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N. Zeevi, G.A. Kuchel, N.S. Lee, I. Staff and L.D. McCullough

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ORIGINAL RESEARCH

Interventional Stroke Therapies in the Elderly: Are We Helping?

N. Zeevi
G.A. Kuchel
N.S. Lee
I. Staff
L.D. McCullough

FELLOWS' JOURNAL CLUB

BACKGROUND AND PURPOSE: It is unclear whether endovascular therapies for the treatment of AIS are being offered or are safe in older adults. The use and safety of endovascular interventions in patients older than 75 years of age were assessed.

MATERIALS AND METHODS: A retrospective review of patients with AIS 75 years or older (n = 37/1064) was compared with a younger cohort (n = 70/1190) by using an established data base. Admission and discharge NIHSS scores, rates of endovascular treatment, SICH, in-hospital mortality, and the mBI were assessed.

RESULTS: Rates of endovascular treatments were significantly lower in older patients (5.9% in the younger-than-75-year versus 3.5% in the older-than-75-year cohort, P = .007). Stroke severity as measured by the NIHSS score was equivalent in the 2 age groups. The mBI at 12 months was worse in the older patients (mild or no disability in 52% of the younger-than-75-year and 22% in the 75-year-or-older cohort, P = .006). Older patients had higher rates of SICH (9% in younger-than-75-year versus 24% in the 75-year-or-older group, P = .04) and in-hospital mortality (26% in younger-than-75-year versus 46% in the 75-year-or-older group, P = .05).

CONCLUSIONS: Patients older than 75 years of age were less likely to receive endovascular treatments. Older patients had higher rates of SICH, disability, and mortality. Prospective randomized trials are needed to determine the criteria for selecting patients most likely to benefit from acute endovascular therapies.

ABBREVIATIONS AIS = acute ischemic stroke; HIAT = Houston intra-arterial therapy; IA = intra-arterial; ICH = intracranial hemorrhage; INR = international normalized ratio; IQR = interquartile range; LDL = low-density lipoprotein; mBI = modified Barthel Index; SICH = symptomatic intracranial hemorrhage; TIMI = thrombolysis in myocardial infarction

A growing number of endovascular therapies are available for the treatment of AIS. These therapies offer options for patients who are outside the IV thrombolytic treatment window, have continued large-vessel occlusion, or have contraindications for IV therapies (ie, recent surgery).[1,2] AIS exerts the heaviest toll in terms of morbidity and mortality on the aged population,[3] making interventions that reduce the poor outcomes in this age group valuable. Several studies evaluating the use of IV tPA in the elderly have found it to be safe and effective.[4-7] However, less information is available regarding the safety and efficacy of endovascular recanalization therapies for the acute management of AIS. Therapies including IA tPA, clot retrieval devices, and combination therapies with IV tPA have been shown to improve revascularization rates and stroke outcomes up to 6 hours after the onset of stroke in younger patients.[8-12] The higher incidence of amyloid angiopathy,[13] decreased tPA clearance,[14] difficult vascular access, polypharmacy, blood-brain barrier impairment,[15] and age-related alterations in coagulation[16,17] has raised concerns of increased complications, mainly SICH, which are associated with increased mortality and disability,[18,19] when applying these treatments to the elderly. The objective of this study was to assess the complication rates and functional outcomes in older patients treated with endovascular techniques.

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From The Stroke Center at Hartford Hospital (N.Z., N.S.L., L.D.M.), Hartford, Connecticut; University of Connecticut Center on Aging (N.Z., G.A.K.) and Department of Neurology (N.Z., L.D.M.), University of Connecticut Health Center, Farmington, Connecticut; and Research Program (I.S.), Hartford Hospital, Hartford, Connecticut.

Please address correspondence to Louise D. McCullough, MD, PhD, The Stroke Clinic at Hartford Hospital, 80 Seymour St, Suite JB603, Hartford, CT 06102; e-mail: lmccullough@uchc.edu

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Materials and Methods

This study was a secondary statistical analysis of existing data in the Stroke Center at Hartford Hospital data base, Hartford, Connecticut. Data of patients presenting to the Hartford Hospital with an acute ischemic stroke between October 2005 and December 2009 were retrospectively reviewed. This study was part of an ongoing research project on stroke outcomes, reviewed and approved by the Hartford Hospital institutional review board. The Stroke Center at Hartford Hospital is certified by the Joint Commission on Accreditation of Healthcare Organizations as a Primary Stroke Center and serves as a tertiary referral center. The stroke team consisting of a neurology resident, stroke nurse or advanced practice registered nurse, and a stroke fellow are alerted to an acute stroke by means of the stroke beeper several minutes prior or on arrival to the emergency department. If the patient is a potential candidate for an endovascular procedure, the on-call neurointerventional radiologist is contacted early on to facilitate transfer to the angiography suite. Age 75 was chosen as the cutoff on the basis of the HIAT score to predict clinical outcomes.[8]

The decision to pursue endovascular treatment for patients presenting with AIS was based on the time from symptom onset of <6 hours, significant neurologic deficits, neuroimaging findings, clinical impression of the attending neurologist and interventional neuroradiologist, and patient and family preference. Exclusion criteria included a time of onset of >6 hours, evidence of ICH, ischemic

changes in more than one-third of the middle cerebral artery territory, contrast sensitivity, or platelet count <30 000. Patients who received endovascular therapy for central retinal artery occlusion were not included.

Femoral access was used for cerebral angiography. Evidence of arterial occlusion was documented before initiation of any intervention. Patients received either IA tPA, mechanical thrombus disruption, or a combination therapy plus or minus IV tPA. Patients are routinely intubated for endovascular procedures. Doses of up to 22 mg of tPA were administered via an IA microcatheter. The procedure was ended when recanalization was achieved, repeat attempts failed to open the occluded vessel, or clinical deterioration occurred.

The rate of endovascular treatment in each age group was calculated. Procedural duration and rate of recanalization were compared. Complications, including SICH and in-hospital death, were calculated. All patients underwent repeat CT or MRI. SICH was identified in patients who received IV tPA with a subsequent hemorrhage on CT within 24 hours of treatment that resulted in neurologic deterioration as defined by an increase in NIHSS score of ≥4.[10]

Acute outcomes were assessed by the drop in the NIHSS score at the time of admission and at discharge. The NIHSS has 15 items of the neurologic examination that correlate well with outcome in acute stroke trials.[20,21] The number of patients with an improvement of ≥4 points was calculated for each age group.[22] Long-term outcomes were measured by using 3-month and 12-month mBI scores. The mBI (a scale of 0–20 with 20 being healthy and 0 for total functional dependence) was obtained by telephone interview at 1 year after stroke by a stroke center nurse and data coordinator.[23] The mBI is a reliable and valid measure of functional independence and serves as a useful tool to assess interventional outcomes.[23] Mild to no disability is indicated by an mBI of ≥15.[24] Comparisons between age groups were done by using the Mann-Whitney *U* test, *t* test, χ^2 test, and Wilcoxon signed rank test. Multivariate analysis was performed to determine which clinical variables were predictive of SICH and mortality and included admission NIHSS score, age, duration of treatment, INR, and recanalization. The Levene tests were performed preliminary to all *t* test assessments; the tests either established that the assumption of equal variance was met or directed that a *t* test with modified *df* be used. All analyses were performed by using SAS (SAS, Cary, North Carolina).

Results

Table 1 shows the baseline characteristics of the patients with AIS, grouped according to age. Nearly half of the patients with ischemic stroke were in the older age group. The mean age for the older cohort (all older than 75 years) was 84 years and that for the younger group was 59 years. The older age group had a higher proportion of women (61% versus 42%, $P = .0001$). Vascular risk factors were significantly increased in the older cohort, including heart disease, atrial fibrillation, and hypertension. The prevalence of diabetes mellitus was higher among the younger age group. The older age group was significantly more likely to be on an anticoagulant. Although rates of statin use were similar, LDL levels were lower in the older cohort (96 in younger-than-75-year versus 86 in 75-year-or-older group, $P < .001$). The median prestroke mBI was significantly lower in patients older than 75 years (20 in the younger versus 19 in the older group, $P < .05$).

Table 2 shows the baseline characteristics of patients with AIS undergoing interventional therapies. Of the 107 patients who underwent an endovascular treatment for AIS, more than one-third were in the older cohort. The mean age for the older cohort was 80 years, and for the younger group, 60 years. The older group had higher rates of atrial fibrillation (31% in younger-than-75-year versus 54% in the 75-year-or-older group, $P = .04$) and hypertension (66% in the younger-than-75-year versus 84% in the 75-year-or-older group, $P = .04$). All of the older subjects receiving warfarin had atrial fibrillation compared with only 62% of younger subjects who were treated with warfarin. LDL level (83 in younger-than-75-year versus 65 in 75-year-or-older group, $P < .01$) and median prestroke mBI scores (20 in younger-than-75-year versus 19 in the 75-year-or-older group, $P < .05$) were lower in the older group.

Table 3 shows the rate of endovascular treatment by age. A significantly lower proportion of older patients were treated with endovascular procedures compared with the younger cohort (70/1190, 5.9% in younger-than-75-year versus 37/1064,

Table 1: Demographics of patients with AIS

	<75 Years of Age	≥75 Years of Age
Patients	1190 (53%)	1064 (47%)
Mean age	59 ± 11	84 ± 6
Sex		
Male	684 (58%)	410 (39%)
Female	506 (42%)[a]	654 (61%)[a]
LDL	96 ± 42[b]	86 ± 37[b]
Warfarin use	113 (9.5%)[a]	191 (18%)[a]
Statin use	453 (38%)	442 (41%)
Diabetes	383 (32%)[a]	294 (28%)[a]
Hypertension	848 (71%)[a]	902 (85%)[a]
Heart disease	410 (34%)[a]	483 (45%)[a]
Atrial fibrillation	171 (14%)[a]	452 (42%)[a]
Arriving to hospital within 8 hours	468 (39%)	457 (43%)
NIHSS admission score		
Median	4b	6[b]
IQR	2–11	2–16
Prestroke mBI		
Median	20[b]	19[b]
IQR	20–20	18–20

[a] $P < .05$, χ^2 test.

Table 2: Demographics of patients with AIS undergoing interventional therapies

	<75 Years of Age	≥75 Years of Age
Patients	70 (65%)	37 (35%)
Mean age	60 ± 13	80 ± 4
Sex		
Male	40 (57%)	14 (38%)
Female	30 (43%)	23 (62%)
LDL	83 ± 37[a]	65 ± 29[a]
INR value	1.1 ± .25	1.2 ± .37
Warfarin use	9 (12%)	10 (24%)
Statin use	19 (44%)	18 (56%)
Diabetes	15 (19%)	13 (32%)
Hypertension	51 (65%)[a]	34 (82%)[a]
Heart disease	29 (37%)	20 (49%)
Atrial fibrillation	23 (30%)[a]	21 (51%)[a]
Admission NIHSS score		
Median	17.5	18
IQR	12.75–21	16–22.5
Prestroke mBI		
Median	20[a]	19[a]
IQR	20–20	19–20

[a] $P < .05$, χ^2 test.

Table 3: Rates of endovascular treatment

	<75 Years of Age	≥75 Years of Age
Total	70/1190 (5.9%)[a]	37/1064 (3.5%)[a]
Male	40/684 (5.8%)	14/410 (3.4%)
Female	30/506 (5.9%)	23/654 (3.5%)
Treatment regimen		
IA only	18 (26%)	8 (22%)
IV and IA	16 (23%)	12 (32%)
IA and device	11 (16%)	5 (14%)
Device only	21 (30%)	12 (32%)
IV, IA, and device	4 (6%)	0
Time to intervention	141 ± 92	153 ± 87
Duration of intervention	204 ± 69[a]	172 ± 55[a]
Recanalization rate	68%	79%

[a] $P < .05$, χ^2 test.

Table 4: Short- and long-term outcomes in patients with AIS receiving endovascular treatment

	<75 Years of Age ($n = 70$)	≥75 Years of Age ($n = 37$)
Decrease in NIHSS score ≥ 4	70%	82%
Symptomatic ICH	9%[a]	24%[a]
In-hospital mortality	26%[a]	46%[a]
mBI ≥ 15 at 3 months	51%[a]	28%[a]
mBI ≥ 15 at 1 year	52%[a]	22%[a]

[a] $P < .05$, χ^2 test.

3.5% in the 75-year-or-older cohort, $P = .007$). The type of recanalization device did not differ among the 2 age groups. There was no sex difference in the percentage of men versus women who underwent endovascular treatment in either age group. The time from symptom onset to the intervention was similar for both age groups. The duration of the intervention was significantly shorter in the older cohort (172 versus 204 minutes, $P < .05$). There was no significant difference in the rates of vessel recanalization between the 2 age groups, though the older age groups had a trend toward increased recanalization (48/70, 68%, in younger-than-75-year versus 29/37, 79%, in the 75-year-or-older group).

Table 4 shows the short- and long-term outcomes in patients with AIS receiving endovascular treatment. The admission NIHSS score was higher in those patients undergoing endovascular treatment compared with patients who did not undergo an intervention for both age groups. Although, in general, stroke severity was significantly worse for the older compared with the younger cohort (median NIHSS score 6 in the 75-year-or-older versus 4 in younger-than-75-year group, $P < .05$), for those undergoing endovascular treatment, stroke severity was similarly high (median NIHSS score 18.0 in the 75-year-or-older versus 17.5 in younger-than-75-year group) and was not significantly different between age groups. Both age groups showed an improvement in the NIHSS score between admission and discharge. In older subjects, 82% had an improvement in their NIHSS score ≥4 points compared with 70% in the younger group. Patients 75 years or older were significantly less likely to have minimal or no disability by the mBI at 3 months (mild to no disability of 28% in the 75-year-or-older versus 51% in the younger-than-75-year group) and at 12-months (22% in the 75-year-or-older versus 52% in the younger-than-75-year group).

Older patients receiving endovascular treatment had a significantly higher rate of SICH (9/37, 24%, versus 6/70, 9%; $P = .04$) as shown in Table 4. The higher rates of SICH in the older cohort were not secondary to elevations in the INR (1.2 versus 1.1), and most patients were in the normal range. Age, female sex, and warfarin use were all predictors of SICH. In-hospital mortality was increased in all patients undergoing endovascular treatment compared with all patients in both age groups. An increased in-hospital mortality in the 75-year-or-older cohort compared with their younger cohort (255/1064, 24%, versus 131/1190, 11%; $P = .001$) was seen in all AIS, as well as in those patients who received IA therapies (17/37, 46%, versus 18/70, 26%; $P = .05$). In multivariate analysis, age and female sex were predictors of mortality. The mortality rate in older patients experiencing SICH was 89%.

Discussion

Several important findings are revealed by this study. Patients 75 years or older are being treated less frequently with endovascular interventions compared with younger patients. Lower rates of intervention were not due to later hospital arrival but may reflect lower preadmission functional status. This supposition is supported by a lower mBI in older patients compared with younger patients undergoing an intervention. In addition, treatment guidelines, patient and care provider preference, as well as difficult-to-quantify social factors may explain the different intervention rates. Advanced directives indicating no aggressive therapies or a higher rate of widowed patients lacking a health advocate may also have played a role. In contrast to previous reports of decreased rates and aggressiveness of stroke interventions and diagnostic testing in women,[25] we found no sex differences in endovascular treatment rates in this study.

Higher rates of SICH in patients 75 years or older appeared to contribute to increased mortality in this cohort, given the high 89% mortality rate associated with SICH. The increased SICH rate in patients 75 years or older may be related to a higher rate of cardioembolic stroke from atrial fibrillation and to the increased use of warfarin.[26] Although we found no significant difference in INR levels between age groups, the mechanism of warfarin-related bleeding may occur via pathways not reflected by INR levels.[27] Lower LDL levels have been shown to increase the risk of ICH[28] and may contribute to SICH in older patients with stroke undergoing catheter-based interventions. The increased prevalence of hypertension among older patients is likely to contribute to SICH. Higher stroke severity, as measured by an increased NIHSS score, is a well-recognized risk factor for SICH following both IV[29] and endovascular procedures.[8] Although the NIHSS score was significantly higher in the complete older cohort compared with the younger group (Table 1), the NIHSS score was not significantly higher in the older intervention group compared with the younger group (Table 2), possibly due to a ceiling effect.

Because the number of patients receiving IV tPA before the endovascular procedure was similar for both age groups, it is unlikely that larger tPA doses contributed to higher SICH in the older cohort. Time from stroke onset to treatment was similar in the older age group; therefore, delay in providing treatment did not contribute to the increased rate of SICH or mortality. We initially hypothesized that intervention times in older subjects would be prolonged due to increased vessel tor-

tuosity and atherosclerotic burden[30]; however, the procedure durations were surprisingly shorter for older patients, making it less likely that the increased SICH rates were secondary to higher rates of iatrogenic vessel injury. Lower recanalization rates could also potentially prolong ischemic duration and increase infarct size, leading to higher ICH rates,[19] but the 75-year-or-older cohort had equivalent, if not slightly better, recanalization rates than the younger group. Previous studies have also reported similar recanalization rates in the old compared with the young groups.[31] Age-related changes such as increased incidence of amyloid angiopathy,[13,32] blood-brain barrier dysfunction,[15] reduced tPA clearance,[14] and impaired clotting mechanisms,[16] which have been previously described, could have predisposed the older patients to ICH.

Because the SICH rate in the younger cohort was similar to that seen in other studies,[33] it is unlikely that the significant increase in SICH rate in the aged is secondary to an unexpected low rate of SICH in the young cohort. The predisposition of the aging brain to bleeding may be more evident in the extended therapeutic window for IA therapies than it is for the more stringent timeframe used for IV therapy. In a recent study by Brinjikji et al,[34] no increase in SICH was seen in older patients undergoing interventions, and a lower mortality (29.7%) than that found in our study (46%) was seen, very likely due to their lower chosen age cutoff of 65 years. We chose age 75 on the basis of the HIAT score, shown to be predictive of outcome.[8] SICH rates remained significantly elevated even when dichotomizing with an age cutoff of 80 years.

Increased medical comorbidities and lower prestroke functional status may also contribute to the high mortality in older interventional patients. Patients 75 years or older may be less tolerant of the general anesthesia induced during IA procedures,[35,36] which is routine for any device interventions at our center. The 2-fold increase in mortality in the older patients was independent of the technique of interventional treatment (IA/device/combination and so forth). Aggressive treatments for AIS such as hemicraniectomy, which are not performed in older patients, may be influencing survival as well. A similarly high mortality rate following interventions in elderly patients with AIS was demonstrated by other studies.[7,31,37]

Favorable recanalization rates following IA procedures may explain the comparable improvement in NIHSS scores between admission and discharge in both age groups (Table 3). Although older patients had a similar rate of improvement in NIHSS score at discharge after intervention, the functional benefit appears to end there for older patients with AIS (Table 4). In younger patients, the proportion of favorable mBI continues to improve (to 52% at 12 months), whereas recovery stopped after 3 months in our older cohort. This finding has implications for rehabilitation approaches following stroke in older adults. Studies have shown decreased neuroplasticity in the aging brain, which may limit the extent of recovery,[38] though it is also possible that older adults are not receiving the full extent of rehabilitative services to reach their potential. Our findings are consistent with prior studies that have found worse functional outcomes in older adults.[31,39,40]

Our study has several limitations and these data must be interpreted with these in mind. This was a single-center retrospective analysis. However, it is one of the largest cohorts that has been examined to date and has the longest follow-up (12 months) compared with currently published data. The decision to administer treatment was not randomized, and a bias exists toward selecting older patients with better premorbid functional status. However, the prestroke mBI was significantly lower in the older patients, suggesting that there were meaningful baseline deficits in the older cohort. Perfusion scans were not performed to guide patient selection. Recent studies have indicated that the extent of perfusion deficits may indicate risk of hemorrhagic transformation.[41] The high mortality rate in the older age group makes analysis of long-term functional outcomes susceptible to selection bias. We did not distinguish between anterior and posterior circulation strokes or the different types of recanalization methods (due to the small numbers). IA tPA and mechanical clot disruption were grouped together for both young and old groups, so it was a less likely source of bias. In addition, during the 4-year study period, new catheter devices emerged[12] adding variability to the interventions, which may have altered observed outcomes. Previous studies have failed to show a significant difference in the complication rate based on the type of procedure.[18] Information on the degree of recanalization was not defined by TIMI guidelines.[42] Rather "successful" revascularization was determined by the interventional neuroradiologist and was equivalent to a TIMI flow of II or above.

Decisions regarding endovascular treatment for the older patients with AIS are often made on an individual basis and can be influenced by many factors, including baseline functional status, time of onset, stroke severity, patient and family preferences, imaging criteria, and ethical considerations. Our findings of higher SICH and mortality in patients 75 years or older make future studies examining the selection criteria for interventional therapies essential. The optimal form of anesthesia and sedation, especially in the older age group, is an important area of investigation. High rates of recanalization and improved neurologic function during the course of hospitalization suggest that some older patients are appropriate candidates for endovascular stroke treatments, offering an alternative to those who do not qualify for respond to IV thrombolysis. The high mortality in the elderly undergoing endovascular procedures likely stems from comorbid factors, medical complications, and the increased rate of SICH. Strategies to improve long-term recovery to maintain the rate of recovery during the hospitalization also need to be explored. Prospective randomized trials are needed to determine criteria for selecting elderly patients with stroke most likely to benefit from acute endovascular stroke therapies, including the use of perfusion imaging.

Conclusions

When one decides whether an interventional stroke therapy should be offered to an older stroke patient, our results indicate that nearly half of IA-treated patients will die in the hospital in part as a result of complications of SICH related to the intervention. The initial recovery in older survivors may "stall," because patients often do not continue to improve with time, unlike younger patients who continue to improve for ≤ 1 year after the intervention. In addition, this is a high-cost labor-intensive treatment, which is not currently the standard of care. In light of aging demographics and limited medical re-

sources, to truly answer this important question requires a randomized controlled trial of elderly patients with stroke, including an analysis of cost-effectiveness.

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