

**Экспериментальная и профилактическая медицина**

UDC 616.831-005.4-085-089-053.9

DOI: 10.54503/0514-7484-2025-65.2-64

**Managing Acute Ischemic Stroke in Patients Aged 80 and Above  
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28 Daniel Varuzhan Street, 0032**Keywords:* Reperfusion Therapy, Stroke, Old Age, Acute Care**Introduction**

The world's population is aging, with the greatest proportional increase in those > 80 years of age. The reports from the World Health Organization (WHO) expect the number of people aged 80 years or older to triple between 2020 and 2050 to reach 426 million globally [36]. The aging society puts a heavy burden on healthcare, not sparing stroke care either, especially in countries with limited financial resources [6, 23]. Age is a major non-modifiable risk factor for stroke leading to an exponential increase in stroke incidence doubling each decade after age 55 [25]. A study by Fonarow et al. investigating the Get Within the Guidelines (GWTG) stroke database showed that 33% of all stroke patients treated in hospitals were over the age of 80 years [8]. Compared to their younger counterparts, patients aged > 80 years differ in many ways in the setting of acute stroke. They have more baseline comorbidities and disabilities, higher initial stroke severity at admission, less favorable outcomes, less access to therapeutic interventions, and less involvement in rehabilitation facilities [24, 28, 33]. On the other hand, the paucity of evidence regarding the optimal methods and particularities of stroke care in the geriatric population leads to controversial approaches in clinical practice. Consequently, this group of patients may have suboptimal management in all phases of care.

This article presents the current image and controversies in the hyperacute management of ischemic stroke in patients  $\geq 80$  years with a focus on the use of reperfusion therapies (RP), stroke outcomes, and future perspectives.

*Intravenous Thrombolysis (IVT) after the age of 80*

IVT by recombinant human tissue plasminogen activator is an approved treatment of acute ischemic stroke (AIS) aiming to restore the blood flow to the salvageable ischemic brain tissue that is not yet infarcted. IVT was first shown to reduce post-stroke disability in the National Institute of Neurological Disorders and Stroke (NINDS) part A and B trials when administered within 3h of stroke onset [21]. The treatment window was subsequently extended to 4-5 h after the publication of the European Cooperative Acute Stroke Study (ECASS) results in 2008 [13]. However, data on the safety and efficacy of IVT in the > 80-year-old population was not obtained as both trials initially enrolled patients aged up to 80 years. This age restriction came from the potential higher risk of IVT-related complications and caused uncertainty about the risk-benefit profile in these patients [35]. The International Stroke Trial (IST-3) was the first largest, randomized thrombolysis trial where more than half of the participants (53%) were older than 80 years of age. The study aimed to determine whether a wider range of patients might benefit from IVT in an extended therapeutic time window, up to 6 hours from stroke symptom onset. Contrary to the expectations that the elderly group may have a poorer 6-month functional outcome, the study showed that patients 80 years of age or older had greater benefits than their younger counterparts [27]. Another study by Emberson et al., evaluating the effect of age on IVT outcome showed similar results for patients aged > 80 years and < 80 years ( $p < 0,0001$ ) [7]. Similarly, the research by Furlan et al. demonstrated that cerebral reperfusion therapy was a viable treatment for ischemic stroke in both elderly and very elderly patients, as it did not increase mortality ( $p < 0,0001$ ) [10].

However, not all studies and trials agreed on the safety and efficacy of IVT in this specific patient population. For example, the ENDOSTROKE study found higher mortality and poorer functional outcomes with increasing age [29]. Another study by Ford GA et al., analyzing the data from Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Register (SITS-ISTR) showed an overall worse prognosis after the age of 80 years [9]. Nevertheless, comparisons of SITS-ISTR with Virtual International Stroke Trial suggested that despite the fact that increasing age was associated with worse prognosis, the association between thrombolysis treatment and improved outcome was maintained in the very elderly people [18].

These controversial results were probably due to the diversity of older adults in general, in terms of co-morbidities and different rates of complications during hospitalization (cardiac, pulmonary, and renal disorders, infections or prolonged bed rest, cognitive decline, frailty) [5, 37].

As a consequence, until 2020, clinical guidelines approved the routine use of IVT only for patients aged 18–80 years. The recommendations to use IVT for patients > 80 years were based on the assessment of individual risk-benefit profiles without specifying the selection criteria for therapeutic decisions [3]. Nowadays,

more and more observational data support the safety and efficacy of IVT after age 80, and based on current clinical recommendations, age alone should not be a reason to exclude patients from receiving IVT [3, 30].

### ***Endovascular Thrombectomy (EVT) after the age of 80***

Five randomized controlled trials, published in 2015, demonstrated the effectiveness of EVT for the treatment of ischemic stroke within 6 hours of symptom onset [2, 11]. Later, in 2018, new trials (Wake up, DEFUSE, DAWN, EXTEND), in accordance with additional criteria compatibility, extended the therapeutic time window from 6 to 24 hours from stroke symptom onset [20, 22, 31]. Although the majority of these trials had no age restriction in eligibility criteria, patients >80 years were under-represented because of higher rates of pre-stroke disability (modified Rankin scale >2) which was exclusion criteria for participation in trials [15]. A recent study by PL Michelle, analyzing patient subgroups from these randomized trials reported that only 334 patients from 1206 (28%) were above the age of 80 years [19]. Nevertheless, in a meta-analysis study by the HERMES group, the authors showed no difference in outcome suggesting that EVT is effective in elderly individuals aged 80 years or older to improve functional outcome (OR 3.68, 95% CI 1.95–6.92) [12].

### ***Real-life scenarios and clinical concerns***

The acute stroke care approach in patients > 80 years remains controversial based on reports of consecutive patient series observations. Different studies show that patients over 80 years old have an increased risk of unfavorable outcomes and higher mortality rates when compared to their younger counterparts. However, based on the outcome, these studies support the safety and feasibility of RT in patients over 80 years of age [14, 32, 34, 16]. Even so, it is worth mentioning that the majority of trials and observational studies in RT used the level of mobility impairment to measure functional outcomes, thus bypassing the assessment of cognitive impairment which is a relevant post-stroke complication affecting functional independence in the elderly population [17]. Moreover, in a real-life setting many patients > 80 years present with pre-stroke functional dependence, which introduces further complexity in defining the benefits of RT. From another point, there is a need to reconsider the definition of good clinical outcome (defined as mRs 0-2) [1] for patients > 80 years as requiring some help in daily life activities (mRs 3) could be a favorable outcome for this age group. In addition, observational studies in RT should focus on the potential role of specialized stroke unit care on functional outcomes and identify age-related acute stroke care particularities to ensure the best therapeutic response. Determination of clinical biomarkers of decreased functional reserve and age-related disease characteristics can serve as a tool for better prediction of early and long-term prognosis.

### *Own experience*

In Armenia, patients aged 80 years or older constitute around 26–32% of all stroke unit admissions based on reports from the ministry of health. The implementation of national stroke program, fully funded by government, has made protocol driven care including RT-ies accessible for a large proportion of population starting from 2019. The latter resulted in overall decrease in mortality and disability rates among stroke survivors. However, it is worth mentioning that despite the wide use of guidelines in Armenian stroke centers, in real life setting, clinicians struggle with the therapeutic decisions regarding ischemic stroke management after the age of 80. The uncertainty of prognosis in acute setting, the fear of non-favorable outcome in case of pre-stroke multimorbidity, frailty and the possible higher complication rate in hospital result in suboptimal management in acute setting. From the other point of view, the overuse of non-justified interventions increases healthcare costs and prolongs hospital stays, which is another challenge in a resource-limited context. Furthermore, the lack of geriatric and palliative care specialists in the country generates another barrier upon providing a holistic and multidisciplinary approach during both the acute and post-acute settings.

To be able to develop age-related management strategies in ischemic stroke, we recommend the evaluation of the performance of daily activities, swallowing and cognitive functioning along with neurological assessment at early and late post-stroke phases. In addition, the identification of clinical and radiological factors associated with poor prognosis is indispensable to ensure best therapeutic outcomes. In the end, to provide a comprehensive care approach we suggest the evaluation of patients' age-specific needs and experiences in acute setting.

In conclusion, the paucity of literature and randomized controlled trials create a gap in clinical practice toward better identification of patients > 80 years who will benefit the most from RT in terms of survival and improved clinical outcomes. The definition of “benefit” from reperfusion-treated ischemic stroke in patients > 80 years must take into consideration the pre-stroke functional state and expected treatment goals. Rather than considering age as a factor of poor stroke outcome, attention should be given to the identification of specific health and age-related disease characteristics potentially impacting prognosis in the geriatric population. Thus, future studies are required to evaluate the factors associated with mortality or poor outcomes in this age group to better predict non-favorable outcomes and to improve patient selection for therapeutic interventions.

Defining “benefit” from reperfusion treatments in this age group, pre-stroke functional status and expected treatment goals should be considered. Instead of viewing age as a barrier to favorable stroke outcomes, attention should be focused on identifying specific health and age-related disease characteristics that impact prognosis. Future studies are needed to better understand factors associated with

mortality or poor outcomes in this age group to improve patient selection for therapeutic interventions and enhance overall care.

*Accepted 11.02.25*

### **Тактика ведения острого ишемического инсульта у пациентов старше 80 лет. От текущих знаний к будущим перспективам**

**Г.Г. Саакян**

Всемирное старение населения, в особенности среди группы людей старше 80 лет, создает новые вызовы для лечения инсульта в странах с ограниченными ресурсами. Внутривенный тромболизис и внутрисосудистая тромбоэкстракция являются единственными признанными методами лечения острого ишемического инсульта, направленными на восстановление кровотока в ишемизированных тканях мозга. Однако многие рандомизированные исследования, изучавшие реперфузионную терапию, не включали пациентов старше 80 лет, что ограничивает адекватное управление этими результатами.

В Армении пациенты старше 80 лет составляют 26–32% от числа поступающих в отделение инсульта. Несмотря на утвержденные клинические рекомендации, сопутствующие заболевания и трудности, связанные с инвалидностью, приводят к необоснованным вмешательствам, что увеличивает медицинские расходы и продолжительность пребывания в стационаре. Кроме того, отсутствие специалистов по уходу за пожилыми людьми и палиативной помощи усугубляет проблему комплексного лечения инсульта.

В данной статье рассматривается текущая ситуация и противоречия в лечении острого ишемического инсульта у пациентов старше 80 лет, с фокусом на реперфузионную терапию (RP), исходы заболевания и будущие перспективы. Для улучшения ухода за пожилыми пациентами с инсультом мы рекомендуем раннюю активацию пациентов, повышение частоты оценки акта глотания, когнитивных функций и неврологического состояния как в острой, так и подострой фазах инсульта.

### **Սուր իշեմիկ կաթվածի բուժումը 80-ից բարձր տարիքի պացիենտների շրջանում: Ընթացիկ պատկերացումներից մինչև ապագա հեռանկարներ**

**Գ.Գ. Սահակյան**

Համաշխարհային ծերացող բնակչությունը, մասնավորապես 80-ից բարձր տարիքային խումբը, կաթվածի բուժման նոր մարտահրավերներ է ստեղծում հատկապես սահմանափակ ռեսուրսներ ունեցող երկրներում: Ներերակային թրոմբոլիզը և ներանոթային թրոմբեկտոմիան այսօր համարվում

են սուր իշեմիկ կաթվածի բուժման միակ հաստատված մեթոդները, որոնք նպատակ ունեն վերականգնելու արյան հոսքը դեպի ուղեղի իշեմիկ հյուսվածք: Այնուամենայնիվ, բազմաթիվ ռանդոմիզացված հետազոտություններ, որոնք ուսումնասիրել են ռեպերֆուզիոն թերապիաների արդյունավետությունը, չեն ընդգրկել 80-ից բարձր տարիքային խմբի պացիենտներին՝ սահմանափակելով տեղեկատվությունը ճշգրիտ մենեջմենթի վերաբերյալ:

Հայաստանում 80 և բարձր տարիքի պացիենտները կազմում են կաթվածի բաժանմունք ընդունվողների 26–32%-ը: Չնայած հաստատված ուղեցույցներին՝ վարման պլանի դժվարությունները, պայմանավորված տարիքի հետ ասոցացվող ուղեկցող խնդիրներով, հանգեցնում են անհարկի միջամտությունների, որի հետևանքով շատանում են առողջապահական ծախսերը, և երկարում հիվանդանոցային մահճակալ օրերը: Բացի այդ, տարեցների և պալիատիվ խնամքի մասնագետների բացակայությունն ավելի է բարդացնում կաթվածի համապարփակ բուժումը:

Այս հոդվածը ներկայացնում է իշեմիկ կաթվածի սրագույն փուլի բուժման առկա պատկերը և հակասական տվյալները 80-ից բարձր տարիքային խմբի պացիենտների շրջանում՝ ընդգծելով ռեպերֆուզիոն թերապիայի կիրառումը, կաթվածի ելքերը և հեռանկարները: Այս տարիքային խմբի պացիենտների բուժական թերապիան բարելավելու համար խորհուրդ է տրվում վաղաժամ ակտիվացում, կլման ակտի, կոգնիտիվ կարողությունների և նյարդաբանական ստատուսի գնահատում ինչպես կաթվածի սուր, այնպես էլ ենթասուր փուլերում:

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