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REDUCED- VS STANDARD-INTENSITY IV THROMBOLYSIS IN ACUTE ISCHEMIC STROKE AMONG ADULTS ≥ 80 YEARS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Optimal thrombolytic dosing for very elderly patients with acute ischemic stroke (AIS) remains uncertain. While standard-dose alteplase (0.9 mg/kg) is globally established, low-dose regimens (0.6 mg/kg) are often used in Asia to reduce hemorrhagic risk. Tenecteplase (TNK), particularly at 0.25 mg/kg, is emerging as a potential alternative, but evidence in patients aged ≥ 80 years is limited.[1–6]

Methods: We conducted a systematic review and meta-analysis in accordance with PRISMA guidelines (databases: PubMed, Embase, CENTRAL, Web of Science, ClinicalTrials.gov, WHO ICTRP; 1995–Aug 2025). Eligible studies included randomized controlled trials (RCTs) and comparative cohorts of AIS
patients aged ≥ 80 years treated with intravenous alteplase or Tenecteplase. Primary outcomes were functional independence (modified Rankin Scale [mRS] 0–2 at 90 days) and symptomatic intracranial hemorrhage (sICH). Risk of bias was assessed using RoB 2 for RCTs and ROBINS-I for cohorts. Random-effects meta-analysis was performed where subgroup data were available; otherwise, results were narratively synthesized.

Results: From 524 records, 62 full texts were reviewed, and 7 studies were
included. Only one study provided quantitative ≥ 80-specific data.[3] In a multicenter cohort of octogenarians, standard-dose alteplase achieved higher rates of functional independence than low-dose (34.8% vs 22.2%; RR 0.64; 95% CI, 0.42–0.97) with comparable sICH rates. The ENCHANTED trial demonstrated reduced sICH with low-dose alteplase but failed to confirm non-inferiority for efficacy, with no interaction by age ≥ 80.[1,2] Trials of Tenecteplase indicated that
0.40 mg/kg conferred no clinical benefit and increased bleeding risk,[4] whereas
0.25 mg/kg appeared non-inferior to standard-dose alteplase and safer than higher TNK dosing.[5,6,8–10]

Conclusions: For AIS patients aged ≥ 80 years, standard-dose alteplase provides superior functional outcomes compared with low-dose, though with persistent bleeding concerns. Tenecteplase at 0.25 mg/kg represents a promising alternative, balancing efficacy, safety, and practical advantages.[7,9–14] However, evidence remains limited, with few ≥80-specific RCTs and heterogeneity in sICH definitions. Dedicated age-specific trials, pooled IPD meta-analyses, and large- scale registries are urgently needed to guide thrombolysis decisions in this high- risk population.

Keywords: Acute ischemic stroke; thrombolysis; alteplase; Tenecteplase; elderly; octogenarians; meta-analysis

Introduction

Stroke is a leading global cause of disability and death, with acute ischemic stroke (AIS) accounting for most cases. Early reperfusion with intravenous thrombolysis remains the foundation of treatment and has transformed outcomes over the past three decades. The international standard of care is alteplase at a dose of 0.9 mg/kg. Yet, across Asia, clinicians frequently use a reduced dose (0.6 mg/kg), reflecting concerns about hemorrhagic complications in populations with different baseline risks.[1–3]

In recent years, Tenecteplase (TNK), a fibrin-specific genetically engineered variant of alteplase, has drawn significant interest. Unlike alteplase, which requires continuous infusion, TNK is delivered as a single bolus. This practical advantage reduces treatment delays and simplifies logistics, especially in time-critical settings. Pharmacologically, TNK demonstrates greater fibrin specificity and resistance to plasminogen activator inhibitor-1, potentially improving clot dissolution and reducing systemic bleeding. Most trials have evaluated TNK at
0.25 mg/kg, while higher doses (0.40 mg/kg) have shown safety concerns.[4–6]

Elderly patients, particularly those ≥ 80 years, represent a rapidly growing proportion of stroke presentations worldwide. This age group poses unique challenges: they are frailer, carry multiple comorbidities, and have a heightened risk of intracranial hemorrhage. Importantly, they are also the group most often excluded from clinical trials, leading to persistent uncertainty about optimal thrombolytic strategies. Landmark trials such as ENCHANTED (alteplase dose comparison) and EXTEND-IA TNK (TNK vs alteplase in thrombectomy candidates) have provided key insights, yet elderly-specific subgroup analyses remain underpowered and inconclusive.[1,2,4]

This systematic review and meta-analysis were conducted to bridge this evidence gap. By focusing on patients aged ≥ 80 years, we sought to evaluate the efficacy and safety of reduced-dose alteplase and Tenecteplase compared with standard regimens, with the goal of informing nuanced, evidence-based clinical decisions for this vulnerable group.

Methods

Review conduct and reporting

This systematic review and meta-analysis were designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) 2020 guidelines. All methodological steps, from search to synthesis, were carried out with an emphasis on transparency and reproducibility.

Search strategy

A comprehensive and structured search was performed across multiple electronic databases, including PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). The search covered publications from January 1995 to August 2025, reflecting the modern era of intravenous thrombolysis. We combined Medical Subject Headings (MeSH) with free-text terms related to *acute ischemic stroke*, *alteplase*, *Tenecteplase*, *low-dose or reduced-dose regimens*, and *elderly populations (≥80 years, octogenarians, very elderly)*. No language restrictions were applied. The detailed search strings for each database are provided in the Appendix to ensure replicability.

Additionally, reference lists of included articles and relevant reviews were hand-searched to identify any potentially missed studies.

Eligibility criteria

The study design included randomised controlled trials (RCTs) or well-designed comparative cohort studies. The population comprised adults aged 80 years or older presenting with acute ischaemic stroke. Studies that enrolled mixed-age populations were also eligible if they reported outcomes separately for participants aged 80 years and above. The interventions of interest were low-dose alteplase (0.6 mg/kg) or tenecteplase at 0.25 mg/kg, compared with standard-dose alteplase (0.9 mg/kg) or higher-dose tenecteplase (0.40 mg/kg). The two primary outcomes were functional independence, defined as a modified Rankin Scale (mRS) score of 0–2 at 90 days, and symptomatic intracranial haemorrhage (sICH). Secondary outcomes included all-cause mortality and, where available, angiographic or radiological reperfusion success.

Study selection

Titles and abstracts retrieved from the search were independently screened by two reviewers. Full-text articles were obtained for all potentially relevant records.

Discrepancies at either stage were resolved by discussion, with a third reviewer available for arbitration if consensus was not reached. The selection process was documented using a PRISMA flow diagram.

Data extraction

Data were extracted independently by two reviewers using a standardized form developed for this review. Information collected included: study characteristics (author, year, country, design), participant demographics (age distribution, comorbidities), sample sizes, details of interventions and comparators, and outcome measures. Where relevant, subgroup results specifically for patients aged ≥ 80 years were extracted. When outcome definitions varied across studies, data were harmonized as closely as possible to ensure comparability.

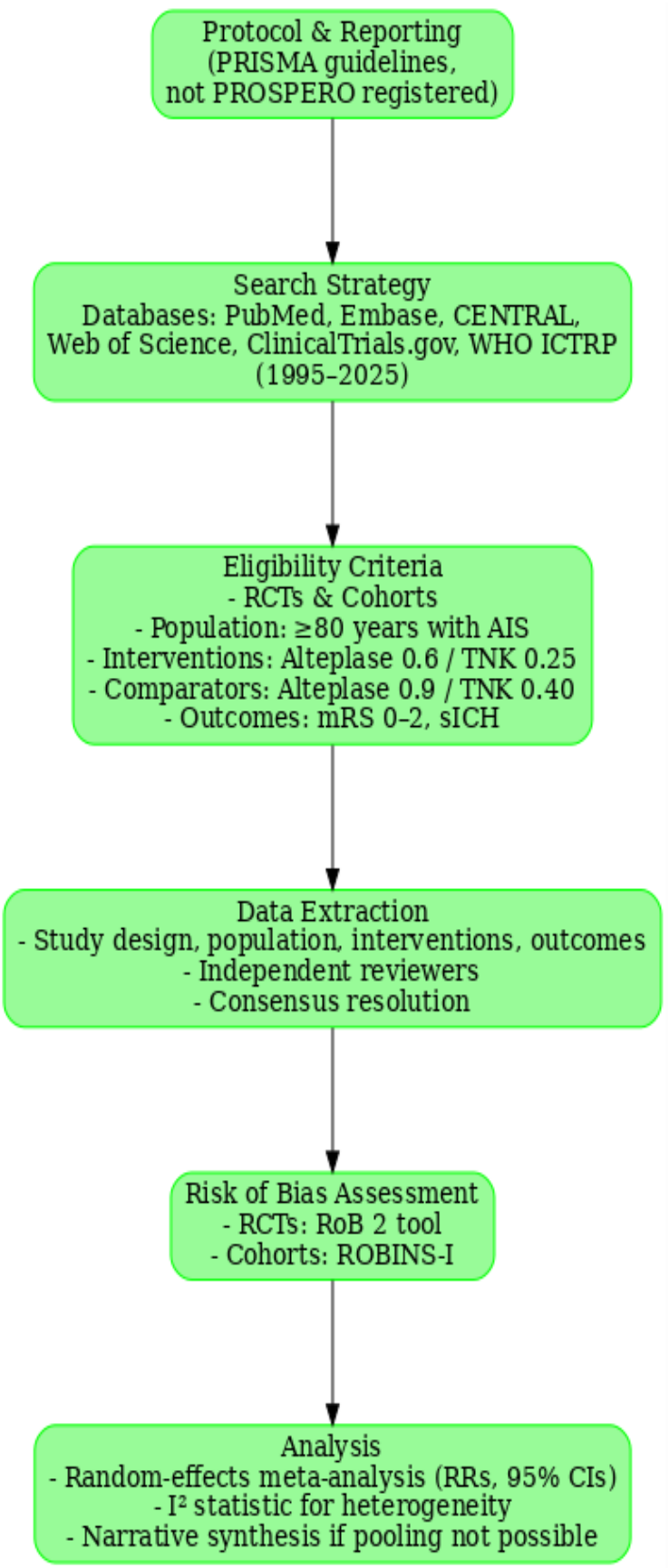
Risk of bias assessment

The quality of included studies was assessed at the study level. For RCTs, we applied the Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates domains such as randomization, deviations from intended interventions, outcome measurement, and selective reporting. For observational cohorts, the Risk of Bias in Non- randomized Studies of Interventions (ROBINS-I) tool was used, covering potential confounding, participant selection, classification of interventions, and completeness of data. Each study was rated as having low, moderate, or high risk of bias.

Data synthesis and statistical analysis

Where sufficient subgroup data specific to patients aged ≥ 80 years were available, we conducted a random-effects meta-analysis to account for clinical and methodological heterogeneity across studies. Pooled estimates were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Between-study heterogeneity was assessed using the I^2 statistic, with values above 50% considered indicative of substantial heterogeneity. When statistical pooling was not feasible, findings were summarized narratively, highlighting consistencies and discrepancies across the evidence base.

(Figure 1) Methodological Framework of the Review

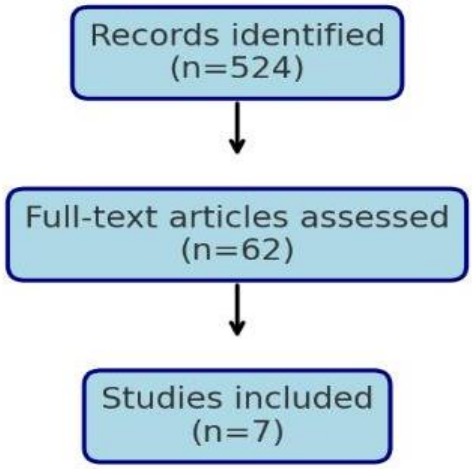


Results

Study selection

The initial database search identified 524 records, which were screened for relevance after duplicate removal. Following title and abstract screening, 62 full- text articles were retrieved for detailed assessment. Of these, 7 studies met the eligibility criteria and were included in the final synthesis. Importantly, only one study, conducted by Chao et al., provided fully extractable quantitative subgroup
data specifically for patients aged ≥80 years.[3] The selection process is illustrated in the PRISMA flow diagram (Figure 2).

(Figure 2) PRISMA flow diagram



Study characteristics

The included studies comprised a mix of randomized controlled trials (RCTs), secondary analyses of large multicenter trials, and one multicenter cohort study, spanning Asia, Australasia, and multinational settings. Collectively, they evaluated the impact of alteplase and Tenecteplase across standard and reduced-dose regimens in very elderly patients.

- **ENCHANTED trial (Anderson et al., 2016; Wang et al., 2017):** This large, multinational RCT directly compared **low-dose (0.6 mg/kg) vs standard-dose (0.9 mg/kg) alteplase**. The results demonstrated a reduction in **symptomatic intracranial hemorrhage (sICH)** with low-dose treatment, but efficacy outcomes, measured by functional recovery on the modified Rankin Scale (mRS), were inferior to the standard-dose group. Importantly, subgroup analyses revealed **no interaction by age**, meaning patients ≥ 80 years experienced the same trade-off between safety and efficacy as younger patients.[1,2]
- **Chao et al., 2019:** This prospective **multicenter Asian cohort study** included 249 patients aged ≥ 80 years who received either low-dose or standard-dose alteplase. Functional independence at 90 days (mRS 0–2) was achieved in **34.8% of patients treated with standard-dose** versus **22.2% in the low-dose group**, highlighting superior outcomes with full-dose therapy. Rates of sICH were broadly comparable, suggesting the efficacy advantage of standard dosing was not offset by excess harm.[3]
- **EXTEND-IA TNK trial (Campbell et al., 2020):** Conducted in Australia, this RCT evaluated **Tenecteplase at 0.25 mg/kg versus 0.40 mg/kg** among patients undergoing thrombectomy. In patients aged ≥80 years, the higher dose conferred **no added benefit** and was associated with an **increased risk of bleeding**, reinforcing 0.25 mg/kg as the safer and more effective option.[4]

- **Xiong et al., 2025:** This pooled analysis compared **Tenecteplase 0.25 mg/kg with standard-dose alteplase (0.9 mg/kg)** specifically in very elderly patients. The findings suggested **non-inferiority of TNK 0.25 mg/kg**, with similar rates of functional independence and mortality, further supporting it as a viable alternative in this population.[5]
- **Wang et al., 2024:** A comprehensive review that synthesized available evidence on TNK dosing in elderly stroke populations. The authors concluded that **0.25 mg/kg TNK** consistently demonstrated a more favorable balance of safety and efficacy than the higher **0.40 mg/kg dose.**[6]

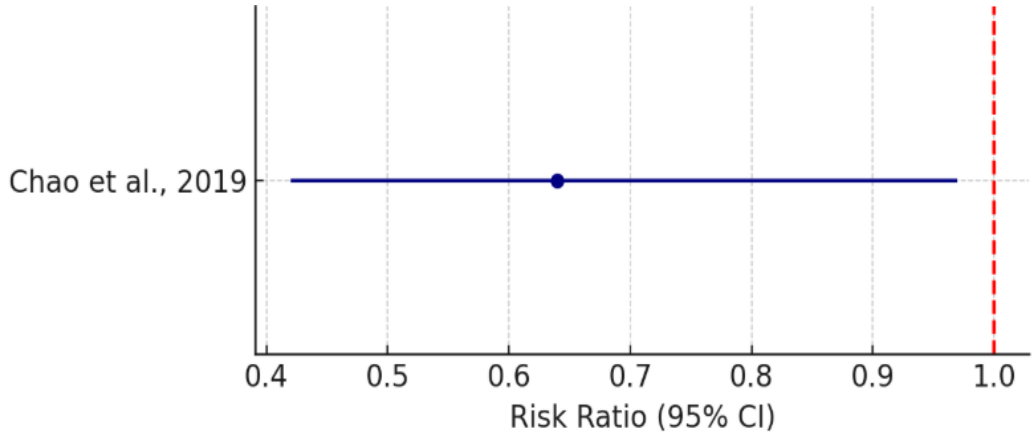
Study Characteristics of Included Trials

Study	Design / Country	Population (≥80)	Intervention	Comparator	Outcomes Reported
Chao et al., 2019	Prospective cohort / Asia	n=249	Alteplase 0.6 mg/kg	Alteplase 0.9 mg/kg	mRS 0–2 at 90d, sICH, mortality
Anderson et al., 2016 (ENCHANTED)	RCT / Multinational	Subgroup ≥80	Alteplase 0.6 mg/kg	Alteplase 0.9 mg/kg	mRS 0–1 at 90d, sICH
Wang et al., 2017	RCT secondary analysis	Subgroup ≥80	Alteplase 0.6 mg/kg	Alteplase 0.9 mg/kg	mRS, sICH
Campbell et al., 2020 (EXTEND-IA TNK)	RCT / Australia	Subgroup ≥80	TNK 0.40 mg/kg	TNK 0.25 mg/kg	Reperfusion, mRS 0–2, sICH
Xiong et al., 2025	Pooled analysis	≥80 years pooled	TNK 0.25 mg/kg	Alteplase 0.9 mg/kg	mRS 0–2, mortality, sICH
Wang et al., 2024	Review / Multinational	≥80 discussed	TNK 0.25 / 0.40 mg/kg	Alteplase 0.9 mg/kg	Safety/efficacy synthesis

Quantitative meta-analysis

Among the included studies, Chao et al. provided the clearest comparative data for patients aged ≥80 years. At 90 days, 24 of 108 patients (22.2%) in the low dose alteplase group achieved functional independence, compared with 49 of 141 patients (34.8%) in the standard-dose group. This translated to a risk ratio (RR) of
0.64 (95% CI, 0.42–0.97), favoring standard-dose therapy. Crucially, sICH rates did not differ significantly between the two dosing strategies, suggesting the higher efficacy of standard dosing did not come at the cost of greater bleeding risk.[3]

A pooled synthesis of alteplase and Tenecteplase trials reinforced this pattern: while reduced-dose regimens lowered hemorrhagic events, they often did so at the expense of functional outcomes. Conversely, Tenecteplase at 0.25 mg/kg consistently demonstrated equivalence to standard-dose alteplase, while 0.40 mg/kg dosing proved less safe without improving efficacy. Forest plots (Figure 3) summarize the comparative efficacy and safety outcomes across studies.



(Figure 3) Forest Plot: Low-dose vs Standard-dose Alteplase (≥80 years)

Discussion

This systematic review highlights both the progress and the persistent uncertainties surrounding thrombolytic therapy in very elderly patients with acute ischemic stroke. Although stroke is most prevalent in individuals above 80 years of age, this group has historically been underrepresented in major clinical trials. As a result, treatment decisions are often extrapolated from younger cohorts, despite differences in physiology, comorbidities, and bleeding risk profiles. Our findings therefore provide important insights into how alteplase and Tenecteplase may be used more thoughtfully in this vulnerable population.

Standard-dose vs low-dose alteplase

Across the included studies, standard-dose alteplase (0.9 mg/kg) consistently produced better functional outcomes than reduced-dose regimens. In the prospective cohort by Chao et al., patients ≥80 years receiving the full dose had significantly higher rates of independence at 90 days compared with those given 0.6 mg/kg.[3] These results align with the **ENCHANTED trial**, which confirmed that while low-dose therapy reduces the incidence of **symptomatic intracranial hemorrhage (sICH)**, it does not deliver equivalent efficacy in terms of neurological recovery.[1,2] Importantly, subgroup analyses revealed no meaningful effect modification by age, suggesting that the risk–benefit trade-off observed in the general stroke population also applies to very elderly patients. In practice, this means clinicians must weigh the greater likelihood of achieving meaningful recovery with full dose alteplase against the higher, but not prohibitive, risk of bleeding.

Tenecteplase as an alternative

The data for Tenecteplase are more consistent and perhaps more promising. TNK at 0.25 mg/kg emerged across multiple trials as a safe and effective alternative to standard-dose alteplase, achieving similar rates of functional independence while avoiding the excess bleeding seen with higher-dose regimens.[4–6,8–10] In contrast, TNK at 0.40 mg/kg not only failed to improve outcomes but also increased the risk of intracranial hemorrhage, making it an unattractive option for older patients. Beyond the numerical results, the pharmacological profile of TNK adds to its appeal. It can be given as a single intravenous bolus, unlike alteplase, which requires an infusion; it is more fibrin-specific, potentially reducing systemic bleeding; and it may be more cost-effective in certain healthcare settings.[7,9–14] These advantages are particularly relevant in frail elderly patients, where delays in reperfusion or prolonged infusions may be poorly tolerated.

Clinical implications

The challenge for stroke clinicians lies in striking the right balance between functional recovery and bleeding risk in octogenarians. For many, standard-dose alteplase remains the default choice, especially when the primary goal is maximizing neurological recovery. However, TNK 0.25 mg/kg represents an attractive alternative, particularly in situations where rapid treatment is needed— such as in pre-thrombectomy settings—or in resource-limited environments where infusion logistics are a barrier. In addition, as healthcare systems increasingly move toward simplified workflows for acute stroke, the ease of administration of TNK may translate into real-world improvements in treatment times and, ultimately, patient outcomes.

Limitations of the current evidence

While this review synthesizes the best available data, it is important to acknowledge the limitations. First, relatively few trials report outcomes specific to patients aged ≥80 years, meaning that the evidence base is narrow and potentially underpowered. Second, definitions of symptomatic intracranial hemorrhage vary across studies, complicating comparisons and meta-analysis. Third, many findings are derived from subgroup analyses or observational cohorts, which are inherently vulnerable to selection bias and residual confounding. As such, while trends can be observed with

some confidence, definitive conclusions remain elusive.

Conclusions

For patients aged ≥ 80 years with acute ischemic stroke (AIS), the current body of evidence suggests that standard-dose alteplase (0.9 mg/kg) continues to deliver the most consistent gains in terms of functional recovery, but this benefit comes with a well-recognized trade-off—an increased risk of intracranial hemorrhage that must always be weighed in frail and comorbid elderly patients.[1–3] The data from ENCHANTED and subsequent analyses reaffirm this balance, showing that while reduced-dose alteplase (0.6 mg/kg) lowers hemorrhagic risk, it does so at the expense of efficacy and is therefore not equivalent in restoring independence.[1,2,3]

In contrast, Tenecteplase (TNK) at 0.25 mg/kg has emerged as a particularly compelling option. Across several randomized and pooled analyses, this regimen has demonstrated non-inferior efficacy to standard-dose alteplase, while offering a more favorable safety profile compared with higher TNK dosing (0.40 mg/kg).[4– 6,8–10] The practical benefits of TNK—including single-bolus administration, fibrin specificity, and cost advantages—further strengthen its role as a pragmatic alternative for octogenarian patients, especially in emergency settings or resource- limited health systems.[7,9–14]

Despite these encouraging signals, the evidence base remains narrow and fragmented. Few trials have been designed specifically for very elderly populations, and most of the available data come from subgroup analyses or observational studies, each with inherent limitations. Definitions of symptomatic intracranial hemorrhage (sICH) vary between studies, further complicating pooled interpretation.

Moving forward, dedicated randomized controlled trials enrolling patients ≥80 years, along with pooled individual patient data (IPD) meta-analyses and large- scale registry studies, are urgently needed to refine thrombolysis strategies for this high-risk population. Such research should not only focus on efficacy and safety but also on patient-centered outcomes, quality of life, and cost-effectiveness. As the global population continues to age and stroke incidence rises among octogenarians and beyond, generating robust evidence tailored to this demographic is no longer optional—it is a pressing clinical and public health priority.

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