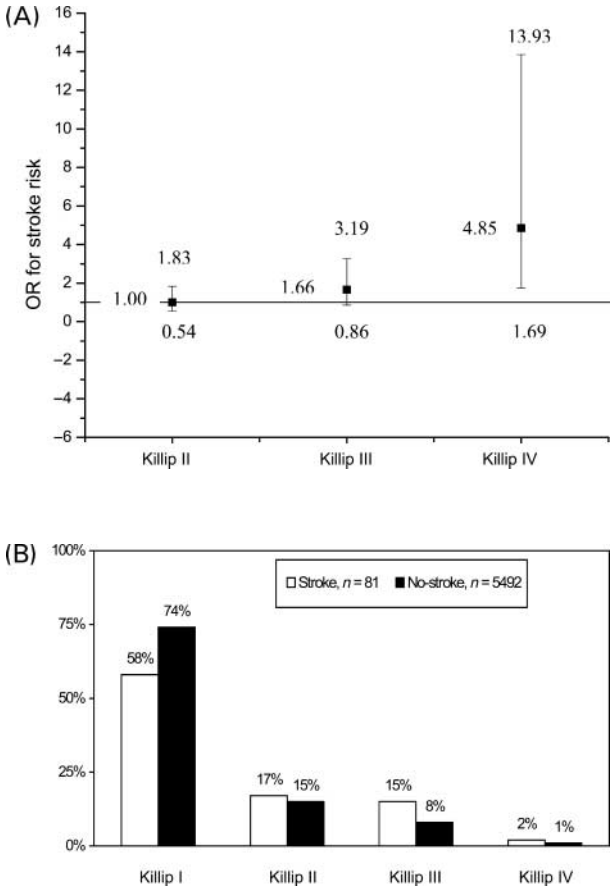

Figure 2 (*A*) ORs and CIs for stroke with increasing Killip Class, compared with Killip Class I, (*B*) Distribution of Killip Class I–IV in the stroke and no-stroke group.

95% CI 1.06–2.82), and Killip Class IV (OR 4.85, 95% CI 1.69–13.93) were independently associated with having a stroke.

Patients who experienced a stroke remained in-hospital longer and were less likely to be discharged home (*Table 3*). In-hospital mortality was more than four times higher (27.2 vs. 6.5%) in patients who had a stroke. Stroke deaths accounted for 5.8% of all in-hospital post-MI deaths. All the factors associated with an increased risk of stroke were also associated with an increased likelihood of death (data not shown).

Discussion

In this contemporary, international population consisting of 5573 patients presenting with either ST- or non-ST-elevation MI, the incidence of in-hospital stroke was 1.5%. We assessed the relative contribution of HF status on admission to the in-hospital risk of stroke. Evidence of HF was present on admission in 38% of patients who developed a stroke vs. 24% of patients who did not. Patients presenting with Killip Class III and above had a substantially increased risk of subsequent stroke, whereas patients in Killip Class II had a risk similar to that of patients without any HF signs.

With contemporary therapy for acute MI, the overall incidence of stroke is reported to be between 1 and 2%.[2,3,5] The use of thrombolytic therapy has been associated with an increase in the proportion of non-haemorrhagic to haemorrhagic strokes, with the contemporary stroke rate between 0.9 and 1.5% in selected trial patients[11,12,13] and between 0.7 and 1.6% in registries.[2,14] With primary PCI, the incidence of stroke is around 1%.[15] Although the incidence of stroke has been reported to be lower in patients undergoing PCI compared with those undergoing thrombolytic therapy,[15] stroke rates were similar with these non-randomized therapies in this registry.

In this study, we found a correlation between higher Killip Class and the occurrence of stroke in a general population with MI. The mechanism for this relationship remains unknown. Killip Class was a predictor of subsequent in-hospital stroke in one thrombolytic trial (in which one-third of strokes were haemorrhagic),[5] but it was not an independent predictor of ischaemic stroke in the GUSTO-1 trial.[3] This discrepancy might be at least partly explained by selection bias for healthier patients but not for patients in Killip Class III or IV, to be enrolled in a trial rather than in a registry. No patients were excluded from the registry on the basis of worse haemodynamic status, which probably would have occurred in a randomized trial, and therefore a trial population would be less appropriate to assess risk factors for stroke in a general MI population. Despite

differences in patient selection and MI characteristics in previous studies, the reported independent predictors of post-MI stroke have been similar, including higher age, prior stroke, higher heart rate, and diabetes.[3,6]

The presence of atrial fibrillation is a powerful risk factor for stroke.[16,17] In this study, in-hospital atrial fibrillation was more frequent in patients who experienced a stroke. However, the proportion of patients with either new-onset or chronic atrial fibrillation was not documented. New-onset atrial fibrillation is an independent predictor of 30-day mortality,[16] which might partially be explained by a higher stroke rate.[17] Atrial fibrillation is a direct cause of as well as a marker for stroke risk and other possible stroke causes, such as embolism from atheromatous aortic arches or platelet emboli from ulcerated carotid plaques. Additionally, the occurrence of new-onset atrial fibrillation following an MI has been independently predicted by other stroke-related states, such as worsening HF, presence of hypotension, and ventricular fibrillation.[17]

Larger and anterior infarcts have been associated with an increased risk of stroke,[6] probably due to a combination of impaired left ventricular function, worse haemodynamic status with low flow mechanisms, and greater regional wall motion abnormalities that contribute to the formation of left ventricular thrombus and systemic embolism. A depressed left ventricular ejection fraction increases the long-term risk of stroke following an MI.[7] This relationship could not be fully assessed in the current study, as left ventricular ejection fractions were not systematically evaluated. However, there was a trend on univariate analysis for patients with stroke to have lower ejection fractions.

Stroke was more frequent in the elderly, and the incidence increased proportionally with age. The lower stroke rate in the very elderly may reflect the higher mortality in this age group.[3,6,18] Approximately one-third of the strokes were fatal, which is lower than the previously reported rates between 40 and 50% in patients with a stroke following MI.[7,11]

Although many risk factors for the occurrence of post-MI stroke have been identified, many mechanisms remain unexplored. Markers of thrombosis and inflammation, such as fibrinogen or C-reactive protein, have been shown to predict the risk of stroke in the long term, though their contribution in the acute phase following an MI is unknown.[19,20]

Limitations

There are a number of limitations to our study related to the nature of a registry. As no cerebral imaging results were available, we were unable to account for the different types of stroke (haemorrhagic or ischaemic) and their relationship to different therapies in this population. Treatment strategies differed non-significantly in patients with stroke, but treatments were not randomly assigned and could be biased by the clinical course; hence, their influence on the risk of stroke cannot be evaluated.

Left ventricular function was examined in only 44% of patients, and without standardization which limited further multivariate analysis. The occurrence of ventricular thrombus was not reported and we did not record the exact timing of the occurrence of a stroke. Also, no adjustment was made for the variation in the length of post-MI hospital stay across different centres.

Conclusion

Stroke complicating an MI is uncommon, but the public health impact is enormous because of the high prevalence of coronary artery disease and the impact on survival, quality of life, and cost. Higher age, prior cerebrovascular disease, and history of hypertension increase the likelihood of a subsequent stroke and point to the importance of treating patients with these features to prevent both MI and stroke. Once a stroke has occurred, the prognosis is poor, with high morbidity and mortality. The duration of hospitalization is 1.5 times longer for these patients, and the associated costs are substantial. Despite the recognition of several different factors that identify patients at heightened risk for stroke following an MI, the mechanisms are multifactorial, and therapies to decrease the incidence are elusive. Major efforts must be directed towards the primary risk factors causing acute MI and towards those factors associated with the occurrence of stroke after MI.

In this study, HF on admission complicated ~24% of the MIs and significantly increased the risk of stroke. Strategies that reduce the incidence of HF in this early time period, when the stroke risk is highest, may decrease the number of early strokes and the associated dismal prognosis. It is not known whether therapies that may improve the outcome of patients who develop HF after MI may also decrease the risk of stroke.

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