AHA/ASA SCIENTIFIC STATEMENT

ENDOVASCULAR TREATMENT AND THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE IN PATIENTS WITH PRE-MORBID DISABILITY OR DEMENTIA.

A SCIENTIFIC STATEMENT FROM THE AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION

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ABSTRACT
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• Patients with pre-morbid disability or dementia have been generally excluded from randomized controlled trials of reperfusion therapies like thrombolysis and endovascular therapy for acute ischemic stroke.
• Consequently, stroke physicians face treatment dilemmas in caring for such patients.
• In this statement, we review the literature on acute ischemic stroke in patients with pre-morbid disability or dementia, and propose principles to guide clinicians, clinician-scientists, and policy-makers regarding the use of acute stroke therapies in these populations.
• Recent clinical-epidemiological studies have demonstrated challenges in our concept and measurement of pre-morbid disability or dementia, while highlighting the significant proportion of the general stroke population that falls under this umbrella, risking exclusion from therapies.
• Such studies have also helped clarify the adverse long-term clinical and health economic consequences with each increment of additional post-stroke disability in these patients, underscoring the importance of finding strategies to mitigate such additional disability.
• Several observational studies – both case series and registry-based studies – have helped demonstrate the comparable safety of endovascular therapy in patients with pre-morbid disability or dementia as in those without, complementing similar data on thrombolysis.
• These data also suggest that such patients have a substantial potential to retain their pre-stroke level of disability when treated, despite their generally worse prognosis overall, although this remains to be validated in higher-quality registries and clinical trials.
• By pairing pragmatic and transparent decision-making in clinical practice with an active pursuit of high-quality research, we can work towards a more inclusive paradigm of patient-centred care for this often-neglected patient population.
INTRODUCTION
INTRODUCTION

- Acute ischemic stroke is a leading cause of disability worldwide, with 30-40% of survivors developing new post-stroke disability.¹
- Thus, the primary focus of reperfusion therapies is the prevention of stroke-related disability.
- However, many patients presenting with an acute ischemic stroke already have pre-existing disability present prior to their stroke, also known as pre-stroke or pre-morbid disability.
- The World Health Organization (WHO) estimates that 15% of the world’s population lives with disability; in the United States, 22% of adults report some disability.¹,²
- Whereas, one may reflexively associate the term “disability” with physical disability, disability can also be intellectual or cognitive.
- The most common type of acquired, pre-morbid cognitive disability seen in the setting of ischemic stroke is dementia.
- Observational studies indicate that pre-existing disabilities exist in approximately one-third of ischemic stroke patients,³ while pre-existing dementia is present in approximately one-tenth.⁴
- Unfortunately, there is an absence of definitive evidence for the use of acute stroke therapies like thrombolysis and endovascular therapy (EVT) in these patients with pre-morbid disability or dementia, as they have been conventionally excluded from randomized-controlled trials.⁵,⁶
INTRODUCTION CONTINUED

• In addition, since these treatments cannot restore patients beyond their pre-morbid state, they will, at best, result in the patients living with the same or worse disability.

• Consequently, stroke physicians face treatment dilemmas in caring for such patients.7

• Indeed, pre-morbid disability is a common reason for exclusion of patients from thrombolysis in routine practice,8 and patients with dementia are less likely to receive thrombolysis or stroke unit care.9

• Current guidelines do not provide a framework for addressing this problem.

• European guidelines recommend that patients selected for acute stroke therapies should have a pre-stroke modified Rankin Scale (mRS) score of 0-1, while noting the lack of evidence for patients with mRS ≥2.10

• The European Stroke Organization’s recently updated EVT guidelines again note the uncertain benefit for patients with significant pre-stroke disability, particularly those older than 80-years.11

• American Heart Association (AHA) guidelines state that pre-stroke disability does not seem to increase the risk of post-thrombolysis hemorrhage and that reperfusion therapies may be reasonable in selected cases, but also state that treatment may be associated with less neurological improvement and higher mortality.12,13

• Therefore, we aim to review the literature on acute ischemic stroke in patients with pre-morbid disability/dementia, and to propose principles to guide clinicians, clinician-scientists, and policy-makers regarding the use of acute stroke therapies in these populations.

• The literature search strategy is described in the Supplement.
DEFINING THE PROBLEM
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• To understand the problem, it is critical to define pre-morbid “disability” and “dementia”.

• Exclusions of these patients from trials have generally been defined using functional outcome measures;

• For example, the seminal trials of EVT generally excluded patients with modified Rankin Scale (mRS) score ≥2 or Barthel Index (BI) score <95.6

• While such definitions seem pragmatic, they do not necessarily capture how disability and dementia manifest in practice.

• Such definitions also vary by the choice of rating scale or the threshold for defining the pre-existing disability within the same scoring tool.14,15

• The most widely accepted definition of disability comes from the WHO’s International Classification of Impairments, Disabilities, and Handicaps.16

• Disability here means “any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being.”

• Per this definition, disability derives from impairment, which in turn is defined as “any loss or abnormality of psychological, physiological or anatomical structure or function.”

• Disability may or may not result in handicap, which is defined as “a disadvantage for a given individual that limits or prevents the fulfillment of a role that is normal.”16

• This is a crucial point that can be easily overlooked when considering the implications of disability in stroke care.
DEFINING THE PROBLEM CONTINUED

- Disability need not inevitably result in handicap.
- Handicap is potentially preventable by means of technological or societal adaptations and accommodations.
- The distinction is important to acknowledge; the modified Rankin Scale (mRS), the most favoured primary outcome measure in acute stroke trials, mixes impairment, disability, and handicap, and also overvalues physical disability relative to cognitive disability.16
- Dementia, also known as major neurocognitive disorder, is defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), as evidence of substantial cognitive decline from a previous level of performance in one or more domains, based on the concerns of the patient, a knowledgeable informant, or the clinician, with a decline in neurocognitive performance (typically on formal testing), and resulting in the patient requiring at least some assistance with instrumental activities of daily living.17
- With the complexity of the definitions above, it is apparent that, in the setting of acute stroke, the identification or evaluation of pre-stroke disability or dementia involves considerable uncertainty, as the quality of available information is almost certainly inadequate to meet these definitions.18
- Scales like the mRS, originally intended for post-stroke measurement with input from patients and carers,19 are often constrained in the acute stroke setting by limited access to reliable informants and by the patient’s inability to communicate due to their stroke.
- This forces physicians to rely on incomplete or inaccurate proxy reports or medical records.20, 21
- The critical time-constraints of acute stroke therapies also rule out any formal assessment of prior cognitive decline, so the physician relies on either a medical record of a dementia diagnosis or a report from the patient or family member.
DEFINING THE PROBLEM CONTINUED

• Besides these limitations of existing tools to evaluate pre-morbid disability or dementia in practice (Supplementary Table 1), we must also consider intersectionality, a crucial sociological concept that is only now gaining traction in the stroke literature.22

• Intersectionality refers to the interconnected nature of categorizations like disability, race, class, and gender, which create overlapping and interdependent systems of discrimination or advantage.

• Applying an intersectionality lens to the prevalent functional status-based (e.g. mRS-based) definitions of disability in stroke trials, we find that exclusion by pre-morbid disability likely also unintentionally promotes exclusion by other demographic factors.

• For example, in the population-based Oxford Vascular Study (OXVASC), patients with pre-morbid disability defined by mRS≥2 were generally older, more often female, and more likely to be socio-economically deprived, even after adjusting for comorbidities.3, 23

• This sex difference in pre-morbid mRS has also been shown in major clinical trials like ENCHANTED, SCASTS, and HeadPoST.24

• As for age and disability, consider for example the largest thrombolysis trial in acute ischemic stroke, the third International Stroke Trial, which encouraged enrolment of older patients but still excluded those with mRS=2, calling into question how representative these patients were of the typical older stroke population.25

• Similar considerations also apply for dementia. In addition to the known association between dementia and increasing age, there are also racial differences; the prevalence and incidence of dementia are higher among Black people in the United States than among non-Hispanic White people.26, 27

• Therefore, exclusion of patients by pre-morbid disability or dementia may limit the generalizability of our treatment evidence for older patients, women, and even certain races.
IMPLICATIONS OF PRE-STROKE DISABILITY AND DEMENTIA ON THE PROGNOSIS OF ACUTE ISCHEMIC STROKE
The presence of pre-existing disability and dementia can affect decision-making and outcomes as the patient moves through the stroke systems of care. This includes difficulties in the pre-hospital, transfer, triage, and in-hospital to post-hospital processes. In the pre-hospital setting, there is often a delay in recognition of acute stroke symptoms as patients may be unable to call for help. Relatives and first responders may also have difficulty recognizing new symptoms or be less inclined to seek medical attention in the setting of pre-existing illness. Once patients do present, their prior deficits confound the assessment of the stroke severity scale. This confounding often leads to a higher severity assessment with the resulting perception that they will have a worse outcome. These patients are less likely to receive thrombolysis. There are documented delays in treatment times for those patients with disability who are treated with thrombolysis, or with endovascular treatment. Such delays are known to adversely affect stroke outcomes. Once admitted to the hospital, these patients are less likely to receive defect-free evidence-based stroke care. There are fewer admissions to stroke units and fewer investigations for secondary stroke prevention in patients with pre-stroke disability or dementia.
Additionally, this population has a 3 to 4 times higher nosocomial infection rate, longer average hospital stay and a 3 to 5.4 times higher odds of in-hospital mortality, with a higher rate of withdrawal of care.

Patients with pre-existing dementia or disability who are not treated and who survive to discharge, have a higher probability of being discharged to a nursing home or being institutionalized.

The long-term consequences and social care costs of the additional disability of untreated stroke in patients with pre-existing neurological deficits are staggering.

In the Oxford Vascular Study, 79% of patients with pre-stroke disability were alive at 3 months and these patients lived an average of 1.35 years (95% CI, 1.20-1.51) post-stroke.

Among these patients, 30.8% did not return to community dwelling and required new institutionalization.

Each added degree of post-stroke disability (ΔmRS at 3 months post-stroke) had a worse outcome with hazard ratio for 5-year mortality/institutionalization ranging from 1.62-5.45 depending on the degree of change.

ΔmRS also directly correlated with increasing social and health care costs.

ΔmRS ≥ 2 was associated with a $40,533 (95%CI $8,827-72,240, p=0.012) increased cost over 5 years.

This highlights the high societal costs of routinely withholding acute stroke treatments in patients with pre-stroke disability, as well as the potential opportunities for care and mitigation of further disability with therapies like thrombolysis and EVT in these patients.
CURRENT EVIDENCE FOR THE SAFETY AND EFFICACY OF THROMBOLYSIS AND EVT IN PATIENTS WITH PRE-STROKE DISABILITY OR DEMENTIA
CURRENT EVIDENCE FOR THE SAFETY AND EFFICACY OF THROMBOLYSIS AND EVT IN PATIENTS WITH PRE-STROKE DISABILITY OR DEMENTIA

- Current evidence on thrombolysis (Table 1) and EVT (Table 2) in patients with pre-stroke disability or dementia is mostly from observational studies, namely case-control studies and some registries.
- These studies are subject to significant selection bias; a lower proportion of patients with pre-stroke dementia or disability receive intervention than those without.
- Studies comparing outcomes for patients with pre-morbid disability/dementia treated with thrombolysis or EVT to patients with disability/dementia who are managed medically are scarce, as are randomized trials for populations with pre-stroke disability or dementia.
- The only major EVT trial that permitted the enrollment of patients with pre-stroke disability was MR CLEAN, which included 45 patients with pre-stroke mRS≥2 (of whom 26 had mRS 2), but these patients were not analyzed separately.41
- Variable thresholds for the definition of “disability” further hamper efforts at direct comparison between studies.
- Notwithstanding these limitations, at present, there is no consistent evidence to support the concern that pre-stroke dementia or disability may be associated with increased risk of sICH associated with reperfusion therapies (Tables 1 and 2).
- Noting the paucity of data comparing treated patients with pre-stroke disability/dementia to untreated patients (versus patients without pre-stroke disability/dementia), there is also no convincing evidence for a loss of treatment benefit with reperfusion therapies in these populations.
- There is some (albeit inconsistent) evidence for increased mortality and reduced return to pre-stroke function following thrombolysis of patients with pre-stroke dementia/disability.
- On the other hand, for EVT, the rates of accumulated post-stroke disability (versus return to pre-stroke function) appear similar for patients with versus without pre-stroke disability.
ETHICS OF INCLUSION VS EXCLUSION OF PATIENTS WITH DISABILITY OR DEMENTIA FROM TREATMENT
ETHICS OF INCLUSION VS EXCLUSION OF PATIENTS WITH DISABILITY OR DEMENTIA FROM TREATMENT

- When considering the question of providing or withholding acute stroke therapies for patients with pre-stroke disability or dementia, we must also consider the various ethical dimensions involved.
- These are discussed further in the Supplement.
- Briefly, in the absence of definitive evidence regarding the balance of risks versus benefits of therapy, it is challenging to make treatment decisions based only on the ethical pillars of beneficence and non-maleficence.
- Under such circumstances, stroke teams should seek to respect a patient’s autonomy – or their wishes and values as expressed by their proxies in the acute stroke setting – whenever possible.
- Basing decisions on a perceived lack of cost-effectiveness or futile resource use is difficult to justify in the absence of high-quality effectiveness or cost data in this patient population.
- On the other hand, enthusiasm to treat these patients must be tempered by the reality that individuals with multiple comorbidities and disability are more likely to succumb to complications of acute stroke.
• Providing good end-of-life palliative care to stroke patients and their families is an inherent moral obligation of the stroke community.

• This aspect needs to be weighed when discussing acute treatment allocation and its merits.

• Furthermore, several biases can influence a physician’s or caregiver’s decision-making process when considering the use of acute stroke therapies in patients with pre-morbid disability or dementia.

• These include ableism, impact or ineffectual bias, optimism bias, fragility bias, catastrophe bias, therapeutic nihilism, medical paternalism, and biases from lived experience (or lack thereof), which are discussed further in Supplementary Table 2.

• Being cognizant of these biases can help physicians think critically about their decision-making and better cater to patient-centred ethical principles.
CONSIDERATIONS FOR THE USE OF ACUTE STROKE THERAPIES IN PATIENTS WITH PRE-MORBID DISABILITY OR DEMENTIA IN ROUTINE PRACTICE
CONSIDERATIONS FOR THE USE OF ACUTE STROKE THERAPIES IN PATIENTS WITH PRE-MORBID DISABILITY OR DEMENTIA IN ROUTINE PRACTICE

• Given the limitations of existing data and the many nuances involved in the care of patients with pre-morbid disability or dementia, as discussed above, it is difficult to draw any firm recommendations about the use of acute stroke therapies like thrombolysis or EVT in this patient population at this time.

• However, based on the best available literature, it seems reasonable to conclude that a blanket disability cut-off, like pre-morbid mRS 2, probably should not be used as a protocolized threshold to exclude patients from acute stroke therapies.

• Instead, we may consider a pragmatic, case-by-case approach to the use of acute stroke therapies in patients with pre-morbid disability or dementia, pending the availability of more definitive evidence (Figure 1).
CONSIDERATIONS FOR THE USE OF ACUTE STROKE THERAPIES IN PATIENTS WITH PRE-MORBID DISABILITY OR DEMENTIA IN ROUTINE PRACTICE CONTINUED

<table>
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| Pre-stroke, non-acute setting: E.g. Stroke Prevention Clinic | • Discuss quality of life concerns and future care preferences with patients and families  
• Encourage advance care planning for future emergencies like major stroke  
• Examine own personal biases that may influence treatment decision-making under time-pressured situations |
| Acute Stroke setting: Time-critical Treatment Decision | • Acknowledge the spectrum of possible post-stroke outcomes; avoid thinking dichotomously in terms of "good" or "bad" outcome  
• Disclose uncertain state of evidence about the magnitude of treatment effects in this population  
• Disclose the potential risks of treatment in this population, such as the high mortality compared to patients without pre-stroke disability/dementia  
• Avoid routinely withholding therapies solely on the basis of pre-morbid status, given potential benefits of mitigating further post-stroke disability  
• Adopt patient-centered care strategies as far as possible: seek to understand what the patient would value in such situations, recognizing this will vary by age, ethnicity, religious beliefs etc. and will be challenging to achieve meaningfully in the acute care setting |
| Post-acute care setting: Prognosticating and planning further care | • Recognize that patient’s outcome will depend not only on the immediate treatment decision but also on high quality of stroke unit care and rehab  
• Consider the patient’s Goals of Care going forward that may be influenced by decision to treat e.g., anticipated need for intubation and intensive care unit admission after EVT |

Figure 1: A pragmatic approach to the use of acute stroke therapies in patients with pre-morbid disability or dementia, involving discussions and considerations across the continuum of stroke care from pre-stroke discussions (when possible) to acute stroke decision-making, through to post-acute care and prognostication.
CONSIDERATIONS FOR THE USE OF ACUTE STROKE THERAPIES IN PATIENTS WITH PRE-MORBID DISABILITY OR DEMENTIA IN ROUTINE PRACTICE CONTINUED```

• Key elements of this approach include acknowledging the spectrum of good and bad outcomes that may be achieved in these patients, disclosing the uncertain state of the evidence when discussing treatment options with patients or proxies, and adopting patient-centered care strategies whenever possible, taking into account their long-term goals of care.

• Such discussions should acknowledge the potential added risks involved in treating these patients, given that observational studies have fairly consistently shown higher mortality among treated patients with pre-morbid disability/dementia compared to those without disability/dementia (notwithstanding the limitations of such comparisons as noted above).

• Treatment risks will also be modified by additional patient-specific data; for example, patients with pre-stroke disability/dementia may have previous neuroimaging showing a considerable burden of white matter hyperintensities or microbleeds, known to increase the risk of post-thrombolysis ICH.\(^{42, 43}\)

• This approach also recognizes that the patient’s outcome will depend not just on the immediate treatment decision at hand, but also on a continuing high quality of post-acute care.

• Indeed, there is also growing evidence regarding the importance of such post-acute care, including rehabilitation and stroke unit care to prevent complications like pneumonia, which may erode any benefits of thrombolysis or EVT even among pre-morbidly healthy patients.\(^{44}\)

• Ensuring access to assistive technologies and psychosocial supports may also help these patients better adapt to life after stroke despite their greater disability.
At present, access to such supports is often dependent on the patients’ socioeconomic and health insurance status and varies considerably from state to state even within the United States of America.\textsuperscript{45, 46}

Outside the acute stroke setting, such as in the stroke prevention or neurovascular clinic, physicians should discuss quality-of-life concerns and future care preferences with patients at risk of major stroke who have pre-existing disability or dementia, including their caregivers or families as appropriate.

Such discussions can facilitate advanced care planning, including living wills or advanced care directives noting patient preferences for acute stroke care, notwithstanding the practical limitations of such advance decisions in influencing eventual care pathways.\textsuperscript{47}

Healthcare systems should invest greater resources towards the accurate documentation of the wishes and values of patients with disability or dementia, and towards ensuring that such documentation is ready available for healthcare teams during emergency situations, without relying on the availability of family members or caregivers.

In this regard, healthcare systems should foster a culture where issues related to quality-of-life and patients’ wishes or values are openly discussed, documented, and shared in a standardized format.
ROADMAP FOR FUTURE STUDIES OF ACUTE STROKE THERAPIES IN PATIENTS WITH PRE-STROKE DISABILITY OR DEMENTIA
ROADMAP FOR FUTURE STUDIES OF ACUTE STROKE THERAPIES IN PATIENTS WITH PRE-STROKE DISABILITY OR DEMENTIA

• As our societies age, the patient population with acute stroke can be expected to increasingly comprise of older patients with multiple co-morbidities, disability, and/or dementia.48

• The stroke community has an obligation to generate higher-quality data to inform stroke care in this expanding population.

• There are several important factors that must be addressed to improve the state of stroke research with regards to patients with pre-stroke disability or dementia (Figure 2).
Figure 2: Methodological, investigator-associated, and societal factors that are critical to consider regarding the representation of patients with pre-morbid disability or dementia in stroke trials, and strategies to address these factors going forward.
• The ascertainment and measurement of pre-morbid disability or dementia in the setting of acute stroke continues to be a challenge.

• If we are to conduct high-quality RCTs including patients with pre-morbid disability, we need harmonized, validated strategies to measure disability and capture these data.

• We also need to develop better measures that are not only reliable in an acute stroke setting, but also help elucidate the nature of a given patient’s disability (e.g. cognitive versus physical) – currently not well captured by the mRS.

• Ideally, such pre-morbid measures should also be captured in clinical registries.

• Such registries could also capture the causes or contributors to pre-stroke disability in each patient, as outcomes likely differ by disability etiology – for example, disability from prior strokes vs from orthopedic causes may have different implications, but such comparisons are missing in the literature.

• In addition, 3-month mRS dichotomies of 0-1/2-6 or 0-2/3-6 fail to capture the potential benefits of treatment in patients with a mix of different levels of pre-stroke disability.
To promote greater inclusion of patients with pre-stroke disability, it is time for acute stroke trials to move away from these conventional dichotomies.

Instead, ordinal mRS approaches including measures like the $\Delta$mRS (capturing the change in mRS from pre-to post-stroke), or more inclusive dichotomous outcomes such as return to pre-stroke mRS or avoidance of the devastating outcome of mRS 5-6, should be strongly considered, being far more reflective of long-term outcomes.\(^3\), \(^49\)

Other measures like home-time (time spent at home post-stroke),\(^50\) healthcare costs, and quality-of-life would also be valuable in this population, at least as secondary outcomes, to facilitate much-needed cost-effectiveness analyses.

There is also a need for high-quality mixed-methods studies involving physicians as well as patients and caregivers to better inform current policies as well as the design of future trials in this population.

The current literature tells us little about how physicians actually deal with the uncertainty of present evidence, i.e. how they balance the uncertain benefits versus risks of therapy when caring for patients with pre-stroke disability/dementia.

Whereas there is a growing body of literature from observational studies (mostly treatment registries), these studies do not help us understand why the patients with pre-stroke disability or dementia captured in these studies were treated – and perhaps more importantly, how many others were not treated and why, and how those untreated patients fared.

Our failure to engage such patients in research on post-stroke recovery and adaptation is unfortunate as we end up excluding the very patients carrying the greatest burden of illness.\(^51\)
ROADMAP FOR FUTURE STUDIES OF ACUTE STROKE THERAPIES IN PATIENTS WITH PRE-STROKE DISABILITY OR DEMENTIA CONTINUED

• If we do not actively incorporate these voices, then the dialogue on acute stroke therapies becomes restricted to doctors and policy-makers, incurring the risks of “groupthink”\textsuperscript{52}, and failing to empower the autonomy of patients with disability/dementia and their caregivers.

• Therefore, we also need to engage these patients and their families/caregivers to capture their views and experiences in relation to (a) the uncertain benefits (versus risks) of acute stroke therapies, (b) potentially living a longer life with greater disability post-stroke, and (c) involvement in acute stroke trials.

• This type of work would ideally include qualitative/mixed-methods studies on patients’ wishes and expectations about stroke care, with emphasis on capturing diverse perspectives (different age groups, ethnicities, physical and cognitive disabilities, etc.).

• The field could also benefit from the reflections and quantitative follow-up assessments (e.g. quality-of-life) of patients with pre-morbid disability/dementia who received acute stroke therapies (versus those who did not) and their caregivers.

• Such data can help us understand their perspectives and satisfaction with their acute treatment decisions; similar data have meaningfully informed discussions about decompressive craniectomy in acute stroke.\textsuperscript{53}

• Equity, Diversity, and Inclusion (EDI) initiatives in stroke research should also promote training and leadership opportunities for physicians living with disability, so that people with disability are also represented among the investigators themselves.

• As an initial step towards better efficacy data in this population, we encourage the systematic measurement and tracking of pre- versus post-stroke functional outcome in patients with pre-stroke disability and dementia in prospective registries of acute stroke.
• Ideally, these registries should capture data on both treated and untreated patients (the latter generally missing from existing data), so that post-treatment outcomes in patients with pre-stroke disability/dementia may be compared to those of untreated patients of similar pre-stroke status, instead of expecting them to meet the arbitrary standard of treated patients without disability/dementia.

• We also encourage the enrollment of patients with pre-stroke disability/dementia in Phase IV trials of thrombolysis/EVT, and in future trials of new therapies.

• Studies enrolling such mixed populations should plan for separate subgroup analyses of patients with physical and cognitive disability.

• Given the potential added limitations to the informed consent process in this patient population (particularly those with intellectual/cognitive disability or dementia), consideration may be given to strategies like caregiver/proxy assent – or if appropriate, waiver of consent – to facilitate the inclusion of these patients.54

• Incorporating telephone-or video-assisted remote follow-up visits can also empower such patients to participate in stroke trials.

• Research and development into better assistive and rehabilitative technologies will also help improve post-stroke outcomes in these patients.

• Our recommendations for future research are summarized in Supplementary Table 3.
CONCLUSION
CONCLUSION

• The absence of definitive evidence regarding the efficacy of thrombolysis and EVT in patients with pre-morbid disability or dementia results in difficult decisions about the use of these therapies.

• Recent clinical-epidemiological studies have demonstrated challenges in our concept and measurement of pre-stroke disability or pre-stroke dementia, while highlighting the significant proportion of the general stroke population that falls under this umbrella, risking exclusion from therapies.

• Such studies have also helped clarify the adverse long-term clinical and health economic consequences with each increment of additional post-stroke disability in these patients, underscoring the importance of finding strategies to mitigate such additional disability.

• Several observational studies – both case series and registry-based studies – have provided complicated safety data regarding EVT and thrombolysis in patients with pre-morbid disability/dementia, demonstrating similar hemorrhagic risks but much higher mortality compared to patients without disability/dementia.

• These observational data also suggest that such patients have a substantial potential to retain their pre-stroke level of disability when treated, despite their generally worse prognosis overall, although this remains to be validated in higher-quality registries and clinical trials.

• By pairing pragmatic and transparent decision-making in clinical practice with an active pursuit of high-quality research, we can work towards a more inclusive paradigm of patient-centred care for this often-neglected patient population.
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<th>Study Design</th>
<th>Patient Population</th>
<th>Study Intervention (# patients/ Study Comparator (# patients)</th>
<th>Post-stroke disability outcomes</th>
<th>Mortality outcomes</th>
<th>ICH, sICH, and other safety outcomes</th>
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<td>Caruso 2020*&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Retrospective, single center, 2015-2017, n=35</td>
<td>AIS treated with IVT (3 also EVT), pre-stroke mRS ≥2</td>
<td>12 pre-stroke mRS 2, 14 pre-stroke mRS 3, 9 pre-stroke mRS 4-5, 247 AIS-IVT with pre-stroke mRS&lt;2</td>
<td>The treated subjects with mRS &gt; 2 showed lower mRS at discharge (median 1; range 0-5) and similar NIHSS% (~75%).</td>
<td>Mortality (unclear timepoint) 2/12 (17%) pre-stroke mRS 2, 3/14 (21.4%) mRS 3, 4/9 (44%) mRS 4-5, vs 4.7% for mRS&lt;2.</td>
<td>In surviving patients, median % change in NIHSS was higher in the mRS 2 and 3 groups (63.3% and 92.3%, respectively) than in the mRS4/5 group (9.1%).</td>
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<td>Morlino 2019*&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Retrospective, single center, 2015-2018, n=110</td>
<td>AIS, IVT-eligible, pre-stroke mRS 3-4, excludes thrombectomy</td>
<td>36 treated with IVT, 74 no IVT</td>
<td>Favorable outcome = 3-month return to pre-stroke mRS associated with IVT vs no IVT; OR 3.5 (1.4-8.9)</td>
<td>Similar 3-month NIHSS (95% CI 0.4-3.3)</td>
<td>Similar rates of ICH (OR 2.2, 95% CI 0.4-12.4) and sICH (2 vs 0; p=0.10)</td>
<td>Neurologic improvement (=8 point NIHSS improvement or NIHSS=0 at discharge, OR 2.9 (1.0-8.0)</td>
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<td>Gumbiner 2019&lt;sup&gt;77&lt;/sup&gt;</td>
<td>German state-wide registry 2008-2014, n=52,741</td>
<td>AIS presenting within 4.5 h; 23.5% with pre-stroke disabilities (mRS&gt;0)</td>
<td>29% of total treated with IVT, inversely correlated with pre-stroke mRS (e.g., 32.9% mRS 0 vs 20.2% mRS 3, 11.2% mRS 5)</td>
<td>Favorable outcome at discharge (mRS 0-1 or return to pre-stroke mRS) independently associated with IVT for all pre-stroke mRS 0-4. Multivariable aORs 1.73 (1.61-1.86) mRS 0 vs 1.57</td>
<td>Morality at discharge not independently associated with IVT for any of the pre-stroke mRS&gt;0 groups,</td>
<td>Not reported in this paper</td>
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</table>

*Table 1 – Studies Evaluating Intravenous Thrombolysis (IVT) for Acute Ischemic Stroke (AIS) in Patients with Pre-existing Disability or Dementia. Studies are presented in reverse chronological order.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design/Setting</th>
<th>Intervention/Comparison</th>
<th>Sample Size</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang 2018&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Retrospective, single-center 2005-2016, 820 consecutive patients</td>
<td>AIS treated with IVT</td>
<td>680 with premorbid mRS 0-1, 140 mRS 2-4</td>
<td>Return to premorbid mRS at 90d in 24.9%, 39.3%, 32.3%, 29.7%, and 25.0% of patients with premorbid mRS 0, 1, 2, 3, and 4 respectively (nonsignificant)</td>
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<td>Zupanic 2017&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Swedish Dementia Registry 2007-2014 with strokes identified by Riksstroke national stroke registry, nested case-control</td>
<td>AIS, restricted to 2010-2014 period when 4.5-hour IVT window was instituted</td>
<td>1356 dementia patients with AIS vs 5755 dementia-free controls matched by age, sex, stroke year, geographic region</td>
<td>Increased 3m mRS score for prestroke dementia (OR for ordinal logistic regression 3.65, OR 2.06-6.46) and new nursing home placement (4.39, 2.07-9.31).</td>
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<tr>
<td>Garasicke 2016&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Prospective registry study, n=7430</td>
<td>Consecutive AIS treated with IVT</td>
<td>6941 with pre-stroke mRS 0-2, 489 pre-stroke mRS 3-5</td>
<td>No difference for 3m poor outcome (defined as mRS=3-6 if pre-stroke ≤2, increased post-stroke mRS if pre-stroke &gt;2; aOR 0.95; 95% CI, 0.75-1.21).</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Cohort</td>
<td>Outcomes</td>
<td>Results</td>
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<td>Karlinski 2014&lt;sup&gt;26&lt;/sup&gt;</td>
<td>SITS-EAST prospective registry 2003-2011, n=7250</td>
<td>Consecutive AIS treated with IVT</td>
<td>171 with pre-stroke mRS 3.5, 293 pre-stroke mRS 2, 790 pre-stroke mRS 1, 5990 pre-stroke mRS 0</td>
<td>For favorable 9m outcome [mRS 0-2 or return to pre-stroke mRS] acRs: 0.80 (95% CI 0.55-1.0), 0.41 (0.28-0.60), 0.59 (0.34-1.01)</td>
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<td>Prestroke mRS 1, 2, and ≥3 were associated with increased risk of death at 3 months (OR 1.3, 2.0, and 2.6). Patients with prestroke mRS 3 had higher mortality than those with mRS 0 (48% versus 39%).</td>
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<td>Multivariable aORs (95% CI) across mRS 1, 2, and ≥3 relative to mRS 0 for sICH: 1.36 (0.99-1.86), 1.12 (0.67-1.88), 1.18 (0.58-2.43). Sensitivity analysis excluding patients with prior stroke showed increased sICH with mRS 3-5.</td>
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<td>For NIHSS ≥4pt improvement day 7, multivariable adjusted ORs across pre-stroke mRS 1, 2, and ≥3 and mRS 0: 1.0 (0.65-1.18), 0.64 (0.49-0.85), 0.59 (0.36-0.90).</td>
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<td>Bual 2013&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Retrospective, single center, 2002-2009, n=153 (110 IVT, 54 IAT, 11 both)</td>
<td>AIS treated with IVT or IAT, age≥80</td>
<td>21 pre-stroke dementia vs 132 no pre-stroke dementia</td>
<td>Favorable discharge (home or acute rehab) 721/761 (33.3%) vs 76/132 (57.8%), OR 0.37 [0.12-1.06] p=0.38</td>
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<td>In-hospital mortality 13/21 (61.9%) vs 41/132 (31.1%), OR 3.6 [123-10.6] p=0.01</td>
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<td>sICH 3/21 (14.2%) with prestroke dementia, 7/132 (5.3%), OR 3 [0.5-14.4] p=0.14 no dementia</td>
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<td>Saposnik 2012&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Canadian Stroke Network registry 2003-2008, retrospective analysis n=10,658 and nested case-control</td>
<td>AIS treated with and without IVT</td>
<td>Total registry: 966 with pre-stroke dementia, 9692 without dementia. Nested case-control: 977 with dementia, 977 without, propensity-matched by age, sex, severity, type comorbidities and treatment characteristics.</td>
<td>Disability at discharge similar between patients with dementia and those without in the matched sample (85.2% vs 82.7%). Slight increase in disability (RR 1.10, 95% CI 1.02-1.19), when including only patients discharged alive.</td>
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<td>In full cohort no difference in 30d mortality with vs without dementia (RR 0.96, 0.81-1.12). In matched analysis, no difference in 30d mortality (RR 0.68, 0.75-1.03). No significant difference in sICH (RR 1.28, 95% CI 0.63-2.60)</td>
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<td>Patients with dementia less likely to receive IVT (10.5% vs 16.2%).</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Sample</td>
<td>AIS treated</td>
<td>Patients with Dementia</td>
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<tr>
<td>Fossi 2003[6]</td>
<td>Prospective observational study, n=112</td>
<td>Consecutive AIS treated with IVT</td>
<td>24 with pre-stroke mRS ≥ 2 vs 88 pre-stroke mRS ≤ 1</td>
<td>Median mRS 3 with pre-morbid disability vs 2 without. No difference in favorable outcome defined as mRS 0-1 or return to pre-mRS baseline (41% vs 42%)</td>
</tr>
<tr>
<td>First Author and Year Published</td>
<td>Study Design</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) and Comparator (# patients)</td>
<td>Post-stroke disability outcomes</td>
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<td>Salwi 2020(1)</td>
<td>Retrospective, dual center, 2012-2018, n=761</td>
<td>Consecutive AIS patients treated with EVT</td>
<td>259 patients with moderate pre-stroke disability mRS 2 vs 502 pre-stroke mRS 1</td>
<td>90-day mRS 1 or unchanged from baseline disability in 56.7% vs 26.7% (OR 0.60–1.35, P=0.6)</td>
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<tr>
<td>Regenhardt 2020(2)</td>
<td>Retrospective, single center, 2011-2019, n=381</td>
<td>Consecutive AIS patients treated with EVT</td>
<td>49 patients with baseline disability (five with mRS 4, 23 mRS 3, 21 mRS 2), 332 without</td>
<td>Baseline disability associated with 900 mRS 0 (OR 0.51, 95% CI 0.37–0.70) but not accumulated disability by delta mRS 50</td>
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<tr>
<td>Salwi 2020(3)</td>
<td>Retrospective, dual center, 2012-2018, n=856</td>
<td>Selected patients with severe baseline disability (mRS 4 or 5)</td>
<td>33 patients (4% of total) identified from 822 patients total</td>
<td>36% return to baseline functional status comparable to historical data on patients without pre-morbid disability</td>
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<tr>
<td>Larsson 2020(4)</td>
<td>Retrospective, single center, 2015-2018, n=591</td>
<td>Consecutive AIS treated with EVT</td>
<td>90 patients with baseline disability mRS 3 vs 501 with mRS 2</td>
<td>Recanalization rates and return to pre-stroke functional baseline were similar between groups. 20% with pre-stroke disability returned to baseline</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Observational Registry Study</td>
<td>Multicenter</td>
<td>Number of Patients</td>
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<td>Oesch 2020&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Prospective, observational registry study, multicenter, 2006-2016, n=1267</td>
<td>Consecutive AIS treated with EVT</td>
<td>84 patients with pre-stroke mRS ≥2 vs 163 with pre-stroke mRS ≤2</td>
<td>Pre-existing disability not associated with clinical outcome (OR 1.08, 95% CI 0.61–1.93)</td>
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<tr>
<td>Leker 2019&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Prospective, observational registry study, multicenter, 2017-2018, n=396</td>
<td>Consecutive AIS treated with EVT</td>
<td>35 patients with previous strokes, 35 patients without previous stroke</td>
<td>Return to previous disability level in 9% of patients with pre-stroke stroke</td>
</tr>
<tr>
<td>Sliwaski 2018&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Retrospective, single center, 2015-2017, n=96</td>
<td>Consecutive patients over 80yrs of age treated with EVT</td>
<td>48 patients with moderate pre-stroke disability mRS 2-4 vs 50 patients with pre-stroke mRS 1</td>
<td>No significant difference in return to baseline disability between mild and moderate baseline disability groups (43% vs. 24%, p = 0.08)</td>
</tr>
<tr>
<td>Goldhoorn 2018&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Prospective, observational registry study, multicenter, 2014-2016, n=1441</td>
<td>Consecutive patients with anterior circulation occlusions treated with EVT</td>
<td>157 patients with moderate pre-stroke disability mRS 3-5 vs 1284 patients with pre-stroke mRS 2</td>
<td>Return to baseline disability in 77% of disabled patients vs 42% of pre-stroke independent patients (OR adjusted, 0.30; 95% CI, 0.58–1.39)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AIS- acute ischemic stroke; mRS- modified Rankin Scale; EVT- endovascular therapy; SICH- symptomatic intracerebral hemorrhage; NIHSS- National Institutes of Health Stroke Scale; OR- odds ratio (aOR- adjusted OR); RR- risk ratio