Acute therapies for patients with pre-morbid disability or dementia: An evidence-based ethical framework with a focus on ischemic stroke

Aravind Ganesh MD DPhil¹ and Anand Viswanathan MD PhD²

¹Department of Clinical Neurosciences, University of Calgary, Calgary, Canada
²Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, United States of America

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Introduction

“Such as thou art, sometime was I,
Such as I am, such shalt thou be.”

- Canterbury tomb of Edward the Black Prince (1330-1376)¹

A currently inescapable reality of aging is that many of us who live long enough are likely to experience a variable period of disability before death.² As we accumulate comorbidities with age, we are likely to develop physical and cognitive impairments, which may prevent us from independently performing certain aspects of our daily activities, and we may therefore be labelled as having some degree of “disability”.³ The growing burden of cognitive impairment (including major neurocognitive disorder⁴ or dementia) with increased longevity is likely to play a major role.⁵ Thus, as our societies age, medicine will increasingly comprise of caring for older patients with a greater burden of comorbidities, disability, and/or dementia.⁶

Healthcare for this patient population with pre-existing disability/dementia will often occur in the context of acute medical presentations: myocardial infarction, stroke, hip fracture, and sepsis being a few examples. In many of these situations, physicians will need to consider whether to proceed with acute medical or surgical therapies in the context of uncertain evidence for their safety or efficacy in the patient before them. This is because of the poor generalizability of most randomized controlled trials (RCTs) to patients with pre-morbid disability/dementia, who are generally excluded from them.⁷ In addition, since acute treatments for emergent conditions generally cannot be expected to restore patients to better functioning than their pre-morbid state, most treatments will at best result in the patient living with the same – or likely higher – degree of disability. As healthcare systems turn to cost-effectiveness analyses to make decisions for resource allocation, they may, in the first instance, consider such therapies to be poorly justified.⁸ Some physicians may worry about risking harm in such patients without achieving meaningful benefits.⁹ On the other hand, some patients and/or other physicians may argue that treatment decisions should not be centred around such debates of optimization (be it of cost or clinical outcome), and that patients or their proxies should remain the adjudicators of their own quality-of-life.¹⁰ Consequently, an ethical tension exists in such cases between providing or withholding acute therapies.

Acute ischemic stroke is a particularly high-stakes and time-pressured example of emergent medical presentations.¹¹ Over the last decade, several interventions have improved acute stroke care: increasing public awareness of stroke symptoms,¹²,¹³ rapid ambulance protocols,¹⁴ and the reorganization of systems of care around stroke units, telemedicine,¹⁵ and hyper-acute reperfusion services.¹⁶,¹⁷ Much of this change has been driven by the findings of multi-centre RCTs demonstrating
the efficacy of intravenous thrombolysis with recombinant tissue plasminogen activator (tPA), hemicraniectomy for malignant middle cerebral artery infarctions, stroke unit care, and endovascular therapy (EVT) for acute strokes with proximal large vessel occlusions. Whereas acute stroke therapies have variable time-windows for known benefit – generally within 4.5 hours post-stroke onset for tPA and up to 24-hours post-stroke onset in select cases for EVT – the benefit of these therapies rapidly declines with time, so treating patients as quickly as possible is crucial. The mantra “time is brain” reflects the reality that patients lose an estimated 1.9 million neurons each minute that the stroke is untreated. Since the key benefit of acute stroke therapies is to improve functional outcome or mitigate post-stroke disability (potentially reducing long-term mortality), there is a reticence on the part of stroke physicians to provide such therapies to patients with pre-morbid disability/dementia. In fact, pre-morbid disability is a commonly cited reason for excluding patients from thrombolysis, despite not being a formal contraindication. As such, acute ischemic stroke provides a useful context to consider the ethical dilemma of offering acute therapies to patients with pre-morbid disability/dementia. In this paper, we will explore various facets of this dilemma via the example of acute stroke, using an evidence-based perspective, and drawing on relevant ethical philosophies, with the aim of providing a framework for decision-making.

I. The determination of pre-morbid disability

The ethical quandary of whether to treat a patient with pre-morbid disability/dementia begins the moment the physician decides to make the determination of said disability. This very act may be viewed as an exclusionary construct, as argued by the philosopher Paul-Michel Foucault (1926-1984) – defining individuals as disabled entails excluding them in some manner from active contribution to society and consigning them to care in institutions like nursing homes. Foucault described this as “exclusion through division and rejection”. Under the Foucauldian lens, magnifying tension between exclusion and emancipation, all disability models may be seen as products of power, facilitating control over selected aspects of an individuals’ functioning. This tension, however, typically eludes the physician, patient, and/or carer as they dip into the murky waters of disability assessment.

The next issue is how to measure the patient’s pre-morbid disability. Often, in medical settings, no real measurement is made, and the physician relies on a dichotomous assessment of the patient’s daily functioning to decide whether they have significant disability. In the setting of acute stroke, a preferred measurement is the modified Rankin Scale (mRS, Table 1), the most favoured primary outcome measure in acute stroke trials, partly because it is simple to administer, has good reproducibility, and avoids major floor or ceiling effects. Acute stroke trials strive to demonstrate improvement on the 3-month mRS, which has sound predictive validity for long-term clinical and health-economic outcomes post-stroke. Although the mRS was designed to evaluate post-stroke outcomes and not
pre-stroke functional status, it is not disease-specific and can reflect general functional decline, leading to its use in over 40 different conditions including Parkinson’s disease, autoimmune encephalitis, and myotonic dystrophy. The pre-stroke mRS turns out to be a robust predictor of post-stroke outcomes like mortality, length of stay, post-stroke complications, and institutionalization, over and above any influence of the pre-stroke mRS on treatment decisions.

However, despite training programs and standardized assessments having been developed for the mRS to address concerns about external reliability, there remains substantial inter-observer variability in mRS grades awarded, even among experienced researchers. When the 3-month mRS is assessed in stroke trials, it is not only recommended that the interview be conducted by a trained rater, but also that it involve both the patient and relevant carers. Substantial inter-observer variability occurs when mRS assessments rely on proxies alone, and mRS scores based on standard hospital records alone are often inaccurate. Unfortunately, in the setting of acute stroke, patients often cannot contribute to the discussion due to aphasia, anarthria, neglect, or decreased level of consciousness, forcing the physician to rely on the report of the patient’s carer/proxy, or worse, the patient’s medical records if the carer/proxy is not available. With pre-morbid dementia, the scenario may be further complicated by concerns about decision-making capacity. It is not uncommon for physicians to discover that a patient had pre-existing dementia well after acute care decisions have been made – given that such diagnoses are often not recorded in hospital charts, particularly in patients who are single or from minority ethnic groups. Physicians may also hear from one family member that a patient is fully independent while another says they require considerable help. Such discrepancies may relate to how well a given proxy knows the patient or their involvement in the patient’s care. With adequate time, a physician may gain a clearer picture of these factors, but in the time-pressured setting of acute stroke, much of this “knowable” information is likely to remain “unknown” (Figure 1). The stakes of inaccurate disability evaluation are raised further if physicians (or the systems they serve) employ a dichotomous approach in their treatment decisions – for example, if they exclude patients with a pre-stroke mRS≥3 from receiving EVT/tPA, based on the typical dichotomy used to define “poor” outcomes in trials. In fact, inter-rater variability appears to be greatest for mRS grades 1 and 2, around which the mRS is dichotomized.

To further complicate matters, when physicians exclude patients using a pre-morbid disability “cut-off”, they may end up disproportionately and unintentionally excluding patients from certain demographics. In the Oxford Vascular Study (OXVASC), the distribution of pre-stroke mRS scores was worse not only in older patients, but also in women and those who were socio-economically deprived. Similarly, if excluding based on dementia, around two-thirds of those with Alzheimer’s Disease (AD) are women, and the incidence of AD seems higher in Black and Hispanic communities in the United
States. There may be additional, hitherto unknown factors contributing to observed discrepancies; for instance, it was recently shown that apolipoprotein E (APOE) alleles – long thought to be the most potent genetic risk factor for intracerebral hemorrhage (ICH) – do not affect ICH risk to the same extent in Black or Hispanic populations as in White populations. In the face of such uncertainty, physicians and healthcare systems should be wary of criteria that risk greater exclusion of certain types of patients. Ageism has been noted in interventional stroke studies, and older patients, women, and socio-economically deprived patients are less likely to receive appropriate acute stroke care; racial-ethnic disparities have also been reported. The magnitude of exclusion merits consideration – in OXVASC, using a pre-stroke disability cut-off of mRS≥3 would have excluded over 17% of the ischemic stroke population, while a cut-off of mRS≥2 would have excluded over 30%. Nevertheless, the vast majority of physicians or health systems who do not carefully compare the characteristics of their treated populations to the general stroke population may remain blind to these issues of representativeness. For example, consider a stroke centre where the percentage of those receiving EVT who are over age 75 is the same as the percentage of all stroke patients in that community over 75, which at first glance seems ideal. However, if the patients being treated are all functionally independent (pre-stroke mRS 0-2) versus only a fraction of those over 75 in the community, the centre is in fact systematically excluding older patients even if it only intends to exclude patients with pre-morbid disability. Even RCTs that use block-randomization or actively enroll different demographic groups – like the third International Stroke Trial (IST3) with older patients – will end up with unrepresentative samples if they exclude patients with pre-morbid disability, as did IST3.

II. Missing voices and the problem of ableism

To suggest that exclusion by disability is troubling only because we might unintentionally exclude by sex, age, race, or socioeconomic status, is itself problematic as it suggests that discrimination based on disability is acceptable even if other forms of discrimination are not. This bias, termed ableism – discrimination or prejudice against people with known or perceived disabilities – is an important determinant of health and socio-economic inequity. For example, a recent Australian study found that disability-based discrimination was reported more commonly by those who were socio-economically deprived. Ableism is being recognized as an important source of bias in medical care, at both a carer/clinician level and healthcare-system level. At the systems-level, a recent study found that regardless of state size or wealth, American states with more “disability prejudice” – as assessed by the Disability Attitudes Implicit Association Test in 325,000 people – directed less Medicaid funding towards home and community-based services, relied on by people with disabilities to receive care without being institutionalized. At the carer/clinician level, ableism-related oppression or negation of perceived personhood may increase patients’ vulnerability to elder abuse or neglect, with its repressive effects potentially heightened when the patient has dementia.
Ableism also complicates a carer's perception of the patient's quality-of-life. The physician and bioethicist Didier Sicard (b. 1938) laments our underlying obsession with the patient's deficits: « La personne handicapée physique et/ou mentale est devenue un préjudice vivant, une faute, qui mérite réparation en tant que telle ». An analysis of explicit and implicit disability attitudes among siblings and other family members of people with disabilities found that most family members appear to harbour negative attitudes about such people, although they generally did not recognize this bias. There is a dearth of such data on non-White or non-Christian populations. Religious beliefs are likely to strongly influence evaluations of a loved one's disability or quality-of-life. For instance, the Hindu scripture Manusmriti (2:235) commands devotion to parents regardless of their life circumstances: “As long as they are alive, no one should devote himself to any other religious undertaking. Rather, he should continue to serve them with full diligence and do whatever pleases them and is beneficial to them.” The Jewish scripture Leviticus (Lev. 19:32) commands devotion to the elderly and God in the same breath: “You shall stand up before the gray head and honor the face of an old man, and you shall fear your God: I am the Lord”. Whereas such beliefs and values may encourage carers to advocate for an older or disabled patient, they may also bias carers towards more aggressive interventions versus a palliative approach.

Returning to the scenario of acute stroke care, this means that there are several patterns of thoughts and beliefs that likely influence how the physician and carer view the patient with pre-morbid disability as they contemplate the decision of acute therapy (Figure 1). These factors, often subconscious, may be unknown to the very individual they influence, and are certainly “unknowable” in the acute setting by the other parties involved. Sicard cautions us: « Si la souffrance réelle d’un individu est inaccessible à la connaissance, la dignité de celui qui souffre s’exprime dans le regard que l’autre lui adresse ». An unfortunate patient’s fate may be sealed by the combination of their inability to speak and the physician’s attitude regarding their visible disability, abetted by their carer’s pessimistic view of their future quality-of-life.

Whereas modern medical ethics have been guided by the principles of autonomy, beneficence, non-maleficence, and justice, there is general consensus that the patient’s voice should carry the greatest weight among all possible points-of-view. If we consider a more ideal situation in which the patient can provide accurate information about their functional status, then an apparently simple step

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1 Page 66, paraphrased: The person with physical and/or cognitive disability becomes a living prejudice, a fault, that needs to be fixed.

2 Page 81, paraphrased: If the true suffering of an individual cannot be directly known, their dignity is determined by how others regard them.
would be to ask the patient what they would like us to do. The ideal process of informed consent in such cases requires the physician to have some appreciation for what the patient thinks about their quality-of-life and their views on potentially living a longer life with greater disability. Such information could help the physician frame the existing medical literature for the patient to fit their unique needs. What the patient (or proxy) decides, then, depends very much on how the physician frames the available treatment options and their risks/benefits, which in the context of ableism, becomes another stumbling block. Whereas the majority of patients prefer receiving detailed information on risks/benefits and utilizing a shared decision-making approach for acute stroke, a 2004 study found that tPA consent was not documented in 15% of cases and was provided by proxies in 63% of cases owing to the patient being unable to participate. In an ideal world, important medical decisions would follow a period of therapeutic relationship-building that allows the physician to gain a better understanding of the patient’s values. However, in emergent settings like acute stroke, the ticking clock of therapeutic windows looms over such discussions. Consequently, consent processes for tPA are generally very brief (mean 2.7 minutes in one study). Bias, stereotyping, prejudice, and clinical uncertainty on the part of the physicians is suspected to play a role in racial/ethnic health disparities, a troubling consideration given a recent finding that tPA refusal is documented twice as often in African-American patients versus non-Hispanic Whites. However, there is a paucity of such data on informed consent or assent for patients with pre-morbid disability/dementia. In a general medical context, many doctors still believe that they “know best” and perceive moral agency to avoid actions that they feel would not benefit or may harm their patients. Such beliefs can impede patient-centered care delivery if they become the major driver of a physician’s actions.

It would also help to have data on what patients with pre-morbid disability think about their own current quality-of-life and how they would imagine their potential future quality-of-life post-stroke. Unfortunately, these patients remain “missing voices” in stroke medicine. There is a nascent literature examining how patients adapt to disability and changed life circumstances post-stroke, but these studies have generally recruited younger patients with less severe disability (e.g. mRS≤3). Our failure to engage such patients in stroke research reflects the general medical literature, which ironically excludes the very patients who carry the greatest burden of illness, despite touting the concept of patient engagement. If we do not actively incorporate these voices, then the dialogue on acute therapies becomes restricted to doctors and policy-makers, incurring the risks of “groupthink” and failing to empower the autonomy of patients with disability/dementia and their carers.

The paucity of data on the effectiveness of therapies like tPA or EVT in patients with pre-morbid disability/dementia may itself reflect ableism. Ableism may influence how clinician-scientists and trialists design studies and how ethics boards approach the accommodation of patients with physical
and/or cognitive disability in medical research. Obtaining ethical approval to enroll such patients in a trial can be very challenging, particularly if trials seek provisions for assent by proxies or waiver or deferral of consent. Moreover, assent by proxies may not be obtainable in time, and deferral of consent has been frowned upon by patients (without pre-morbid disability) enrolled in this manner. These bureaucratic considerations become additional factors (unknown to the patient/carer, Figure 1) that may influence the physician’s decision to treat such patients. On this note, another cause for concern is the absence of physicians or trialists living with disability. Physicians’ lived experiences of disability – their own or those of loved ones – are likely to influence their judgement in high-stakes settings. These challenges deserve further attention and dialogue, as medicine rises to the disability rights movement’s call to action: “nothing about us without us”.

III. Demonstrating efficacy: The ethical problem of dichotomization

If one approaches the issue of acute medical therapy in patients with pre-morbid disability/dementia with a focus on the cardinal principles of beneficence and non-maleficence, one is confronted by an absence of definitive evidence. Indeed, patients with pre-stroke disability (often defined as mRS≥3 or mRS≥2) have generally been excluded from acute stroke trials. This approach is not based on any mechanistic hypothesis about reduced benefit but likely reflects the fact that premorbid disability prevents these patients from contributing to dichotomy-based definitions of favourable outcome (e.g. mRS 0-1 or 0-2). However, measures like the mRS need not be dichotomized; they may also be analyzed using ordinal analyses that assess all changes across the range of the scale. There is a lack of consensus on the optimal analytical method, with over half of stroke trials since 2007 using dichotomous analysis of the mRS, whilst about a quarter used ordinal approaches. Dichotomous analyses are often favoured because they provide results that are easily explained using the absolute risk reduction in outcome between groups. Yet these approaches result in information loss, risk ignoring bi-directional effects, and often require larger samples than ordinal approaches. Arguments favouring ordinal approaches have conventionally relied on such statistical points. However, there are also clinically – and ethically – relevant issues with using dichotomous approaches. As discussed above, dichotomies risk excluding key patient groups. In addition, ordinal analyses may better reflect clinically important differences in long-term outcomes between state-transitions. For example, a recent analysis of 5-year disability, mortality, and health and social-care costs in OXVASC, stratified by 3-month mRS, found that meaningful differences in outcomes were seen across the range of mRS scores, resulting in a significantly better fit in regression models using the ordinal mRS versus those using a dichotomized mRS. Using ordinal analyses would thus not only allow patients with pre-morbid disability to contribute to treatment effects in stroke trials, but also reflect the reality that any reduction in disability is likely beneficial in the long-term.
The reluctance to treat patients with acute stroke and pre-morbid disability is partly because of their perceived poor prognosis, as pre-morbid disability is associated with more severe strokes and higher inpatient mortality. That being said, poorer prognosis does not rule out clinically meaningful acute treatment effects. A recent analysis of long-term outcomes in patients with ischemic stroke and pre-morbid disability in OXVASC found that these patients, untreated, had higher 5-year mortality, institutionalization, and costs with each increment of further post-stroke disability. This highlights the poor long-term outcomes expected if acute interventions are routinely withheld in these patients and suggests that the change in mRS from pre-stroke to post-stroke (ΔmRS) could be a meaningful outcome measure in future trials that enroll a mix of patients with and without pre-stroke disability. Encouragingly, evidence on tPA/EVT safety and efficacy in such patients is slowly emerging, bolstering the ethical arguments of beneficence and non-maleficence in favour of treatment. Small studies of thrombolysis in patients with pre-morbid disability/dementia have shown that they have higher mortality but appear capable of returning to their pre-stroke status as often as patients without pre-existing disability/dementia. In an analysis from the SITS-EAST (Safe Implementation of Treatments in Stroke – Eastern Europe) registry of patients receiving tPA, there was no independent association between pre-stroke disability (mRS≥2, 6.4% of patients) and the risk of symptomatic ICH (sICH) post-thrombolysis, with one-third of previously disabled patients returning to their pre-stroke mRS, despite a higher mortality. In a similar analysis of the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke) EVT registry, stroke patients who had pre-morbid mRS 3-5 (10.9%) were similarly able to retain their pre-stroke mRS as those with pre-morbid mRS 0-2, once adjusted for confounding factors, with similar risk of sICH. These data, although observational, argue that patients with pre-morbid disability/dementia should not be routinely excluded from EVT/tPA.

Moreover, the observed effectiveness of acute therapies like EVT/tPA will also depend on how societies invest in supporting patients living with disability post-stroke. One example is access to rehabilitation services, which is already difficult for patients with financial barriers. About one in four patients demonstrate late functional improvement between 3 and 12 months post-stroke, and one in ten show further improvement in the next four years; the extent to which late improvements can be optimized is presently uncertain. Social networks are a key determinant of recovery and well-being in the setting of disability; patients and carers empowered to build successful networks may do better than those consigned to social isolation. Environments or interventions that foster resilience to added disability – like acceptance and commitment therapy – may also help patients achieve better outcomes in ways not captured by typical outcome measures. There are also practical limits to our ability to assess efficacy. Patients with very severe pre-stroke disability (mRS=5) can certainly accumulate additional post-stroke disability, but this is unmeasurable on the mRS since the next step
up is death (mRS=6); a physician relying on the mRS will not know whether a treatment made a difference in such patients. Improvements potentially seen at a group level in a trial may not be observable at the individual patient level – a patient with pre-stroke mRS of 2 treated with tPA/EVT may have a 3-month mRS of 4, which may seem like a bad outcome, but perhaps without treatment, that patient would have had a 3-month mRS of 5, making this a good outcome. These then are additional “unknowable” factors at the time of the acute treatment decision (Figure 1).

IV. Demonstrating cost-effectiveness: The problem of economic biases
A competing approach to the question of acute medical therapy in patients with pre-morbid disability/dementia is to focus on the ethical principle of justice, particularly that of just allocation of scarce resources. Those ascribing to the philosophy of utilitarianism might argue that investment of such resources simply for a chance of preventing some uncertain degree of incremental disability or morbidity is not justified. In the case of acute stroke, a number of health-economic studies have demonstrated an association between higher stroke severity or post-stroke mRS with higher post-stroke healthcare costs; patients with pre-morbid disability/dementia who already have a higher mRS may therefore be expected to incur higher healthcare costs than other patients. However, using cost-based arguments to withhold acute therapies from a given patient with pre-morbid disability/dementia is highly problematic. Firstly, health-economic evaluations of therapies are intended to make decisions at the level of populations, not individual patients. Secondly, we cannot assume that a treatment is not cost-effective in patients with pre-morbid disability/dementia simply because they normally incur higher costs for the given condition. Upon testing the treatment scenario in cost-effectiveness analyses, we may find that these patients incur lower costs when treated. However, just as they are systematically excluded from trials, patients with pre-morbid disability/dementia are generally excluded from models of cost-effectiveness analyses; for example, cost-effectiveness analyses of EVT assumed that patients were disability-free pre-stroke. These models also typically evaluate post-stroke costs in a dichotomous manner, based on whether patients are predicted to be “independent” or “dependent” post-stroke, which again fails to reflect the spectrum of post-stroke disability. Most models also do not account for the potential for late functional improvement beyond 3-months post-stroke, which may further optimize the post-stroke disability of patients with pre-morbid disability/dementia.

In addition, cost-effectiveness analyses are only as good as the data they use. Whether a given therapy is viewed as cost-effective will depend on whether we take a short-term or long-term view of costs, and the types of costs examined. For many conditions, cost-effectiveness analyses only have access to high-quality data for a short period and are forced to extrapolate further data; they also tend to focus on “direct” costs (directly incurred by the healthcare system and/or the individual) and ignore
“indirect” costs (productivity losses borne by the individual, family, or society, e.g. an adult having to stop working to care for a parent due to their additional post-stroke disability). In fact, for ischemic stroke, most costing studies do not even examine the full spectrum of direct costs, focusing on hospital-based costs, and rarely examining costs beyond 1-year post-stroke. Post-stroke costs vary markedly depending on the follow-up duration, with costs related to intervention, acute rehabilitation, and inpatient admission being concentrated in the first 3-months and then plateauing, whereas social-care costs like institutionalization or home-care, social services assistance, and productivity losses become much more prominent over subsequent years. Yet even when long-term cost data are considered, health-economic analyses tend to “discount” future costs, essentially decreasing their value by variable rates. Put simply, this assumes that we would prefer to spend less now, even if it means having to spend more two years later. This methodology is particularly problematic if the costs of further disability diverge over time across different levels of disability. Studies examining longer-term post-stroke costs across the spectrum of the mRS have also found that each additional increment of post-stroke disability worsens 5-year post-stroke costs, even among patients with pre-morbid disability.

Cost-effectiveness analyses evaluate treatment benefit in terms of quality-adjusted life-years (QALYs) gained. Calculating QALYs requires both mortality data as well as health utilities, which assign preference weights to each possible health state. However, using utilities to evaluate an individual patient’s quality-of-life may be inappropriate because utilities are ultimately derived from unaffected individuals who imagine a given health state, and vary by beliefs and sociodemographic factors. This raises the ethically troublesome question of who should be the judge of a meaningful life. These value-based differences can affect how different people interpret the same RCT, as recently seen with the interpretation of a trial of craniectomy for raised intracranial pressure (RESCUE-ICP), which reduced mortality but left many survivors with moderate-to-severe disability. Some contended that keeping patients alive with substantial disability was unethical, questioning whether such lives were “worth living”. However, others questioned the role of physicians in deciding the ultimate value of such lives, or in balancing the associated cost versus benefit for society.

Therefore, how each party involved in a discussion about acute therapies defines quality-of-life will affect how they judge the patient’s present quality-of-life, and in turn affect their preference for or against treatment (Figure 1). The economic biases of physicians and policy-makers – unknowable to patients and carers – also comes into play. If the physician or the system they serve ascribes to a more utilitarian philosophy, they may be more likely to withhold therapies, particularly if they are only thinking about short-term in-hospital costs. However, if the physician stands to benefit from treating the patient – for example, if reimbursed by a fee-for-service model – he/she may be incentivized to
appropriately provide acute therapies. On the other hand, a physician with a capped salary may be disincentivized from treating a potentially challenging patient who may benefit from therapy.¹²⁵

Discussion
In 2012, when Didier Sicard was tasked with advising the President of France on the enactment of end-of-life legislation, his team embarked on a detailed assessment of the views of the public and the care they received, identifying key issues related to the perception, practice, and availability of palliative medicine that needed to be addressed.¹²⁶ In other words, Sicard’s commission concluded that it was not French law or protocols, but the culture, that had to change. In seeking to develop an evidence-based ethical framework for decisions about acute medical therapies in patients with pre-existing disability/dementia, we face a similar disquieting revelation. Even if we adopt the narrowest focus and examine what transpires in the precious minutes preceding a decision about EVT/tPA in acute ischemic stroke, we realize that there are numerous intra-personal, inter-personal, and systemic factors operating beyond any single individual’s control (Figure 1). Our deeper examination of these factors has identified key ethical and scientific challenges to assumptions made about this treatment dilemma, including: flaws in the concept and measurement of pre-morbid disability; a persistent absence of evidence in these patient populations and negation of their autonomy due to ableism; issues stemming from dichotomous concepts of treatment efficacy; and methodological and cognitive biases in health-economics that pervade arguments about cost-effectiveness.

It becomes apparent that no decision-making checklist or protocol can encapsulate these issues, and that it would be unreasonable if not impossible to task a physician with taking all these issues into account in an acute medical scenario. Nevertheless, realizing that there are many “knowable” and “unknowable” factors at play, this can help us be humbler and less prescriptive in our recommendations in such settings. This acknowledgement of uncertainty can be the first building-block of our decision-making framework (Figure 2). Some of the key factors – ableism, cultural or religious values, experience with disability (or lack thereof), biases for/against treatment – also operate within the physician and are therefore amenable to critical introspection, even if they may be “unknowable” to others. The next step in our framework, then, calls for physicians to examine these inner values, beliefs, or biases in their daily life, so that when a time-critical treatment decision inevitably arises, they will be more aware of why they feel pulled towards one direction or the other. This includes confronting their own ableist views and how these may be playing into their evaluation of disability and its implications for care – and, ideally, encouraging their colleagues and trainees to do the same. This concept of appreciating the aspects of our personalities that operate beneath the publicly presented self¹²⁷ has been described by the physician and educator Roger Neighbour (b. 1947) as discovering “the inner physician”.¹²⁸ Physicians should also recognize the opportunity
present in every interaction with the patient and/or their carer before an acute medical crisis to understand some of the “knowable” factors that will later influence their decisions around acute therapy. Such opportunities may be encountered in both specialist (e.g. counselling for carotid endarterectomy) and generalist settings (e.g. renewing prescriptions), and physicians may draw on principles described in the palliative literature for engaging in “serious illness conversations”. Any ethical framework that acknowledges the Foucauldian power differential involved in the care of people with disability should discourage forms of knowledge that generate exclusion, and seek to foster self-realization and emancipation of individuals with disability. Thus, for the clinician-scientist, our framework must expand further, as there is now an opportunity to actively change the paradigm of systematic exclusion of patients with pre-morbid disability/dementia from medical research. Clinician-scientists should encourage recruitment of patients with disability/dementia in trials of acute medical therapies, at the very least in Phase IV RCTs or registries for approved therapies (like tPA/EVT).

Using ordinal rather than dichotomous analyses, with measures permitting assessment of changes in disability (like ∆mRS), we can successfully conduct trials enrolling a mix of patients with different levels of pre-morbid disability. In addition, we should strive to fill the void of “missing voices” in the literature on how patients with pre-morbid disability/dementia cope with the added morbidity of conditions like stroke, how they view their quality-of-life, and how they (or their carers) perceive the uncertain benefits versus risks of acute medical therapies. We also need to develop and validate better approaches to evaluating pre-morbid disability and/or quality-of-life in the first place.

Furthermore, our framework issues a challenge to policy-makers who can change some of the higher-level factors that complicate clinical decision-making about acute medical therapies. In particular, we need to challenge the biomedical model of disability, and incorporate helpful aspects of the social model. Whereas the biomedical model highlights anatomical, physical, and psychological properties as criteria for disability, the social model emphasizes how the individual may or may not be able to function in society. A purely biomedical model can overlook individual experiences or perceptions, and as a crude “yardstick” to classify individuals as disabled versus not, involves an exercise of power by the assessor over the patient. In contrast, a social model of disability may help promote better opportunities for people with disability by characterizing disability as the result of societal inequity or inadequate accommodation, versus a flaw with the individuals themselves. Adopting a social model can allow policy-makers to change the lens that they use to evaluate the cost-effectiveness of medical therapies in those with pre-morbid disability/dementia, switching a “short-term lens” with a focus on direct costs to a “long-term lens” that also examines indirect costs and the potential for adaptation to (or accommodation for) further disability. Such a model would also empower ethics boards to develop strategies to avoid disproportionately excluding the patients for whom we have the scarcest evidence.
Cautioning us about the delusions of omnipotence and omniscience that may easily seep into the medical establishment, Sicard remarks: « *La médecine ne peut pas remplacer Dieu*. » III,67 Indeed, if we physicians insist on imposing our recommendations upon patients with pre-morbid disability/dementia in high-stakes discussions about acute therapies, we are deserving of this chastisement. However, by developing and implementing an evidence-based ethical framework for these challenging scenarios, like that proposed in this paper, we can continue to work towards a more inclusive model of healthcare for our patients.

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REFERENCES

7. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 2005;365:82-93.


Table 1. Categories of the modified Rankin Scale (mRS)\textsuperscript{133}

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<tr>
<th>mRS score/category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>Able to carry out all usual duties and activities, despite symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Unable to carry out all previous activities, but able to look after own affairs without assistance (Slight Disability)</td>
</tr>
<tr>
<td>3</td>
<td>Requiring some help, but able to walk without assistance (Moderate Disability)</td>
</tr>
<tr>
<td>4</td>
<td>Unable to walk without assistance and unable to attend to own bodily needs without assistance (Moderately Severe Disability)</td>
</tr>
<tr>
<td>5</td>
<td>Bedridden, incontinent, and requiring constant nursing care and attention (Severe Disability)</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>
Figure 1. Discussions about acute therapies revolving around the patient and including their carer/proxy and their physician include various known, knowable, and unknowable factors. During the time-pressured discussions involved in decision-making about acute medical therapies in patients with pre-morbid disability/dementia – like whether or not to treat with thrombolysis or endovascular therapy for acute ischemic stroke – certain types of information are expected to be available to help with the decision making, provided by (or obtained from) the physician, the patient, and/or their carer or proxy. These are "known" factors. Crises like acute stroke often prevent patients from engaging in meaningful dialogue, and thus their concerns or wishes may not be directly accessible. There are additional factors about the patient or that influence what the carer/proxy or physician says or what decision they favour, which are “knowable” but require additional investment of time that may not be feasible. There are several other factors operating in the background or that may come into play in the future that will influence what each party views as the correct treatment decision, but they are “unknowable” to some or all involved.
Figure 2. An evidence-based ethical framework for policy-makers, clinical researchers, and clinicians examining the question of providing an acute medical therapy to patients with pre-morbid disability/dementia.