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# Thrombolysis and mechanical thrombectomy for acute ischemic stroke in octogenarian patients: a regional observational study

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Année : 2020

**THROMBOLYSIS AND MECHANICAL THROMBECTOMY FOR ACUTE ISCHEMIC  
STROKE IN OCTOGENARIAN PATIENTS: A REGIONAL OBSERVATIONAL  
STUDY**

THÈSE  
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE  
DIPLOME D'ÉTAT

Manon MICHELARD

[Données à caractère personnel]

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## **ABSTRACT**

**Introduction:** Elderly patients represent a growing stroke population characterized by a higher frailty, underrepresented in clinical trials. We investigated safety, efficacy and prognosis factors of intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) in elderlies.

**Methods:** We conducted a retrospective analysis of acute ischemic stroke patients hospitalized in the 4 Stroke Units of the French Northern Alps Emergency Network (RENAU-AVC) between 2014 and 2019. We compared clinical characteristics, functional outcome and mortality between  $\geq 80$  years old (yo),  $< 80$ yo patients, and subgroup of nonagenarians ( $\geq 90$ yo).

**Results:** Number of  $\geq 80$ yo patients admitted has doubled in 6 years with a 5-fold increase of IVT and/or MT (30 procedures in 2014 vs 173 in 2019). After IVT and/or MT,  $\geq 80$ yo patients had a poorer functional outcome at discharge (modified Rankin scale 0 to 2 = 34.1% vs 60.8%) and at 6 months (18.1% vs 43.1%). Mortality rate was higher in  $\geq 80$ yo compared to  $< 80$ yo patients (21.1% vs 5.6%). For patients undergoing IVT and/or MT, age over 80 years and high initial NIHSS (National Institute of Health Stroke Scale) were poor prognosis factors. Interestingly, no difference was observed for functional independence or mortality between octogenarians ( $\geq 80$ yo) and nonagenarians ( $\geq 90$ yo).

**Discussion:** IVT and MT in AIS management are feasible in octogenarians and nonagenarians but functional outcome remains poor compared to younger patients. Studies including elderlies are needed to better select patients that would benefit from IVT and/or MT.

**Keywords:** ischemic stroke, octogenarians, nonagenarians, intravenous thrombolysis, mechanical thrombectomy, outcome

## **TABLE OF CONTENTS**

### LIST OF ABBREVIATIONS

### INTRODUCTION

### METHODS

- 1) Patient selection
- 2) Data collection
- 3) Recanalization procedures
- 4) Outcomes
- 5) Statistical analysis

### RESULTS

- 1) Number of ischemic strokes and recanalization attempts evolution in the French Northern Alps Emergency Network (RENAU-AVC)
- 2) Characteristics of overall patients with AIS
- 3) Characteristics of patients with AIS and undergoing a recanalization attempt
- 4) Functional outcomes
- 5) Prognosis factors

### DISCUSSION

- 1) Epidemiology: increasing of number of elderly patients in stroke units
- 2) Safety and efficacy of recanalization strategies
- 3) Prognosis factors in elderly stroke patients
  - a. Age
  - b. Delays
  - c. Successful of recanalization
  - d. NIHSS score initial
- 4) Pre-stroke disability in elderly
- 5) Selection patient
- 6) Limitations

### CONCLUSION

### BIBLIOGRAPHY

## **LIST OF ABBREVIATIONS**

IVT: intravenous thrombolysis

MT: mechanical thrombectomy

RCTs: randomized clinical trials

AIS: acute ischemic stroke

LVO: large vessel occlusion

NIHSS: National Institute of Health Stroke Scale

MRI: Magnetic Resonance Imaging

CT: Computerized Tomography

mTICI: modified Thrombolysis In Cerebral Ischemia

mRS: modified Rankin Scale

med: median

IQR: interquartile range

CI: confidence interval

OR: odd ratio

yo: years old

ref: reference

## **INTRODUCTION**

About one-third of stroke occurred in subjects over 80 years and 17% in those over 85 years (1). A result of ageing and growth of the population, the burden of cardioneurovascular disease will substantially increase. Due to improvement in health care and better standards of living, the number of stroke events is also expected to more than double (2) by the year 2050, with the majority of the increase among the elderly (3). As one of the fastest growing portions of the population, octogenarians will constitute a significant percentage of the stroke patient population in the near future. Octogenarians are nevertheless not specifically targeted by most clinical guidelines. Elderly were often excluded or under-represented in randomized clinical trials (RCTs).

When delivered within 4.5 hours, intravenous thrombolysis (IVT) significantly improves the overall odds of a good stroke outcome. Proportional treatment benefits were similar irrespective of age or stroke severity (4). In most European countries in 2014, IVT is also restricted to patients younger than 80 years but this meta-analysis shows the effect of Alteplase treatment was similar for patients aged 80 years or younger.

Mechanical thrombectomy (MT) trials that included elderly patients (over 80 years) showed better outcomes when treated with IVT+MT (“bridging therapy”) compared to IVT alone, with more favorable odds ratios than among younger patients (5).

However, the efficacy of IVT+MT for acute ischemic stroke in octogenarians is still controversial. Recent studies have reported higher morbidity and mortality in elderly patients than in their younger counterparts (6–9).

We aim to describe ageing and growth evolution of population in Northern French Alps Stroke Units (RENAU-AVC network) and investigate safety, efficacy and prognosis factors of IVT and/or MT in octogenarians and nonagenarians.

## **METHODS**

### 1) Patient selection

All consecutive patients referred to the 4 Stroke Units of Northern French Alps (Annecy, Annemasse, Chambéry, Grenoble) for acute ischemic stroke (AIS) between January 2014 and December 2019 were prospectively included in the registry. Ischemic stroke was diagnosed by a stroke neurologist based on clinical and imaging data.

### 2) Data collection

Clinical and radiological baseline data, including age, sex, large vessel occlusion (LVO), wake-up stroke, National Institute of Health Stroke Scale (NIHSS) score at presentation, brain imaging type, etiology of stroke, management delays (door-to-imagery, door-to-needle, door-to-puncture (for MT), door-to-recanalization), in-hospital mortality and functional outcomes were collected from medical records by a trained physician. Quality controls were performed before analysis.

### 3) Recanalization procedures

All IVT were administered at dose of 0.9mg/kg Alteplase and MT was performed using contact aspiration and/or stent retriever. Modified Thrombolysis In Cerebral Ischemia (mTICI; 0 to 3) recanalization grading scores were collected. Successful recanalization was defined as a mTICI score  $\geq 2$ .

### 4) Outcomes

A clinical assessment was realized at discharge and between three and six months post-stroke by a neurologist. Functional outcome was assessed using the modified Rankin Scale (mRS), ranged from 0 (no symptom) to 6 (death). Favorable outcome is defined as mRS 0-2 (i.e. alive and independent) and poor outcome is defined as mRS 3-6. We divided the patients into age

groups for analysis. Firstly, we compared younger patients <80 years old (<80yo) and elderly patients  $\geq 80$ yo and secondly, we compared octogenarians (80-89yo) with nonagenarians ( $\geq 90$ yo).

#### 5) Statistical analysis

Continuous variables were presented as the mean  $\pm$  standard deviation or median and interquartile range (IQR) with 25th and 75th percentiles and compared with the Student's t-test or Mann-Whitney U test. The assessment different variables to predict good or poor outcomes after recanalization procedure in elderly patients compared with younger adults used multivariate stepwise logistic regression. SPSS version 26.0 was used for all statistical analysis.

## **RESULTS**

### 1) Number of ischemic strokes and recanalization attempts evolution in the French Northern Alps Emergency Network (RENAU-AVC)

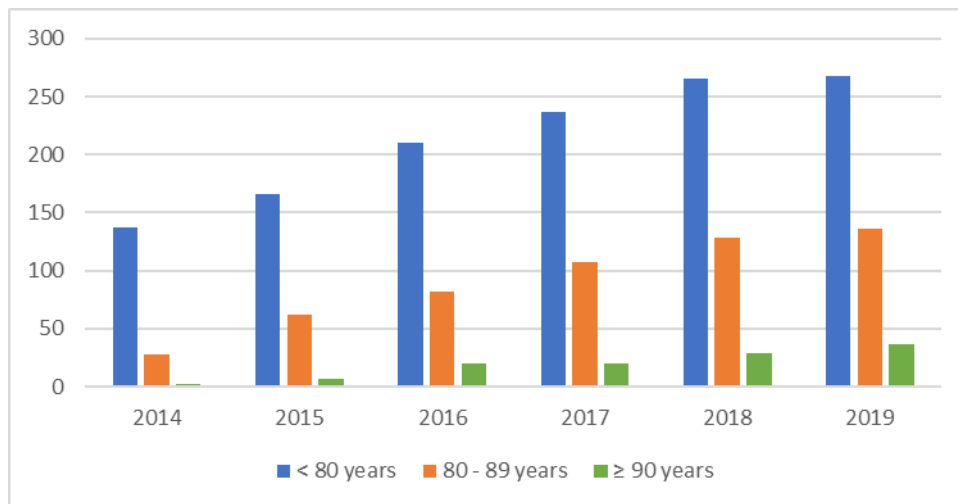
The number of AIS patients over the age of 80 years in stroke units increased from 225 (24% of patients) in 2014 to 500 (35% of patients) in 2019. Indeed, proportion of 80-89yo increased about of 222% and proportion of  $\geq 90$ yo increased about of 324% during the same period. (Table 1)

Number of recanalization attempts also dramatically increased (Table 1 and Figure 1) with 137 recanalization attempts for  $<80$ yo patients in 2014 *versus* 268 in 2019, 28 for 80-89yo patients *versus* 136 in 2019, and 2 for  $\geq 90$ yo in 2014 *versus* 37 in 2019. Number of MT 4-fold increased between 2015 (n = 26) and 2016 (n = 110) among all patients hospitalized for AIS in stroke units with the rise of MT during the year 2015 and continue to increase (n = 191 in 2019), especially in octogenarians (n = 3 in 2015 and n = 69 in 2019) and nonagenarians (n = 1 in 2015 and n = 12 in 2019).

		2014	2015	2016	2017	2018	2019
<80yo	<b>AIS</b>	<b>699</b>	<b>859</b>	<b>957</b>	<b>915</b>	<b>1018</b>	<b>936</b>
	<b>Reca</b>	<b>137</b>	<b>166</b>	<b>210</b>	<b>237</b>	<b>266</b>	<b>268</b>
	- IVT	125	144	135	144	148	158
	- MT/B	12	22	75	93	118	110
80-89yo	<b>AIS</b>	<b>192</b>	<b>287</b>	<b>360</b>	<b>374</b>	<b>424</b>	<b>393</b>
	<b>Reca</b>	<b>28</b>	<b>62</b>	<b>82</b>	<b>107</b>	<b>128</b>	<b>136</b>
	- IVT	28	59	50	65	69	67
	- MT/B	0	3	32	42	59	69
≥90yo	<b>AIS</b>	<b>33</b>	<b>66</b>	<b>75</b>	<b>80</b>	<b>105</b>	<b>107</b>
	<b>Reca</b>	<b>2</b>	<b>7</b>	<b>20</b>	<b>20</b>	<b>29</b>	<b>37</b>
	- IVT	2	6	17	17	21	25
	- MT/B	0	1	3	3	8	12
Overall	<b>AIS</b>	<b>924</b>	<b>1212</b>	<b>1392</b>	<b>1369</b>	<b>1547</b>	<b>1436</b>
	<b>Reca</b>	<b>167</b>	<b>235</b>	<b>312</b>	<b>364</b>	<b>423</b>	<b>441</b>
	- IVT	155	209	202	226	238	250
	- MT/B	12	26	110	138	185	191

yo: years old

**Table 1:** Number of acute ischemic stroke (AIS) patients admitted in Northern French Alps stroke units and number of recanalization attempts (Reca) with number of Intravenous Thrombolysis alone (IVT) and Mechanical Thrombectomy alone or Bridging (MT/B) by age groups between 2014 and 2019.



**Figure 1:** Evolution of annual number of recanalization attempts by age group between 2014 and 2019



## 2) Characteristics of overall patients with AIS

In this cohort of 7880 AIS patients, 5384 are <80yo, 2496 are ≥80yo of which 466 are ≥90yo. Patients ≥80yo were more female and had more severe strokes compared with <80yo (median NIHSS = 7 [3 – 15] vs 4 [1 – 8], p < 0.001). Nonagenarians were more female compared with octogenarians and had more severe strokes (median NIHSS = 8 [3.75 – 18] vs 6 [2 – 14], p < 0.001). The baseline characteristics are summarized in Table 2.

	<80yo (n=5384)	≥80yo (n=2496)	p values	80-89yo (n=2030)	≥90yo (n=466)	p values
Men (n, %)	3542 (65.8%)	1086 (43.5%)	< 0.001	933 (46.0%)	153 (32.8%)	< 0.001
Age (med, IQR)	66 [56 - 73]	85 [82 – 88]	< 0.001	84 [82 – 86]	92 [91 – 94]	< 0.001
NIHSS scale at presentation (med, IQR)	4 [1 – 8]	7 [3 – 15]	< 0.001	6 [2 – 14]	8 [3.75 – 18]	0.001
NIHSS ≤ 5 (n, %)	3256 (60.5%)	1060 (42.5%)		899 (44.3%)	161 (34.5%)	
NIHSS 6-10 (n, %)	832 (15.5%)	483 (19.4%)		393 (19.4%)	90 (19.3%)	
NIHSS 11-15 (n, %)	423 (7.9%)	269 (10.8%)		213 (10.5%)	56 (12.0%)	
NIHSS 16-20 (n, %)	344 (6.4%)	266 (10.7%)		201 (9.9%)	65 (13.9%)	
NIHSS > 20 (n, %)	273 (5.1%)	296 (11.9%)		226 (11.1%)	70 (15.0%)	
LVO (n, %)	1045 (19.4%)	598 (24.0%)	< 0.001	491 (24.2%)	107 (23.0%)	0.600
MRI (n, %)	2016 (37.4%)	765 (30.6%)	< 0.001	662 (32.6%)	103 (22.1%)	< 0.001
Wake up stroke (n, %)	321 (6.0%)	147 (5.9%)	0.900	119 (6.3%)	28 (6.6%)	0.800
Recanalization attempt (n, %)	1284 (23.8%)	658 (26.4%)	0.030	543 (26.7%)	115 (24.7%)	0.300

*IQR = interquartile range; IVT = intravenous thrombolysis; LVO = large vessel occlusion; NIHSS = National Institute of Health Stroke Scale; MRI = Magnetic Resonance Imaging; med = median; IQR = interquartile range; yo = years old*

**Table 2:** Characteristics baseline of overall patients with acute ischemic stroke (AIS)

### 3) Characteristics of patients with AIS and undergoing a recanalization attempt

In this cohort of 7880 AIS patients, 1942 underwent a recanalization attempt (IVT alone or MT alone or bridging), 658 patients (33.9%) were  $\geq 80$ yo. The baseline characteristics are summarized in Table 3.

Patients  $\geq 80$ yo are more female (60.0% vs 37.7%,  $p < 0.001$ ) and have more severe ischemic strokes (median NIHSS = 13[8 - 20] vs 9 [5 - 16,75],  $p < 0.001$ ) than younger patients (<80yo). Patients  $\geq 80$ yo have significantly more LVO (60% vs 50.5%,  $p < 0.001$ ) and more cardioembolic etiology stroke (52.5% vs 33.2%,  $p < 0.001$ ) than <80yo. There were no significant difference concerning recanalization strategies between both groups: 64.7% vs 66.5% for IVT alone, 13.4% vs 12.9% for MT alone and 21.9% vs 20.6% for bridging (IVT+MT),  $p = 0.700$ . Proportion of patients receiving MRI rather than CT was not different between groups. Proportion of successful recanalization was not different between both groups (61.6% of  $\geq 80$ yo vs 67.2% for <80yo,  $p = 0.060$ ). Onset-to-treatment delay was not different between both groups (180 min for both,  $p = 0.630$ ). Door-to-treatment time was significantly longer for  $\geq 80$ yo (80 min vs 73 min,  $p = 0.001$ ).

We compared 543 octogenarians with 115 nonagenarians who underwent a recanalization attempt. Nonagenarians were more female (67.0% vs 58.6%,  $p < 0.001$ ) and had more severe strokes (median NIHSS = 17 [9 - 21] vs 13 [7 - 20],  $p < 0.001$ ) with more LVO. Nonagenarians had even more cardioembolic etiology stroke than octogenarians (58.8% vs 51.4% respectively,  $p < 0.001$ ). Proportion of patients receiving MRI rather than CT was not different between both groups. There were more IVT alone (76.5% vs 62.2%) and less bridging (10.4% vs 24.3%) in the  $\geq 90$ yo group compared with octogenarians. The rate of successful recanalization was comparable between nonagenarians and octogenarians (59.3% vs 62.0%,  $p = 0.400$ ).

Onset-to-treatment time are not different between both groups (180 min vs 179 min,  $p = 0.820$ ).

Door-to-treatment time is significantly longer for nonagenarians (81 min vs 78 min,  $p = 0.001$ ).

	<80yo (n=1284)	≥80yo (n=658)	p values	80-89yo (n=543)	≥90yo (n=115)	p values	
Men (n, %)	800 (62.3%)	263 (40.0%)	< 0.001	225 (41.4%)	38 (33.0%)	< 0.001	
Age (med, [IQR])	67 [56 – 74]	85 [82 – 88]	< 0.001	84 [82 – 86]	92 [90 – 94]	< 0.001	
NIHSS at presentation (med, [IQR])	9 [5 – 16,75]	13 [8 - 20]	< 0.001	13 [7 - 20]	17 [9 - 21]	< 0.001	
NIHSS ≤ 5 (n, %)	365 (28.4%)	93 (14.1%)		84 (15.5%)	9 (7.8%)		
NIHSS 6-10 (n, %)	317 (24.7%)	150 (22.8%)		121 (22.3%)	29 (25.2%)		
NIHSS 11-15 (n, %)	221 (17.2%)	123 (18.7%)		104 (19.2%)	19 (16.5%)		
NIHSS 16-20 (n, %)	183 (14.7%)	136 (21.1%)		112 (21.2%)	24 (20.9%)		
NIHSS > 20 (n, %)	158 (12.7%)	142 (22.0%)		108 (20.4%)	34 (29.6%)		
LVO (n, %)	649 (50.5%)	395 (60.0%)	< 0.001	324 (59.7%)	71 (61.7%)	< 0.001	
MRI (n, %)	852 (66.4%)	410 (62.3%)	0.077	343 (63.2%)	67 (58.3%)	0.130	
Wake up stroke (n, %)	41 (3.2%)	13 (2.0%)	0.100	10 (1.8%)	3 (2.6%)	0.600	
Recanalization type strategy (n, %)	IVT alone	854 (66.5%)	426 (64.7%)	338 (62.2%)	88 (76.5%)	0.020	
	MT alone	165 (12.9%)	88 (13.4%)	73 (13.4%)	15 (13.0%)		
	IVT + MT	265 (20.6%)	144 (21.9%)	132 (24.3%)	12 (10.4%)		
Etiology (n, %)	Atheroma	210 (27.3%)	83 (24.5%)	74 (25.7%)	9 (17.6%)	< 0.001	
	Cardio-embolic	256 (33.2%)	178 (52.5%)	148 (51.4%)	30 (58.8%)		
	Others	304 (39.5%)	78 (23.0%)	63 (21.9%)	11 (21.6%)		
Delays (med, [IQR])	Door to imagery	35 [22 - 54]	39 [24 - 59]	0.009	38 [23 – 58]	43 [27 – 70]	0.003
	Door to needle	71 [55 – 93]	76 [59 – 101]	0.002	75.5 [59 – 101]	78 [62 – 110]	0.005
	Door to puncture for MT only	129 [84 – 197]	137 [105 – 192]	0.180	135 [102 – 193]	144 [120 – 173]	0.330
	Door to treatment	73 [55 – 98]	80 [60- 110]	0.001	78 [59 – 108]	81 [64 – 221]	0.001
	Door to recanalization for MT only	170 [126.5 – 134.5]	182 [145 – 216.5]	0.274	182 [140 – 117]	183.5 [180 – 204]	0.430
	Onset to treatment	180 [144.8 – 231.3]	180 [144.3 – 220]	0.630	180 [145 – 221]	179 [139.3 – 210]	0.820
	Onset to door	98 [67 – 151]	90 [64.25 – 135.75]	0.010	93 [65 – 140]	81 [60 – 117]	0.400
mTICI score (n, %)	mTICI ≤ 2a	73 (17.0%)	57 (24.6%)	0.060	48 (23.4%)	9 (33.3%)	0.400
	mTICI ≥ 2b	289 (67.2%)	143 (61.6%)	127 (62.0%)	16 (59.3%)		
	TICI missing	68 (15.8%)	32 (13.8%)	30 (14.6%)	2 (7.4%)		

*IQR = interquartile range; IVT = intravenous thrombolysis; MT = mechanical thrombectomy; LVO = large vessel occlusion; NIHSS score = National Institute of Health Stroke score; MRI = Magnetic Resonance Imaging; med = median; IQR = interquartile range; mTICI: modified Thrombolysis In Cerebral Ischemia; yo = years old.*

**Table 3:** Characteristics of patients with acute ischemic stroke (AIS) and undergoing a recanalization attempt

#### 4) Functional outcomes

Whatever recanalization strategies (IVT alone, MT alone or bridging),  $\geq 80$ yo had significantly lower rate of good outcome at discharge (mRS 0-2 = 34.1% vs 60.8%;  $p < 0.001$ ) compared with  $< 80$ yo. In-hospital mortality was significantly higher in  $\geq 80$ yo group (21.1% vs 5.6%,  $p < 0.001$ ). There is no significant difference between nonagenarians and octogenarians for good functional outcome rate at discharge (27.7% vs 35.5% respectively,  $p = 0.100$ ). In-hospital mortality have a non-significant trend to be higher for nonagenarians compared to octogenarians (27% vs 19.9%;  $p = 0.090$ ). (Table 4, Figures 2 and 4)

$\geq 80$ yo patients had also a lower rate of good outcome after 3-6 months compared with  $< 80$ yo patients (18.1% vs 43.1%;  $p < 0.001$ ), whatever recanalization strategies. There is no significant difference between nonagenarians and octogenarians for good functional outcome at 3-6 months (17.4% vs 18.2%,  $p = 0.800$ ). (Table 4, Figures 3 and 5)

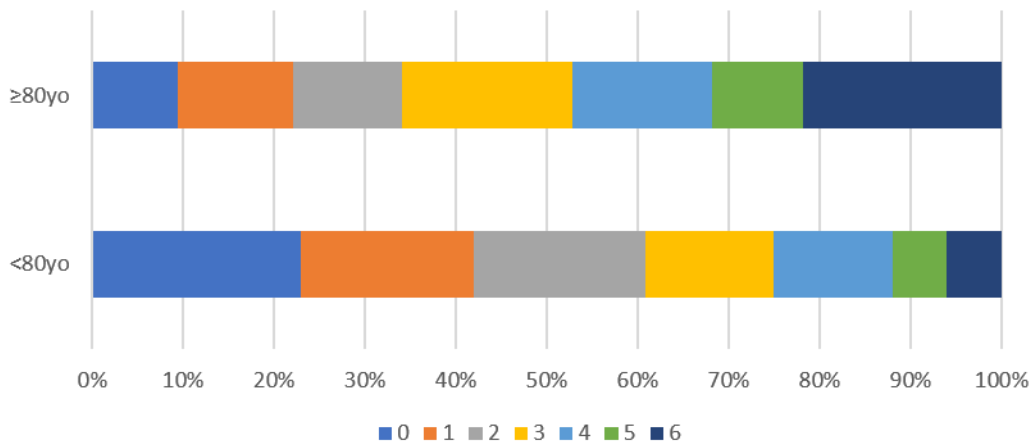
Younger ( $< 80$ yo) patients have significantly better rates of good outcome (mRS 0-2) at discharge, whatever for IVT (68.7% vs 39.3%,  $p < 0.001$ ) or MT/bridging (45.1% vs 24.7%,  $p < 0.001$ ) compared with the  $\geq 80$ yo patients. We found same results at 3-6 months, whatever for IVT (49.1% vs 21.4%,  $p < 0.001$ ) or MT/bridging (31.4% vs 12.1%,  $p < 0.001$ ). (Table 4)

Octogenarians had not better rates of good outcome (mRS 0-2) at discharge compared to nonagenarians, whatever for IVT (41.6% vs 30.6%,  $p = 0.100$ ) or MT/bridging (25.5% vs 18.5%,  $p = 0.400$ ). Results were the same at 3-6 months, whatever for IVT (21.9% vs 19.3%,  $p = 0.600$ ) or MT/bridging (12.2% vs 11.8%,  $p = 0.900$ ). (Table 4)

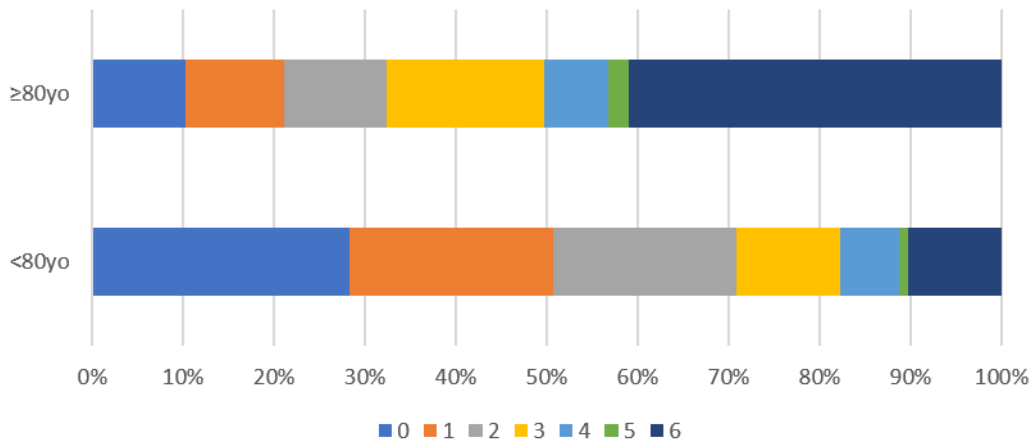
		< 80yo (n=1284)	≥ 80yo (n=658)	p values	80-89yo (n=543)	≥ 90yo (n=115)	p values
In hospital mortality (n, %)		72 (5.6%)	139 (21.1%)	< 0.001	108 (19.9%)	31 (27.0%)	0.090
mRS 0-2 at discharge	IVT (n, %)	549 (68.7%)	162 (39.3%)	< 0.001	136 (41.6%)	26 (30.6%)	0.100
	MT/B (n, %)	181 (45.1%)	56 (24.7%)	< 0.001	51 (25.5%)	5 (18.5%)	0.400
	<b>Overall (n, %)</b>	<b>730 (60.8%)</b>	<b>218 (34.1%)</b>	<b>&lt; 0.001</b>	<b>187 (35.5%)</b>	<b>31 (27.7%)</b>	<b>0.100</b>
mRS 0-2 at 3-6 months	IVT (n, %)	419 (49.1%)	91 (21.4%)	< 0.001	74 (21.9%)	17 (19.3%)	0.600
	MT/B (n, %)	135 (31.4%)	28 (12.1%)	< 0.001	25 (12.2%)	3 (11.8%)	0.900
	<b>Overall (n, %)</b>	<b>554 (43.1%)</b>	<b>119 (18.1%)</b>	<b>&lt; 0.001</b>	<b>99 (18.2%)</b>	<b>20 (17.4%)</b>	<b>0.800</b>

mRS = modified Rankin Scale; yo = years old

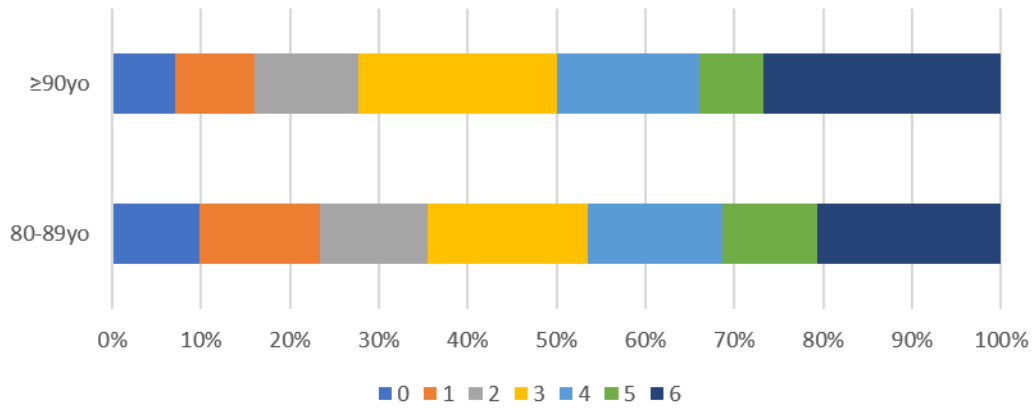
**Table 4:** Functional outcome after recanalization attempt by Intravenous Thrombolysis alone (IVT) and Mechanical Thrombectomy alone or Bridging (MT/B)



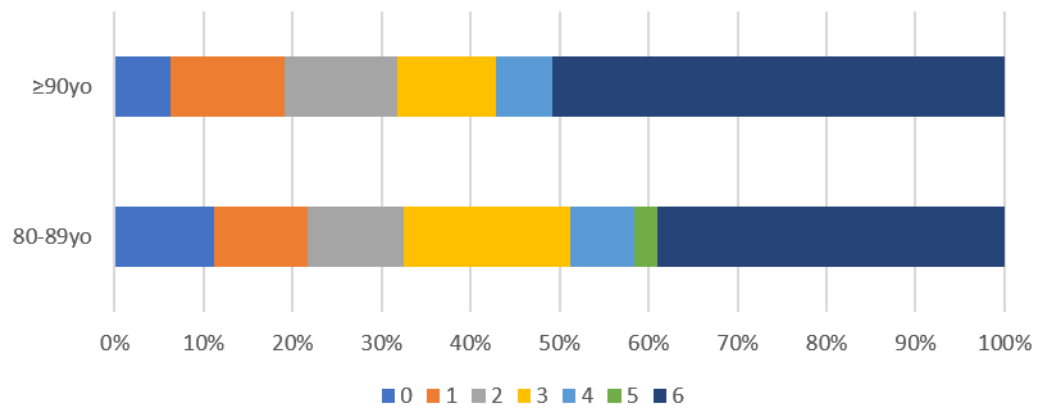
**Figure 2:** Distribution of modified Rankin Scale (mRS) scores at discharge after a recanalization attempt between patients aged < 80 years old and ≥ 80 years old



**Figure 3:** Distribution of modified Rankin Scale (mRS) scores at 3-6 months after a recanalization attempt between patients aged < 80 years old and ≥ 80 years old



**Figure 4:** Distribution of modified Rankin Scale (mRS) scores at discharge after a recanalization attempt between octogenarians and nonagenarians



**Figure 5:** Distribution of modified Rankin Scale (mRS) scores at 3-6 months after a recanalization attempt between octogenarians and nonagenarians

5) Prognosis factors of poor outcomes after recanalization attempt

Regarding all acute ischemic stroke patients hospitalized in stroke units, recanalization attempts were associated with lower odds of poor outcome (mRS 3-6) at discharge for <80yo (OR 0.624, CI (0.497-0.785),  $p < 0.001$ ) and  $\geq 80$ yo (OR 0.664, CI (0.495-0.890),  $p < 0.006$ ). Higher admission NIHSS was a significant predictor of poor outcome (mRS 3-6) at discharge for the both groups. Onset-to-door delay is not significant. (Table 5)

	<80yo (n=5384)			$\geq 80$ yo (n=2496)		
	OR	CI 95%	p value	OR	CI 95%	p value
Recanalization attempt	0.624	0.497 – 0.785	< 0.001	0.664	0.495 – 0.890	0.006
NIHSS $\leq 5$ (ref)			< 0.001			< 0.001
NIHSS 6-10	4.651	3.629 – 5.961	< 0.001	3.828	2.773 – 5.283	< 0.001
NIHSS 11-15	12.486	9.132 – 17.072	< 0.001	7.458	4.999 – 11.126	< 0.001
NIHSS 16-20	30.594	22.324 – 41.928	< 0.001	23.152	15.186 – 35.297	< 0.001
NIHSS > 20	40.202	17.818 – 90.706	< 0.001	27.024	11.156 – 65.460	< 0.001
Onset-to-door > 90 min	1.446	1.166 – 1.794	0.001	1.079	0.823 – 1.415	0.581

*NIHSS = National Institute of Health Stroke Scale; OR = odd ratio, CI = confidence interval; ref = reference*

**Table 5:** Multivariate analysis for predictors of poor outcome at discharge by age group in all acute ischemic stroke patients and hospitalized in stroke units



An age of  $\geq 80$  years old was associated with higher odds of poor outcome at discharge in patients undergoing IVT (OR=2.601, CI (1.933 – 3.501),  $p < 0.001$ ) and patients undergoing MT or bridging (OR=3.439, CI (1.847 – 6.407),  $p < 0.001$ ) independently. Higher admission NIHSS is a significant predictor of poor outcome for the both groups. Delays (onset-to-door  $> 90$  min, door-to-IVT  $> 60$  min, door-to-puncture  $> 120$  min) were not significant. (Table 6)

	IVT			MT alone or bridging		
	OR	CI 95%	p value	OR	CI 95%	p value
Age $\geq 80$ yo	2.601	1.933 – 3.501	$< 0.001$	3.439	1.847 – 6.407	$< 0.001$
NIHSS $\leq 5$ (ref)			$< 0.001$			0.012
NIHSS 6-10	2.127	1.475 – 3.067	$< 0.001$	1.367	0.369 – 5.066	0.640
NIHSS 11-15	4.302	2.817 – 6.568	$< 0.001$	1.618	0.510 – 5.139	0.414
NIHSS 16-20	9.287	5.622 – 15.341	$< 0.001$	3.632	1.203 – 10.960	0.022
NIHSS $> 20$	29.137	14.859 – 57.135	$< 0.001$	4.355	1.403 – 13.518	0.011
Onset-to-door $> 90$ min	1.348	1.004 – 1.811	0.047	1.711	0.944 – 3.102	0.077
Door-to-needle $> 60$ min	1.014	0.733 – 1.404	0.932	1.061	0.565 – 1.993	0.854
Door-to-puncture $> 120$ min (for MT)				1.216	0.637 – 2.321	0.553

IVT = intravenous thrombolysis; MT = mechanical thrombectomy; NIHSS = National Institute of Health Stroke Scale; OR = odd ratio, CI = confidence interval; ref = reference

**Table 6:** Multivariate analysis for predictors of poor outcome (mRS 3-6) at discharge after recanalization attempt by recanalization strategy

An age of  $\geq 80$  years old was associated with higher odds of poor outcome at 3-6 months in patients undergoing IVT (OR=2.950, CI (2.174 – 4.004),  $p < 0.001$ ) and patients undergoing MT or bridging (OR=3.242, CI (1.622 – 6.481),  $p < 0.001$ ) independently. Higher admission NIHSS was a significant predictor of poor outcome for the both groups. Time of door-to-puncture  $> 120$  min was significantly associated with odds of poor outcome (OR = 3.320, CI (1.657 – 6.653),  $p < 0.001$ ). (Table 7)

	IVT			MT alone or bridging		
	OR	CI 95%	p value	OR	CI 95%	p value
Age $\geq 80$ yo	2.950	2.174 – 4.004	$< 0.001$	3.242	1.622 – 6.481	0.001
NIHSS $\leq 5$ (ref)			$< 0.001$			0.037
NIHSS 6-10	1.286	0.940 – 1.760	0.116	2.267	0.594 – 8.657	0.231
NIHSS 11-15	1.933	1.297 – 2.880	0.001	1.604	0.508 – 5.060	0.420
NIHSS 16-20	3.556	2.129 – 5.938	$< 0.001$	4.025	1.305 – 12.416	0.015
NIHSS $> 20$	10.778	5.028 – 23.106	$< 0.001$	4.245	1.333 – 13.520	0.014
Onset-to-door $> 90$ min	1.073	0.817 – 1.409	0.613	1.268	0.673 – 2.389	0.463
Door-to-needle $> 60$ min	1.022	0.755 – 1.382	0.889	0.517	0.259 – 1.034	0.062
Door-to-puncture $> 120$ min (for MT)				3.320	1.657 – 6.653	0.001

*Abbreviations are defined in Table 6.*

**Table 7:** Multivariate analysis for predictors of poor outcome (mRS 3-6) at 3-6 months after recanalization attempt by recanalization strategy

Etiology and delays (onset-to-door, door-to-needle, door-to-puncture) were not associated with higher risk of poor outcome in elderly ( $\geq 80$ yo) undergoing a recanalization attempt (Table 8, 9 and 10). Higher admission NIHSS was a significant predictor of poor outcome (Table 8 and 9). For elderly ( $\geq 80$ yo) patients undergoing MT or bridging, TICI  $\geq 2b$  was significantly associated with lower odd of poor outcome (OR = 0.149, CI (0.074 – 0.302),  $p < 0.001$ ). (Table 10)

	$\geq 80$ yo with recanalization attempt		
	OR	CI 95%	p value
NIHSS $\leq 5$ (ref)			$< 0.001$
NIHSS 6-10	2.078	0.892 – 4.839	0.090
NIHSS 11-15	3.186	1.329 – 7.639	0.009
NIHSS 16-20	13.565	5.272 – 34.902	$< 0.001$
NIHSS $> 20$	14.034	5.522 – 35.663	$< 0.001$
Etiology = atheroma (ref)			0.387
Etiology = cardio-embolic	0.914	0.488 – 1.712	0.779
Etiology = others	1.474	0.684 – 3.177	0.322
Onset-to-door $> 90$ min	1.497	0.880 – 2.545	0.137

NIHSS = National Institute of Health Stroke Scale; OR = odd ratio; CI = confidence interval; ref = reference; yo = years old.

**Table 8:** Multivariate analysis for predictors of poor outcome at discharge after recanalization attempt for  $\geq 80$ yo patients

	$\geq 80$ yo with IVT		
	OR	CI 95%	p value
NIHSS $\leq 5$ (ref)			$< 0.001$
NIHSS 6-10	2.420	0.951 – 6.160	0.064
NIHSS 11-15	3.105	1.178 – 8.189	0.022
NIHSS 16-20	13.464	4.503 – 40.259	$< 0.001$
NIHSS $> 20$	20.071	5.990 – 67.254	$< 0.001$
Onset-to-door $> 90$ min	1.208	0.637 – 2.291	0.563
Door-to-needle $> 60$ min	0.792	0.376 – 1.672	0.542
Etiology = atheroma (ref)			0.394
Etiology = cardio-embolic	0.826	0.401 – 1.700	0.604
Etiology = others	1.456	0.602 – 3.523	0.404

IVT = intravenous thrombolysis; MT = mechanical thrombectomy; NIHSS = National Institute of Health Stroke Scale; OR = odd ratio; CI = confidence interval; mTICI = modified Thrombolysis In Cerebral Ischemia; ref = reference; yo = years old.

**Table 9:** Multivariate analysis for predictors of poor outcome at discharge after IVT for  $\geq 80$ yo patients

	≥ 80yo with MT alone or bridging		
	OR	CI 95%	p value
NIHSS ≤ 5 (ref)			< 0.033
NIHSS 6-10	0.493	0.066 – 3.705	0.492
NIHSS 11-15	0.943	0.145 – 6.120	0.951
NIHSS 16-20	3.170	0.532 – 18.906	0.205
NIHSS > 20	4.213	0.662 – 26.831	0.128
Onset-to-door > 90 min	0.743	0.299 – 1.848	0.523
Door-to-puncture > 120 min	1.452	0.471 – 4.475	0.516
TICI ≥ 2b	0.149	0.074 – 0.302	< 0.001

*IVT = intravenous thrombolysis; MT = mechanical thrombectomy; NIHSS = National Institute of Health Stroke Scale; OR = odd ratio, CI = confidence interval; mTICI = modified Thrombolysis In Cerebral Ischemia; ref = reference; yo = years old*

**Table 10:** Multivariate analysis for predictors of poor outcome at discharge after MT alone or bridging for ≥ 80yo patients

## **DISCUSSION**

We demonstrated the sharp increase of number of octogenarian and nonagenarian patients together with the large increase of number of IVT and MT in Northern French Alps stroke units between 2014 and 2019. IVT and MT are feasible procedures in elderly ( $\geq 80$ yo) but older are worse prognostic than younger ( $< 80$ yo) with higher mortality in-hospital and lower good outcome (mRS 0-2) at discharge and at 3-6 months after stroke. Door-to-treatment (including door-to-needle and door-to-puncture) is significantly longer in elderly people.

In our “in-hospital” cohort, AIS in elderly are more severe with more LVO which could explain higher mortality and disability. Interestingly, there is not significant difference between octogenarian and nonagenarian groups. There seems to be some kind of “cut-off” limited to 80 years old. Multivariate analysis showed recanalization procedures in elderly are beneficial to patients with severe stroke with high NIHSS (Table 8). Speed of patient management with door-to-puncture delay is necessary to improve functional outcome (Table 7). Successful of recanalization (mTICI  $\geq 2$ b) was significantly associated with better outcome (Table 10). Etiology of AIS has no significant effect in our study (Table 8 and 9).

### 1) Epidemiology: increasing of number of elderly patients in stroke units

Since few years in Northern French Alps stroke units, number of IVT and MT had increased over than expected (10), particularly in elderly population because of aging, growth of the population and improvement in health care (3). The number of patients  $\geq 80$ yo admitted to stroke unit has doubled in 6 years, with a 5-fold increase of recanalization procedures. Number of AIS nonagenarians in stroke units has tripled. With the rise of MT during the year 2015 after pivotal RCTs (11–16), number of annual MT has quadrupled between 2015 ( $n = 26$ ) and 2016 ( $n = 110$ ) and continue to increase ( $n = 191$  in 2019) among all patients hospitalized for AIS in stroke units, especially for  $\geq 80$ yo patients ( $n = 4$  in 2015 and  $n = 81$  in 2019). More and more elderly

patients are admitted (3) for stroke and the adaptation of the means dedicated to the whole health network (emergency unit, stroke unit beds, geriatric stroke unit, neurorehabilitation unit) is necessary in order to receive and care the greatest number of patients whatever their age.

Elderly patients were underrepresented in RCTs. They are undergoing a kind of “discrimination” according to some studies (17,18). Patients  $\geq 80$ yo and with preexisting disabilities had a lower chance of being treated with IVT whereas disabilities were not a contraindication (19). In our study, imaging or recanalization strategies were not statistically different between groups but there is a significant difference for delays between  $< 80$ yo and  $\geq 80$ yo.

Our study shows an increasing incidence of atrial fibrillation in the elderly population compared to younger. This increasing incidence of atrial fibrillation is expected to increase the number of AIS caused by LVO and stroke severity in this population (20,21).

## 2) Safety and efficacy of recanalization strategies

In our cohort, recanalization attempts are associated with lower odds of poor outcome at discharge for  $< 80$ yo and  $\geq 80$ yo. The rates of successful recanalization were not statistically different between groups. These findings suggest age should not be a contraindication because of age alone. Door-to-treatment delay was significantly longer for older groups but few minutes in practice. IVT and MT are feasible for elderly. Some studies have reported a higher likelihood of arterial tortuosity which may prolong the time to successful recanalization by MT. Aging would promote twisting of arteries and may make catheter access more time-consuming (22). However, several studies found no age-related difference in recanalization rate, procedural time, and complication rate in MT between elderly ( $\geq 80$ yo) and younger people ( $< 80$ yo) (23,24). With the

evolution of catheters and devices, access to the occlusion site can be easier, regardless of patients' age and vascular course (7).

IST-3 trials showed that IVT is beneficial for older people ( $\geq 80$ yo), even those with severe stroke and with important comorbidities such hypertension, diabetes mellitus and previous stroke (25,26). Nonagenarians treated with IVT showed lower stroke-related disability at 90 days than those not treated. These observations cannot exclude a confounding effect but provide evidence that IVT should not be withheld from nonagenarians on the basis of age alone (27).

In a meta-analysis, Emberson *et al.* showed IVT benefits were similar irrespective of age or stroke severity (4). Moreover, Goyal *et al.* showed, in a meta-analysis of MT trials that included elderly patients ( $>80$ yo), better outcomes when treated with MT (with or without IVT) compared to IVT alone (5). Malhotra *et al.* (2019) also showed that patients undergoing MT have a wider range of possible outcomes (28). In a large real-world multicenter cohort of patients stratified with the SC score (Stroke Checkerboard score) including age and stroke severity, the oldest and more severe patients had the largest benefit from MT+/-IVT (29). Systematic review and meta-analysis of published observational studies and RCTs of MT in acute ischemic stroke (AIS) demonstrated one-quarter of elderly patients ( $>80$  yo) achieved good functional outcome at 90 days, while one-third of patients died. These findings suggest that MT+/-IVT would provide substantial benefit to a sizeable proportion of octogenarians, despite the associated comorbidities (8).

Our study had a significantly higher in-hospital mortality and lower likelihood of functional independence at discharge and at 3-6 months after IVT and/or MT than younger patients. But we found a higher proportion of AIS patients with LVO and severe stroke presentation in  $\geq 80$ yo group. Others factors have been identified to explain these poorer functional outcome and higher mortality rate in older patients including preexisting neuronal loss and reduced neuronal plasticity, higher rate of comorbidities and poststroke complications (eg, infections and injuries

due to falls) (30–33). Moreover, functional outcomes may be poorer than younger patients because of collateral blood supply that would be worse in elderly, resulting in earlier tissue loss (20).

Bluhmki *et al.* assessed outcomes of almost 3000 patients aged  $\geq 80$ yo who received IVT in RCTs or in clinical practice. Patients aged  $\geq 80$ yo, regardless of treatment allocation (IVT vs placebo or control), had worse functional outcomes and higher mortality rates following AIS compared with younger patients (34). Other observational studies have raised concerns about the utility of MT or IVT in the elderly because of a lower likelihood of functional independence at 90 days compared with younger patients (35,36).

### 3) Prognosis factors in elderly stroke patients

#### *a. Age*

In our study, an age of  $\geq 80$  years was associated with higher odds of poor outcome at discharge in patients undergoing IVT or MT or bridging independently. Age itself was a factor that affect clinical outcome in the elderly group ( $\geq 80$ yo) according to Son *et al.* (7).

#### *b. Delays*

In this cohort, the time of door-to-puncture (for MT)  $> 120$  min when patients are  $\geq 80$ yo is associated with higher odds of poor outcome at 3-6 months. Futhermore, many studies in literature associate earlier treatment with bigger proportional benefits (4,14). Son *et al.* shows that time to reperfusion is a factor that affect clinical outcome in the elderly group ( $\geq 80$ yo). However, long-term clinical outcomes were significantly poorer in elderly patients. So, we can speculate that we have less time to salvage the infarcted brain in elderly patients (7).



### *c. Successful of recanalization*

In our study, rates of successful recanalization are poorer than literature (unfortunately, we have many missing data about mTICI) and could explain poor outcome and in-hospital mortality in elderly, but patients with mTICI  $\geq 2$  score were significantly associated with better outcome for elderly. Although the higher TICI score is correlated to better outcome only in younger but not elderly patients in literature (9).

### *d. NIHSS score initial*

In this cohort, higher admission NIHSS score is a significant predictor of poor outcome for the both groups. In many studies, baseline stroke severity was associated with worse outcome and a poor 90-day functional independence in elderly ( $\geq 80$ yo) compared to younger patients ( $< 80$ yo) (7,23). According to Sallustio *et al.*, major determinants of outcomes in this old population are initial NIHSS score and clinical improvement at 24 hours (33).

#### 4) Pre-stroke disability in elderly

Thirty-three percent of octogenarians who present an AIS are not independent at baseline (37). A mRS of 3 may confer a relatively good quality of life for  $\geq 80$ yo patients and the potential shift effect of MT towards a lower mRS may be considered as a favorable outcome after MT (8).

Many studies report good functional outcome after recanalization strategies for elderly people without baseline disability and suggest the need to select patient. STRATIS (Systematic Evaluation of Patients Treated with Neurothrombectomy Devices for Acute Ischemic Stroke) registry relates good outcome in 43.2% of  $\geq 80$ yo patients without baseline disability undergoing MT. Nevertheless, this rate of good outcome decreased significantly with age, 52.4% for 80 to 84 yo patients, 38.3% for 85 to 90 yo, and 26.5% for  $\geq 90$ yo. An increasing of mortality was

observed, 24.5%, 27.9%, and 35.1% for the age groups respectively. 76% (748/984) of patients had a prestroke mRS score of 0 (38). We found the same evolution according to age with our results. Bluhmki and al. suggest elderly patients should be selected carefully based on their general health and baseline neurological status before IVT (34).

The definition of « good outcome » should be expanded to include return to premorbid functional status. In a study, included patients were categorized as independent premorbid (mRS 0-1) or disabled premorbid (mRS 2-4), patients with pre-existing disability may still benefit from IVT as one fourth to one third returned to the same premorbid functional level at 3 months (39).

#### 5) Selection patient

It could be necessary to select patients with a good baseline status. Nonagenarians without pre-stroke disability, receiving IVT, showed lower disability at 90 days after AIS than patients not treated (27). In a prospective observational study, 60% of elderly patients (> 80 years), with almost all previous functional independence (mRS 0-1), regained their functional independence at 3 months (mRS 0-2) after MT (40). Many studies suggest that nonagenarians with a good pre-stroke functional status can benefit from MT for LVO (20). Nevertheless, it is difficult to know baseline status in case of emergency.

After careful imaging selection (using DWI-FLAIR mismatch selection), MT with modern devices for AIS among nonagenarians was safe and may improve neurologic recovery and functional outcome at 90 days compared with IVT alone (41).

Our study and the findings in literature highlight the need for careful patient selection for IVT and/or MT for elderly patients. The challenge remains how to identify those older patients who will not benefit from recanalization to avoid futile and potentially harmful interventions.

IVT and MT can provide benefits but magnitude of effect is carried by morbidity and mortality post-procedure (42).

Scores have been developed. In a large real-world multicenter cohort of patients, a prognosis score (the SC score, a combination of NIHSS score and patient age) was implemented and validated to sort patients who could benefit of MT into 3 different prognosis categories. The two most severe outcome categories had a marked benefit of MT and the study suggested the oldest and more severe patients had the largest benefit (29).

Campbell *et al.* showed that estimated ischemic core volume was independently associated with functional independence and functional improvement. However, this ischemic core volume did not modify the treatment benefit of MT compared with standard medical therapy for improved functional outcome. To help physicians to make MT treatment decisions and improve assessment of prognosis, combining ischemic core volume with age and expected imaging-to-reperfusion time could be useful (43).

Machine learning algorithms are currently implementing in order to help therapeutic decision including patient age. SPOT (Stroke Prognosis in Octogenarians under-going Thrombectomy) is a useful tool, based on baseline clinical and radiological data, to determine which patients to exclude from MT, and has been implemented in an online calculator for public use (44). All these artificial intelligence developments must be validated in large clinical trials.

## 6) Limitations

There are some limitations to this study. Firstly, the retrospective nature is one of these limitations with a selection bias: only patients hospitalized in stroke units are registered. Secondly, pre-stroke mRS and comorbidities of our patient are missing in the registry to better identify good responder to recanalization attempt. Thirdly, our registry has some important missing data (3-6 months mRS, mTICI) despite of a stable collection method carried out on a regional register in four hospitals since 2014.

## **CONCLUSION**

Older age ( $\geq 80$ yo) and a higher stroke severity (with higher initial NIHSS score) are poor prognostic factors in patient with AIS. Time of door-to-MT  $> 120$  min is a poor prognostic factor in  $\geq 80$ yo. Poor functional outcome and mortality are higher in elderly stroke patients. The number of patients  $\geq 80$ yo admitted to stroke units has doubled during the last 6 years, with a 5-fold increase of recanalization procedures (n=30 in 2014; n=173 in 2019). These procedures are feasible and limit subsequent handicap in octogenarians. A careful selection of oldest patients eligible to recanalization must be considered. Moreover, stroke cases will increase in next decades notably due to aging of population. Thus, upgrade of the whole stroke network from emergency and stroke units to geriatric and rehabilitation departments is necessary in order to improve stroke cares for more patients including oldest ones.

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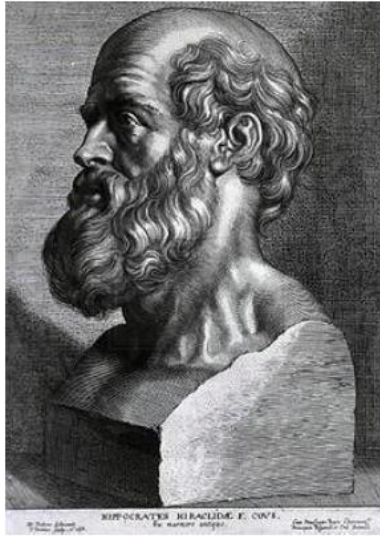
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## **SERMENT D'HIPPOCRATE**

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*

**THÈSE SOUTENUE PAR : Manon MICHELARD**

**TITRE : THROMBOLYSIS AND MECHANICAL THROMBECTOMY FOR ACUTE ISCHEMIC STROKE IN OCTOGENARIAN PATIENTS: A REGIONAL OBSERVATIONAL STUDY**

**CONCLUSION :**

Older age ( $\geq 80$  years old) and a higher stroke severity (with higher initial NIHSS score) are poor prognostic factors in patient with AIS. Time of door-to-MT  $> 120$  min is a poor prognostic factor in  $\geq 80$ y. Poor functional outcome and mortality are higher in elderly people. The number of patients  $\geq 80$ y admitted to stroke units has doubled during the last 6 years, with a number of recanalization procedures multiplied by 5 (n=30 in 2014; n=173 in 2019). These procedures are feasible and limit subsequent handicap in octogenarians. A careful selection of oldest patients eligible to recanalization must be considered. Moreover, stroke cases will increase in next decades notably due to aging of population. Thus, upgrade of the whole stroke network from emergency and stroke units to geriatric and rehabilitation departments is necessary in order to improve stroke cares for more patients including oldest people.

**VU ET PERMIS D'IMPRIMER**  
Grenoble, le 18/09/2020 :

**LE DOYEN**



**Pr. Patrice MORAND**

Pour le Président  
et par délégation  
Le Doyen de Médecine  
Pr. Patrice MORAND

**LE PRÉSIDENT DE LA THÈSE**

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