Elderly Patients Are at Higher Risk for Poor Outcomes After Intra-Arterial Therapy

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Background and Purpose—Conflicting data exist regarding outcomes after intra-arterial therapy (IAT) in elderly stroke patients. We compare safety and clinical outcomes of multimodal IAT in elderly versus nonelderly patients and investigate differences in baseline health and disability as possible explanatory factors.

Methods—Data from a prospectively collected institutional IAT database were analyzed comparing elderly (80 years or older) versus nonelderly patients. Baseline demographics, angiographic reperfusion (Thrombolysis in Cerebral Infarction scale score 2–3), rate of parenchymal hematoma type 2, and 90-day modified Rankin Scale scores were compared in univariate and multivariate analyses.

Results—There were 49 elderly and 130 nonelderly patients treated between 2005 and 2010. Between the 2 cohorts, there was no significant difference in Thrombolysis in Cerebral Infarction 2 to 3 reperfusion (71% vs 75%; P=0.57), time to reperfusion (P=0.77), or rate of parenchymal hematoma type 2 (4% vs 7%; P=0.73) after IAT. However, elderly patients had significantly lower rates of good outcome (modified Rankin Scale score 0–2: 2% vs 33%; P<0.0001) and higher mortality (59% vs 24%; P<0.0001) at 90 days. Atrial fibrillation, coronary artery disease, hypertension, hyperlipidemia, and baseline disability were significantly more common in elderly patients. Adjusting for baseline disability, stroke severity, and reperfusion, elderly patients were 29-times more likely to be dependent or dead at 90 days (odds ratio, 28.7; 95% confidence interval, 3.2–255.7; P=0.003).

Conclusions—Despite comparable rates of reperfusion and significant hemorrhage, elderly patients had worse clinical outcomes after IAT, which may relate, in part, to worse baseline health and disability. The use of IAT in the elderly should be performed after a careful analysis of the potential risks and benefits. (Stroke. 2012;43:2356-2361.)

Key Words: elderly ■ stroke ■ thrombolysis

Elderly patients are disproportionately affected by stroke; in an analysis of half a million ischemic stroke admissions, elderly (80 years or older) patients accounted for one-third of admissions and almost half of in-hospital deaths. This health care burden will grow as the United States population older than 85 years increases 5-fold by 2050.

Elderly acute ischemic stroke patients have poorer overall outcomes. However, there remains a paucity of data regarding the safety and effectiveness of intra-arterial therapy (IAT) in the elderly. Major IAT trials either excluded such patients or did not report age-related outcomes. Evidence from a small number of case series demonstrates increased mortality in elderly patients treated endovascularly. Data regarding functional outcomes among survivors are conflicting. Because reported rates of recanalization and symptomatic hemorrhage appear equivalent between elderly and nonelderly cohorts, factors influencing these variable outcomes remain unclear.

This study aimed to compare safety and clinical outcomes between patients aged younger than 80 years and 80 years or older in a large cohort treated with contemporary multimodal IAT. Moreover, we sought to compare baseline health and disability to identify differences that might explain discrepancies in treatment outcomes.

Patients and Methods

Patient Selection, Data Collection, and Study Endpoints

From a prospective observational database, we identified acute anterior circulation stroke patients presenting to our hospital between February 2005 and November 2010 who underwent IAT. During this time period, 2897 stroke patients were assessed, of whom 1482 presented within 8 hours, and 179 with anterior circulation strokes

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were treated with IAT. A subset of these patients was included in a previous study examining preexisting dementia and outcomes in elderly patients undergoing intravenous (IV) tissue plasminogen activator (tPA) and/or IAT between February 2002 and December 2009.13 Baseline demographic and treatment data were collected. Safety endpoints were the rate of parenchymal hematoma type 2 (PH2; hemorrhage in >30% of the infarction with substantial mass effect) at 24 to 36 hours after stroke and 90-day mortality. Given that existing data showing that PH2 are associated with worse stroke outcomes, PH2 was used as an indicator of significant hemorrhage.14 Primary treatment endpoints were reperfusion on the modified Thrombolysis in Cerebral Infarction (TICI) scale15 and 90-day functional outcome using the modified Rankin Scale (mRS) score. The previous article from our institution utilized discharge outcome.13 The TICI reperfusion was evaluated both ordinarily and dichotomized at TICI score 2 to 3. Good outcome was defined as mRS score 0 to 2. Secondary endpoints were 7-day National Institutes of Health Stroke Scale (NIHSS) score improvement (difference between the baseline and 7-day NIHSS scores, performed by a board-certified neurologist), discharge mRS, and discharge destination. This study was approved by the Institutional Review Board and performed in compliance with the Health Insurance Portability and Accountability Act.

**Acute Stroke Therapies:**

**Intravenous Thrombolysis**

Patients meeting standard IV tPA criteria were administered 0.9 mg/kg IV tPA (10% bolus; 90% continuous infusion during 1 hour; maximum 90 mg) after initial computed tomography imaging.

**Intra-Arterial Reperfusion Therapy**

General treatment criteria for IAT included: (1) imaging assessment completed <8 hours after ictus; (2) noncontrast computed tomography without hemorrhage; (3) noncontrast computed tomography or magnetic resonance imaging diffusion-weighted imaging abnormality less than one-third of the middle cerebral artery territory; (4) proximal cerebral artery occlusion (internal carotid artery, middle cerebral artery M1 or M2 branches) on computed tomography angiography; (5) NIHSS score >8 or with significant aphasia; and (6) unresponsiveness to IV tPA, if administered. At >6 hours after ictus, after full-dose IV tPA, with international normalized ratio >1.5, or after recent major surgery, only mechanical treatment approaches were used. The decision to treat with IAT was made jointly by the stroke neurologist and neurointerventionist. No patients were excluded on basis of age.

Endovascular treatment was performed under general anesthesia. For chemical thrombolysis, urokinase (Abbott Laboratories; typical doses 250 000–750 000 U) or recombinant tPA (Genentech; typical doses 5–10 mg) was administered through a microcatheter directly into the clot. Mechanical therapy included the Merci Retrieval System (Concentric Medical, Mountain View, CA), the Penumbra System (Penumbra, Alameda, CA), microwire maceration, balloon angioplasty, and, rarely, stent placement. IAT was ceased when full or satisfactory recanalization (as judged by the stroke neurologist and neurointerventionist) was achieved, when time from ictus exceeded 9 hours, or when complication was encountered.

**Statistical Analysis**

Baseline characteristics and study endpoints were compared between patients aged younger than 80 (nonelderly) and 80 or older (elderly). The Student t test was used for normally distributed continuous data, the Mann-Whitney test was used for ordinal or non-normal data, and the Fisher exact test was used for categorical data. Normality was tested with the Kolmogorov-Smirnov test. Missing data points were excluded from analysis and are noted in Table 1.

A univariate analysis was performed to identify predictors of good versus poor clinical outcome. Univariate predictors, as well as baseline disability, were tested in multivariate logistic regression analysis to identify independent predictors of poor outcome. In addition, a receiver-operating characteristic curve analysis was performed to identify the optimal age cut-point to predict outcome. All statistical analyses were performed using MedCalce for Windows version 9.3.9.0 (MedCalc Software, Mariakerke, Belgium). Statistical significance was defined as a 2-tailed P<0.05.

**Results**

One hundred seventy-nine patients met the study criteria. There were 130 (73%) patients aged younger than 80 and 49 (27%) aged 80 or older. Table 1 outlines the baseline characteristics; for elderly patients, mean age was 86 years compared with 61 years in the nonelderly. Elderly patients had significantly higher rates of coronary artery disease, atrial fibrillation, hypertension, and hyperlipidemia. Moreover, they had higher levels of baseline disability, with 33% (16/49) having mRS score ≥2 versus 10% (13/130) of younger patients (P=0.0005). Elderly patients were less likely to have cervical or intracranial internal carotid artery occlusions (16% vs 35%; P=0.02). Despite this, there was a trend toward worse neurological deficit at presentation in the older group (median NIHSS score 18 [interquartile range, 14–22] vs 17 [interquartile range, 14–20]; P=0.08).

There were no significant differences between the 2 age cohorts in the rate of IV tPA treatment before IAT or the use of IAT or mechanical therapies. The only significant difference was a higher rate of cervical ICA stenting in the nonelderly cohort (14% vs 0%; P=0.004).

Treatment outcomes are summarized in Table 2. Rates of reperfusion with TICI 2 to 3 were similar. However, there was a trend toward higher degrees of reperfusion in younger patients; the rate of TICI 2B to TICI 3 reperfusion (≥50% reperfusion of the involved territory) was 40% in nonelderly patients versus 25% in elderly patients (P=0.06). The time from stroke onset to reperfusion was not significantly different.

In the early posttreatment period, there were no significant differences in the rate of any hemorrhage (47% vs 50%) or PH2 (7% vs 4%) between nonelderly and elderly patients. Early neurological improvement was less dramatic in elderly patients who had a 7-day median NIHSS score improvement of 1 point (interquartile range, −1–5) compared with 4 points (interquartile range, 0–10) in younger patients; this difference was not significant (P=0.21). Elderly patients had worse outcomes at discharge (median discharge mRS of 5.5) and were 2.7-times more likely to die as an inpatient or be discharged to hospice care (53% vs 20%). Elderly patients were significantly more likely to have medical care withdrawn (27/49 [55%] vs 25/130 [19%]; P<0.0001). Independent predictors of care withdrawal were age 80 years or older, lesser degrees of reperfusion, and higher baseline mRS scores.

Three elderly and 2 nonelderly patients were lost to 90-day clinical follow-up. For the remainder, functional outcomes were far worse than in nonelderly patients (Figure). The 90-day mortality rate for patients 80 years or older was 59% (vs 24%). All deaths in the elderly were related to withdrawal of care. Among 19 elderly survivors, only 1 (5%) had a good clinical outcome (mRS score 0–2) at 90 days and 14 (74%) were severely disabled (mRS score 4–5). Among 97 nonelderly survivors, 42 (43%) had a good 90-day outcome and 36 (37%) were severely disabled.
In univariate analysis, age 80 years or older was a significant predictor of poor 90-day outcome (mRS score 3–6; Table 3). Greater baseline disability and longer time to reperfusion demonstrated statistical trends for predicting poor outcome (both \( P < 0.07 \)). After adjusting for baseline disability and univariate predictors including admission NIHSS score and TICI reperfusion, elderly status remained an independent predictor of poor outcome (odds ratio, 28.7; 95% confidence interval, 3.2–255.7; \( P = 0.003 \)). Receiver-operating characteristic curve analysis confirmed age 80 years or older as the optimal cutpoint for a poor outcome, with a sensitivity of 34.4% and specificity of 97.7% (area under the curve, 0.68; \( P = 0.0001 \)).

Univariate and multivariate predictors of mortality are provided in Supplemental Table I. The only independent predictors of mortality were admission NIHSS score (\( P = 0.01 \)) and withdrawal of care (\( P < 0.0001 \)).

### Discussion

In this large single-center experience with IAT, elderly patients demonstrated dismal clinical outcomes compared with patients younger than 80 years. Among the elderly cohort, only 1 patient achieved an independent outcome at 90 days, and \( 90\% \) were severely dependent or dead (mRS score 4–6). These poor outcomes are despite similar rates of TICI 2 to 3 reperfusion and are not attributable to intracranial hemorrhage.

Compared with younger patients, there is little published data to guide intravenous and intra-arterial reperfusion therapies in the elderly cohort. A recent review of the SITS-ISTR registry revealed that patients aged older than 80 had significantly higher mortality than younger patients after IV tPA treatment, despite a similar symptomatic intracranial hemorrhage rate.\(^{16}\) A meta-analysis of 2244 patients that included 477 patients aged 80 years or older also yielded similar findings.\(^{17}\)

However, a nonrandomized comparison of outcomes in patients...
treated versus not treated with IV tPA alone demonstrated treatment benefit extending to patients older than 80 years.18

Among IAT trials, PROACT II and the IMS trials excluded patients older than 80 to 85 years.5,6 Although the MERCI and Penumbra trials did not have upper age limits, no age-related outcomes were reported.3,4 To date, only a few case series, which used varying recanalization strategies, have reported outcomes among elderly patients treated with IAT.7–12

Regarding revascularization, our findings concur with previous studies that report no significant difference in rates of partial to complete reperfusion between elderly and nonelderly patients. The 71% rate of partial–complete reperfusion we achieved in our elderly cohort is within the range reported by these series (63%–81%).7–10,12 However, when we removed TICI 2A reperfusion (<50% of the affected territory), we found that the rate of major reperfusion (TICI 2B–3) was lower in elderly patients (25% versus 40%; \(P=0.06\)), a finding also noted by Mazighi et al.10 This result likely contributed to the worse clinical outcomes in our older patients, and occurred despite a lower proportion of internal carotid artery occlusions (which are more resistant to revascularization). Potential explanations for lower reperfusion rates include increased vessel tortuosity (decreasing device effectiveness) and diminished operator aggressiveness in older patients.

In terms of procedural safety, our data agree with previous findings demonstrating no significant difference in major posttreatment hemorrhage rates between the 2 age groups. The 4% rate of PH2 hemorrhage among our elderly patients is low compared with previous studies (6%–14%), although it should be noted that these studies utilized symptomatic hemorrhage as their endpoint.7–10,12 Our low PH2 rate likely stems from selection of patients with small infarcts at presentation because it has been shown that large (>100 mL) pretreatment infarcts are associated with a higher risk of symptomatic bleeds.19

Also similar to our data, previous studies found a significantly higher mortality rate among IAT-treated patients older than 80 years. Mortality rates in this group ranged from 40% to 63%.7–12 In some measure, this excess mortality reflects the
higher incidence of medical comorbidities and poststroke complications in the elderly.1,16,20 In addition, a major contributory factor in our study was the greater likelihood of withdrawing life-prolonging care in older patients because of advance directives or communicated wishes of the patient by the health care proxy. Age 80 years or older independently predicted care withdrawal by families and physicians, resulting in a “self-fulfilling prophecy” of poor outcomes. It is unknown what the outcomes would have been in this cohort if care had not been withdrawn. However, this is an accurate reflection of real-world practice. This last issue complicates any comparison of mortality rates between studies of the elderly. There is conflicting data regarding functional outcomes after IAT. Four previous studies found functional outcomes were worse for elderly survivors compared with their younger counterparts,7,10–12 consistent with our data. However, 2 studies found similar rates of good outcome between the 2 age groups.8,9 This discrepancy suggests that the clinical response to IAT may be highly variable among older patients. This idea is further supported by the large difference in good outcome rates within the literature. Among studies that examined long-term functional outcomes,7,9–12 four reported that approximately 45% of elderly survivors achieved an independent outcome, in contrast to our 5% rate and the 0% rate reported by Flaherty et al.11 Mono et al12 reported the largest of these studies and included 43 patients aged 80 years or older. Good outcome (mRS score 0–2) rates were 28% in the overall elderly cohort and 46% in elderly survivors. Although our worse results could relate to chance, patients in our cohort were older (mean age 86 vs 82) and had more severe strokes (median NIHSS score 18 vs 17). The difference in stroke severity was likely related to differences in the inclusion criteria related to neurological deficit: NIHSS score >8 or with significant aphasia in our study versus NIHSS >4 or severe aphasia or complete hemianopsia in the study by Mono et al.12 The difference in NIHSS score criterion may have had an influence on clinical outcomes, because previous data have shown that almost half of patients presenting with NIHSS score <8 have improvement to NIHSS score 0 to 1 in 48 hours without thrombolysis21 and, regardless of type of treatment instituted, many have good 3-month functional outcome.22 Other factors that may account for these disparate results is the potentially wide variation in prestroke health and disability in older patients. For instance, our patients demonstrated substantial rates of comorbidity relative to other study cohorts (Supplemental Table II). Compared with the study by Mono et al,12 our elderly cohort had higher rates of coronary artery disease (63% vs 30%) and smoking (24% vs 2%). Compared with Kim et al,7 our elderly cohort had higher rates of coronary artery disease (63% vs 30%), hypertension (92% vs 58%), and hyperlipidemia (60% vs 27%). A comparison with Loh et al8 yielded similar results. Furthermore, our elderly patients had significant baseline disability, approximately one-third had a premorbid mRS score ≥2. The majority of the previous studies did not report baseline mRS scores; Mono et al12 excluded patients with premorbid mRS scores of ≥2. A large observational study of acute ischemic stroke patients recently demonstrated that premorbid mRS was an independent predictor of 1-month death and disability.20 In our series, the sole elderly patient with good outcome had a baseline mRS of 0. Reduced neurological reserve secondary to age-related neuronal loss additionally may explain poorer functional recovery in elderly patients after IAT. This may be the reason why elderly patients have more speech impairment, paralysis, swallowing problems, urinary incontinence, and confusion acutely.23 Furthermore, elderly patients less frequently receive guideline-recommended stroke care1 and have higher rates of in-hospital medical complications, which may independently predict death and disability.20 Finally, rehabilitation can be hampered by reduced neuronal plasticity, poorer social supports, and baseline disability in the elderly.23 Our study has several limitations. First, this represents the experience of a single center. As such, local practice patterns may have influenced outcomes. The majority of patients are referred through our Telesstroke network, covering hospitals in several states in the northeastern United States. Although many patients arrive via helicopter or fixed-wing aircraft, this referral pattern increases time from symptom onset to recanalization for many patients. Although the median time from symptom onset to recanalization was 439 minutes, overall rates of good functional outcome and mortality are comparable with published IAT studies, and there were no significant differences between the 2 age cohorts in time to treatment. Nonetheless, it is uncertain if the increased time to recanalization may have a greater impact on outcome in the elderly cohort because of reduced neuronal reserve. In addition, all patients were treated under general anesthesia, which has been shown in recent studies to be associated with worse outcomes compared with conscious sedation.24 Second, consideration of initial infarct size and angiographic collateral

| Table 3. Univariate and Multivariate Predictors of 90-Day Clinical Outcome |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Good Outcome (mRS Score 0–2; n=43) | Poor Outcome (mRS Score 3–6; n=131) | Univariate P | Multivariate P | Adjusted OR for Poor Outcome (95% CI) |
| Age ≥80 y                   | 1 (2.3%)                      | 45 (34.4%)                   | <0.0001       | 0.003          | 28.7 (3.2-255.7)            |
| Mean admission blood sugar (mg/dl ± SD) | 131.1 ± 33.4 (n=41) | 145.8 ± 50.9 (n=120) | 0.04          |                |                             |
| Median baseline NIHSS score (IQR) | 14 (11-17)                   | 18 (15-21)                   | <0.0001       | 0.003          | 1.2 (1.1-1.3) for every point |
| IA Thrombolytic             | 17 (39.5%)                    | 26 (19.8%)                   | 0.01          | 0.04           | 0.4 (0.1-1.0)              |
| Median TICI (IQR)           | 2B (2A-2B)                    | 2A (1-2A)                    | <0.0001       | <0.0001        | 0.2 (0.1-0.4) for every step |

CI indicates confidence interval; IA, intra-arterial; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SD, standard deviation; TICI, Thrombolysis in Cerebral Infarction.
grade, which may have impacted on outcome, were beyond the scope of this study. However, all patients were selected using the same criteria. Third, selection bias may exist among our elderly cohort; families of eligible elderly patients with any prestroke disability may be more likely to decline IAT. Further complicating the IAT decision may be previously expressed wishes regarding end-of-life care. However, this potential selection bias would be a specific confounder if a positive impact from IAT in the elderly cohort had been observed.

Conclusions

Our findings further support that contemporary multimodal IAT in elderly patients (aged 80 or older) can be performed with comparable rates of revascularization and significant treatment-related hemorrhage as in younger patients. However, dismal clinical outcomes after IAT are seen in patients 80 years or older, with significantly higher mortality and very low rates of long-term independence among survivors. Therefore, recanalization in patients older than 80 years at a median of 7 hours may be futile; only 1 of 49 patients achieved a good outcome. Comparison with other studies suggests that functional outcomes are highly variable in this population, which may be related to time to recanalization, preexisting comorbidities, and baseline disability. Further research is needed to clarify the role and cost-effectiveness of IAT, particularly in the rapidly expanding cohort of elderly patients, and to identify the subset of patients most likely to benefit from intervention. Until then, the use of IAT in the elderly should be performed after a careful analysis of the risks and benefits.

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Disclosures

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References

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http://stroke.ahajournals.org/content/43/9/2356

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**Supplemental Table 1: Univariate and multivariate predictors of 90-day mortality**

<table>
<thead>
<tr>
<th></th>
<th>Survival (n=116)</th>
<th>Death (n=58)</th>
<th>Univariate P value</th>
<th>Multivariate P value</th>
<th>Adjusted odds ratio for mortality (95% CI)</th>
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<tbody>
<tr>
<td>Age ≥80 years</td>
<td>19 (16.4%)</td>
<td>27 (46.6%)</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>36 (31.0%)</td>
<td>29/57 (50.9%)</td>
<td>0.02</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>77 (66.4%)</td>
<td>48/57 (84.2%)</td>
<td>0.02</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median baseline mRS (IQR)</td>
<td>0 (0-0)</td>
<td>0.5 (0-2)</td>
<td>0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median baseline NIHSS score (IQR)</td>
<td>16 (14-19)</td>
<td>18 (16-22)</td>
<td>0.0003</td>
<td>0.01</td>
<td>1.2 (1.0-1.4) for every step</td>
</tr>
<tr>
<td>Median TICI score (IQR)</td>
<td>2A (2A-2B)</td>
<td>2A (0-2A)</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Withdrawal of care</td>
<td>1 (0.9%)</td>
<td>51 (87.9%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>1174 (115-11963)</td>
</tr>
</tbody>
</table>

mRS, modified Rankin Scale; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; NS, not significant
### Supplemental Table 2: Comparison of baseline characteristics among elderly (≥80 yrs) study cohorts

<table>
<thead>
<tr>
<th>Condition</th>
<th>Our cohort</th>
<th>Mono et al. 1</th>
<th>P value*</th>
<th>Kim et al. 2</th>
<th>P value*</th>
<th>Loh et al. 3</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>44/48 (92%)</td>
<td>36/43 (84%)</td>
<td>0.40</td>
<td>19/33 (58%)</td>
<td>0.0007</td>
<td>21/31 (68%)</td>
<td>0.01</td>
</tr>
<tr>
<td>CAD</td>
<td>30/48 (63%)</td>
<td>13/43 (30%)</td>
<td>0.004</td>
<td>10/33 (30%)</td>
<td>0.006</td>
<td>21/31 (68%)</td>
<td>0.81</td>
</tr>
<tr>
<td>HL</td>
<td>29/48 (60%)</td>
<td>22/43 (51%)</td>
<td>0.50</td>
<td>9/33 (27%)</td>
<td>0.006</td>
<td>10/31 (32%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10/48 (21%)</td>
<td>9/43 (21%)</td>
<td>0.80</td>
<td>4/33 (12%)</td>
<td>0.38</td>
<td>2/31 (6%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29/49 (59%)</td>
<td>19/43 (46%)</td>
<td>0.22</td>
<td>20/33 (61%)</td>
<td>1.00</td>
<td>25/31 (81%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>8/48 (17%)</td>
<td>10/43 (23%)</td>
<td>0.60</td>
<td>14/33 (42%)</td>
<td>0.02</td>
<td>1/31 (3%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* indicates p-value for comparison with our study cohort.

HTN, hypertension; CAD, coronary artery disease; HL, hyperlipidemia; TIA, transient ischemic attack

### References