Cost-effectiveness of multimodal CT for evaluating acute stroke

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ABSTRACT

Objective: Multimodal CT, including noncontrast CT (NCCT), CT with contrast, CT angiography (CTA), and perfusion CT (CTP), is increasingly used in acute stroke patients to identify candidates for endovascular therapy. Our goal is to explore the cost-effectiveness of multimodal CT as a diagnostic test.

Methods: A Markov model compared multimodal CT to NCCT in a hypothetical cohort of nonhemorrhagic stroke patients presenting within 3 hours of symptom onset who were potential IV tPA candidates. Patients who failed to improve after IV tPA or in whom IV tPA was contraindicated were candidates for endovascular therapy. Direct costs (2008 USD), outcomes, and probabilities were obtained from the literature.

Results: For the 3-month time horizon, multimodal CT had lower costs (−$1,716), had greater quality-adjusted life-years (QALYs, 0.004), and was the cost-effective choice 100% of the time for a willingness-to-pay of $100,000/QALY (probabilistic sensitivity analysis). The number needed to screen with multimodal CT to avoid 1 diagnostic angiogram was 2. Over a lifetime, multimodal CT had lower costs (−$2,058), had greater QALYs (0.008), and was cost-effective, with a 90.1% likelihood, for a willingness-to-pay of $100,000/QALY.

Conclusions: Multimodal CT appears to be a cost-saving screening tool over the short term. However, additional data regarding clinical outcomes following multimodal CT–guided intra-arterial treatment are needed before the long-term cost-effectiveness can be suitably addressed. This analysis can be incorporated into future discussions of multimodal CT as a diagnostic test for unselected patients, within and beyond the 3-hour IV tPA time window. ***Neurology*® 2010;75:1678–1685**

GLOSSARY

CTA = CT angiography; **CTP** = perfusion CT; **IA** = intra-arterial; **ICER** = incremental cost-effectiveness ratio; **mRS** = modified Rankin Scale; **NCCT** = noncontrast CT; **NE** = northeast; **NW** = northwest; **QALY** = quality-adjusted life-year; **SE** = southeast; **SW** = southwest; **tPA** = tissue plasminogen activator; **WTA** = willingness to accept; **WTP** = willingness to pay.

Recommendations for treatment of acute ischemic stroke emphasize timely IV tissue plasminogen activator (tPA) administration. The minimum requirement is imaging excluding hemorrhage while allowing for other MR or CT-based imaging so long as IV tPA is not delayed.[1] At some institutions, multimodal CT imaging is performed prior to intra-arterial (IA) procedures. CT-based imaging is typically utilized because it requires less time to complete than MR-based imaging, thus minimizing the time to IA procedures in the setting of acute stroke. Multimodal CT imaging including CT with and without contrast, CT angiography (CTA), and perfusion CT (CTP) rapidly identifies the presence or absence of clot suitable for extraction and salvageable ischemic tissue.[2,3]

At centers providing endovascular therapies for stroke, multimodal CT rapidly identifies candidates for these therapies in lieu of conventional angiography. However, multimodal CT is a costly screening tool where a proportion of subjects will be screened without a subsequent change in clinical management. Thus, the objective of this study was to compare cost-

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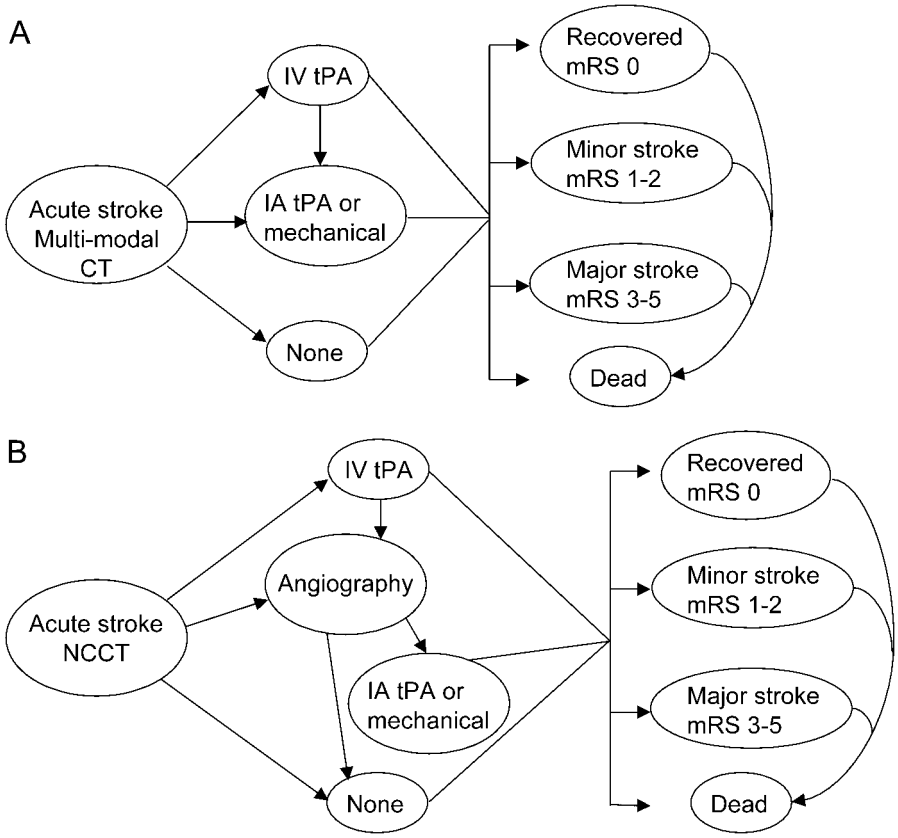
Figure 1 Diagram of the procedures and health states used in the Markov model following an initial imaging strategy of multimodal CT (A) or NCCT (B)



IA = intra-arterial; mRS = modified Rankin Scale; NCCT = noncontrast CT; tPA = tissue plasminogen activator.

effectiveness of 2 strategies in patients who would be considered for IV tPA and subsequently for IA procedures if IV tPA failed or could not be given: 1) noncontrast CT (NCCT) followed by conventional cerebral angiography to screen candidates for IA procedures vs 2) multimodal CT followed by IA procedures in those with identified intraluminal thrombus. IA procedures include any emergent endovascular thrombolysis, thrombectomy, or combination of treatments.

METHODS

Model description. We developed a Markov model to calculate future costs and quality of life over the lifetime of the cohort. Permanent health states, based on the modified Rankin Scale (mRS), were categorized as complete recovery (mRS 0), minor stroke (mRS 1–2), major stroke (mRS 3–5), and death (mRS 6). IA data were primarily grouped as indicated and this stratification simplified analysis.

The hypothetical cohort started either with multimodal CT or with NCCT alone. Subjects in either group who received IV tPA and showed appreciable improvement after 1 hour would not undergo IA procedures.[4] Outcomes for those showing symptom improvement within the first hour were assumed to follow the established outcomes after IV tPA.[5] Patients ineligible for IV tPA or who failed to improve in the first hour after IV tPA could undergo IA procedures if there were no clinical contraindications and intraluminal thrombus was found on multimodal CT scans (multimodal CT branch) or by conventional diagnostic angiography (NCCT branch) (figure 1).[4] The costs, probabilities, and utilities of the model are listed in table 1.

Target population. The target population was a hypothetical cohort of stroke patients presenting within 3 hours of symptom onset who would be considered for IV tPA and for IA procedures, when needed. The 3-hour time window was chosen because meta-analysis data for IV tPA outcomes and trials of IA procedures reflect the 3-hour time IV tPA window.

Perspective and time horizons. The payer perspective (including direct medical costs) was used (2008 USD). No indirect costs were included. Two time horizons were considered. First, a 3-month time horizon was evaluated since outcome data for IV tPA administration and stroke outcomes are well-established at 3 months follow-up. The second time horizon was the lifetime of the cohort; the analysis was continued until the cohort had accumulated in the Markov state for death.

Probability data. Eligibility for IV tPA and IA procedures were taken from a cohort presenting within 3 hours of symptom onset.[6] Six percent of the hypothetical cohort were ineligible for both IV tPA and IA procedures. Almost 80% had no contraindication to either IV tPA or IA procedures. The rest were ineligible for IV tPA but remained eligible for IA procedures. The outcomes after IV tPA and after no intervention were taken from a

Table 1 Detailed input variables for the cost-effectiveness model[a]

Measures	Expected value	Range	Distribution	References
Age, y	71	50–90	Triangular	Author est.
Cost, USD				
Angiogram	3,571	1,786–5,356	Triangular	15
Multimodal CT, incremental	769	385–1,154	Triangular	14
Hospitalization for stroke	8,400	3,600–14,400	Triangular	16
Stroke with IV tPA	17,200	7,200–30,000	Triangular	16
Stroke with IA procedures	33,500	18,500–48,500	Triangular	16
Long-term care				
Minor stroke, per year	7,000	1–15,000	Triangular	17–22
Major stroke, 1st year	59,000	40,000–80,000	Triangular	18, 19, 21, 22
Major stroke, 2+ years	34,267	15,000–55,000	Triangular	18, 19, 21, 22
Probabilities				
Sensitivity of CTA	0.937	0.9–1	Triangular	30
Specificity of CTA	0.963	0.9–1	Triangular	30
Suitable clot	0.086	0–0.2	Triangular	Author est.
Ineligible for IV and IA treatment	0.059	0–1	β	6
Eligible for IV and IA treatment	0.798	0.1–1	β	6
Eligible for IA treatment but not IV tPA[b]	0.143			
Outcomes for no treatment				5
mRS 0–2	0.4065	0–1	β	
mRS 3–5[b]	0.415			
mRS 6	0.176	0–0.85	β	
Outcomes for IV tPA				5
Symptoms improve at 1 hour[c]	0.22	0–0.9	β	4
mRS 0–2	0.4965	0–1	β	
mRS 3–5[b]	0.3265			
mRS 6	0.177	0–0.85	β	
Outcomes for IA procedures				
IA lytic ± IV tPA[d] (no devices)	0.03	0–0.3	β	Author est.
mRS 0–2	0.3818	0–1	β	5, 7
mRS 3–5[b]	0.4605			
mRS 6	0.1577	0–0.8	β	
Mechanical ± IA tPA ± IV tPA	0.97			8
mRS 0–2	0.4193	0–1	β	5, 8
mRS 3–5[b]	0.285			
mRS 6	0.2957	0–1		
Angio complication	0.007	0–0.06	β	12, 13
Utilities				
Recovered (mRS 0)	0.95	0.9–1	Triangular	
Minor stroke (mRS 1–2)	0.71	0.5–1	Triangular	23
Major stroke (mRS 3–5)	0.22	0–0.4	Triangular	23

Abbreviations: CTA = CT angiography; IA = intra-arterial; mRS = modified Rankin Scale; tPA = tissue plasminogen activator.

[a] The expected value is the point estimate used in the base case analysis. The ranges indicate the upper and lower limits tested by the sensitivity analysis. For the probabilistic sensitivity analyses, variables are sampled from the indicated distributions.

[b] These values are not sampled. They are calculated based on the other sampled values. See Methods.

[c] Those with symptom improvement within 1 hour of IV tPA do not go to the angiography suite. Final mRS does not depend on this immediate recovery.

[d] mRS of 0–2 and mRS of 6 were taken from the cited studies. The breakdowns for individual levels of the mRS of 1–5 are based on IV tPA data from a meta-analysis.[5]

Table 2 Base case analysis for the 3-month and lifetime horizon[a]

Measures	Costs, USD	Incremental $	QALYs	Incremental QALYs	ICER, $/QALY
Potential IV tPA candidates					
3 months					
NCCT	21,881		0.167		
Multimodal CT	20,165	−1,716	0.171	0.004	Dominant
Lifetime					
NCCT	225,287		6.663		
Multimodal CT	223,229	−2,058	6.671	0.008	Dominant
Alternative model: NIH Stroke Scale ≥10					
3 months					
NCCT	29,295		0.147		
Multimodal CT	28,810	−485	0.148	0.001	Dominant
Lifetime					
NCCT	228,333		5.762		
Multimodal CT	230,009	1,676	5.756	−0.007	Dominated

Abbreviations: ICER = incremental cost-effectiveness ratio; NCCT = noncontrast CT; QALY = quality-adjusted life-year; tPA = tissue plasminogen activator.
[a] The hypothetical cohort includes any potential IV tPA candidates. An alternative model incorporated a hypothetical cohort with severe stroke, a higher likelihood of thrombus, and poorer outcomes with IV tPA or no treatment.

meta-analysis.[5] This meta-analysis also provided the proportion of subjects in each mRS category.

Outcomes after IA thrombolysis alone were assumed to be the same as outcomes after IV tPA plus IA thrombolysis.[7] Outcome probabilities after mechanical thrombectomy were calculated from Penumbra POST and Multi-MERCI mechanical thrombectomy with IA thrombolysis data.[8,9] Outcomes after mechanical thrombectomy alone were also assumed to be the same as outcomes after mechanical thrombectomy plus IV tPA.

The recent trials involving IA procedures reported outcomes in the following categories: mRS of 0–2 and mRS of 6.[7,8,10,11] The remaining population was assumed to represent the likelihood of a mRS of 3–5. The distribution of mRS scores of 0, 1, and 2, as individual scores, were assumed to be distributed as the IV tPA branch for mRS 0–2 from a meta-analysis.[5] Finally, the prevalence of thrombus was a weighted estimate from the IMS, IMS2, MERCI, and Multi-MERCI trials, where the range of subjects with thrombus divided by the number screened was 2%–16%.[7,8,10,11]

Minor stroke and major stroke due to cerebral angiography were also accounted for as adverse events.[12,13] Half of the complications from angiography were considered minor strokes, the other half were major strokes.[12] Adverse events for contrast reaction, renal failure, and radiation exposure were not included in the model because they would be present in both arms to varying levels.

Sensitivity and specificity of CTA to detect thrombus were included with conventional angiography as the gold standard. A priori, CTP scan data relating to penumbra were not included in the main model. Improvements in functional outcomes due to CTP data were tested in a deterministic (one-way) sensitivity analysis by increasing the relative risk of the probability of a mRS 0–2 after IA procedures.

Cost and utilization data. All costs were adjusted to 2008 USD using the Consumer Price Index for medical care. As our purpose was to explore potential benefits of multimodal CT, only direct medical costs that would differ between multimodal CT and NCCT were included. For example, the cost of a NCCT was not included because it was initially incurred by both branches. The incremental cost of multimodal CT over NCCT and the cost of angiography plus intervention were estimated from the literature.[14,15] Costs for the hospitalization were based on nationwide US estimates of Medicare costs.[16] Long-term care costs were estimated from the literature.[17-22]

Utility data. Health state preferences were obtained from the literature and represented utilities that describe the mRS scores used in our study.[23] Perfect health was anchored at 1 and death was 0. Quality-adjusted life-years (QALYs) were the utility of a health state multiplied by the duration of the health state.

Analysis. For the analysis over the lifetime of the cohort, the Markov cycle length was 3 months. Three months was chosen as it was a common time frame for reporting outcome measures in recent acute stroke trials. Multimodal CT was considered the intervention, because it was the newer technique. NCCT was the comparator. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in costs divided by the difference in QALYs $[(\$_{\text{Multimodal CT}} - \$_{\text{NCCT}})/(\text{QALYs}_{\text{Multimodal CT}} - \text{QALYs}_{\text{NCCT}})]$. Future costs and utilities were discounted at 3%.[24] For the base case analysis, each variable is set to its expected value. Assumptions about each variable were tested individually over prespecified ranges using a deterministic (one-way) sensitivity analysis. Since variables are unlikely to change in isolation, a probabilistic sensitivity analysis simultaneously sampled from distributions of cost, probability, and utility values (n = 1,000 trials).

Cost-effectiveness plane. The costs and health gains of NCCT were placed at the origin of a cost-effectiveness plane. The incremental costs and incremental QALYs for multimodal CT were plotted relative to NCCT. The quadrants (northeast [NE], southeast [SE], northwest [NW], southwest [SW]) were interpreted as follows: (NE) willingness to pay (WTP) more money for better health, (SE) multimodal CT is the dominant, favored, imaging strategy because of increased QALYs at lower costs, (NW) NCCT was dominant because of reduced costs for increased QALYs, and (SW) willingness to accept (WTA) QALY losses for lower costs.[25]

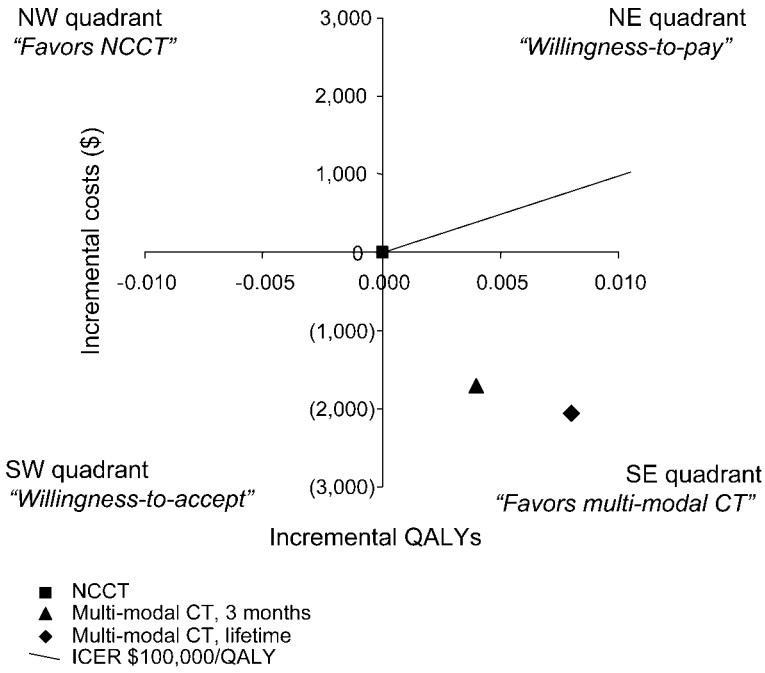
RESULTS

Base case analysis: 3-month time horizon. The model predicted 0.171 QALYs for multimodal CT and 0.167 QALYs for NCCT over a 3-month time horizon. The costs of multimodal CT were $20,165, while the costs of NCCT were $21,881 (table 2). Because multimodal CT had a lower incremental cost (−$1,716) with greater QALYs, it was the dominant imaging strategy (figure 2).

The number needed to screen with multimodal CT to avoid 1 unnecessary diagnostic cerebral angiogram was 2.

Sensitivity analyses: 3-month time horizon. A series of deterministic sensitivity analyses were conducted for each variable. None of the individual assumptions about the variables influenced the cost-effectiveness estimate of multimodal CT. It remained the dominant strategy with lower costs and greater QALYs.

Figure 2 Base case analysis for the 3-month and lifetime horizons



A cost-effectiveness plane is illustrated with quality-adjusted life-years (QALYs) on the x-axis and costs on the y-axis. Incremental costs and QALYS for multimodal CT are graphed with respect to noncontrast CT (NCCT), which is placed at the origin. The cost-effectiveness estimate for multimodal CT is in the southeast (SE) quadrant with lower costs and greater QALYs at 3 months (diamond) and over a lifetime (square). The line representing an incremental cost-effectiveness ratio (ICER) of $100,000/QALY is graphed as a reference. NE = northeast; NW = northwest; SW = southwest.

We tested the assumption that information from CTP scans could select patients who may have more favorable outcomes. Increasing the relative likelihood of mRS of 0–2 caused minimal QALY gains and cost savings over a 3-month time horizon as multimodal CT remained the dominant imaging strategy.

A probabilistic sensitivity analysis, sampling all variables simultaneously, showed which choice, multimodal CT or NCCT, was beneficial at different economic values for 1 year of optimal health ($/QALY, net monetary benefits). Multimodal CT was the cost-effective option with 99.7% probability for a WTP of $0/QALY and with 100% probability for WTP of $100,000/QALY.

Base case analysis: Lifetime. Over the lifetime of the cohort, multimodal CT was associated with 6.671 QALYs at a cost of $223,229. NCCT produced 6.663 QALYs at a cost of $225,287 (table 2). The incremental costs were −$2,058 while the incremental QALYs were 0.008. With a longer time horizon, multimodal CT remained the dominant imaging strategy (figure 2).

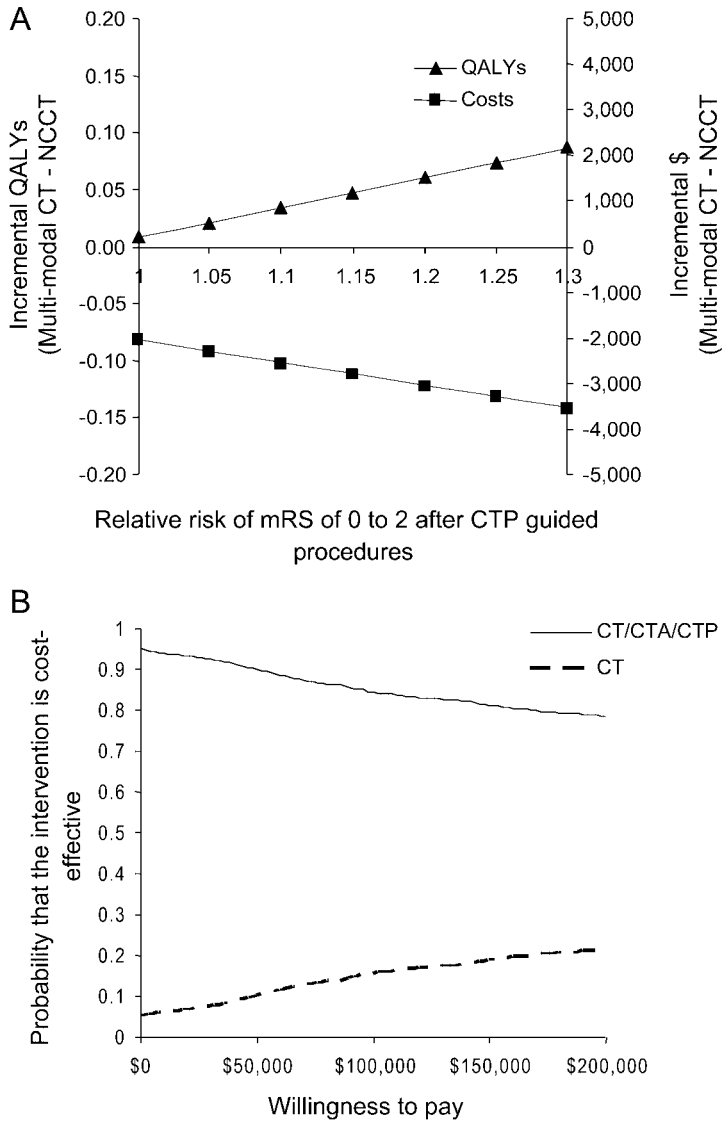
Sensitivity analyses: Lifetime. Each variable was tested over a range of values for the deterministic sensitivity analyses. In contrast to the 3-month time horizon, several variables affected the cost-effectiveness estimate over the lifetime of the cohort. Assuming the sensitivity and specificity of CTA for finding intraluminal thrombus was less than conventional angiography, on average, more patients in the NCCT branch with conventional angiography will undergo IA procedures. Thus, increasing favorable outcomes after IA procedures (≥61% likelihood of a mRS 0–2) led to a net gain in QALYs for NCCT. Costs for multimodal CT remained below the costs of NCCT, thereby shifting the cost-effectiveness estimate into the SW quadrant (figure e-1 on the *Neurology*® Web site at www.neurology.org). Similarly, decreasing the likelihood of mRS 0–2 after IV tPA would lead to fewer QALYs in both branches, though decreasing QALYs in the NCCT branch could be offset by the QALY gain from more IA procedures. When the likelihood of mRS 0–2 after IV tPA was ≤38%, the cost-effectiveness estimate again moved into the SW quadrant (figure e-1). Finally, if the probability of symptom improvement 1 hour after IV tPA was ≥91%, the costs of multimodal CT exceeded the costs of NCCT, moving the point estimate into the NE quadrant (figure e-2).

Assumptions about the quality of life after a stroke influenced the model. When the utility for the recovered state was <0.53, the cost-effectiveness estimate moved into the SW quadrant. However, the ICER for a WTA did not decrease below $3.5 million/QALY. Changing the sensitivity or specificity of CTA did not influence the model. To incorporate the putative benefits of CTP acquired during multimodal imaging in identifying salvageable tissue, a relative risk term increased the likelihood of a mRS of 0–2 following IA procedures. Better outcomes led to additional QALY gains and increased cost savings (figure 3A). Specifically, an increase of 10% in relative risk by incorporating presumed benefits of CTP generated 0.034 incremental QALYs and −$2,562, making multimodal CT an even more favorable choice.

The probabilistic sensitivity analysis showed that for a WTP of $0/QALY multimodal CT was the cost-effective option with 95% probability. For a WTP of $50,000/QALY, multimodal CT was the cost-effective option with 90.1% probability. Finally, for a WTP of $100,000/QALY, multimodal CT was the cost-effective option with 84% probability (figure 3B).

An alternative model: Presenting with a severe stroke. In an alternative model, subjects had NIH Stroke Scale scores ≥10, thus increasing the likelihood of clot (expected value: 78%).[7] The outcomes for IV tPA and no treatment were modified to reflect severe stroke.[7] For the 3-month time horizon, multi-

Figure 3 Sensitivity analyses



(A) A deterministic, 1-way sensitivity analysis varied the likelihood of a modified Rankin Scale (mRS) of 0–2 by using perfusion CT (CTP) data in addition to CT angiography (CTA) detection of clot. Incorporating information about the ischemic penumbra to improve outcomes leads to increased incremental quality-adjusted life-years (QALYs) for multimodal CT and increased cost savings. The time horizon is the life of the cohort. (B) A probabilistic sensitivity analysis sampled model variables simultaneously over the lifetime of the cohort. The probability that multimodal CT is the optimal imaging pathway (solid line) or that noncontrast CT (NCCT) is the optimal pathway (dashed line) varies with the willingness to pay ($/QALY, x-axis). Note that the probability of multimodal CT being the optimal choice never falls below 79% out to $200,000/QALY.

modal CT had reduced costs, −$485, and slightly greater QALYs, 0.001. Over a lifetime, NCCT was the dominant strategy with lower incremental costs, $1,676, and an incremental QALY gain of 0.007. Increasing the likelihood of mRS of 0–2 with CTP data also influenced this cost-effectiveness estimate. An increase of 1% in the probability of favorable outcomes was enough to create an ICER for multimodal CT of $76,005/QALY. Once the likelihood of mRS of 0–2 with CTP data were ≥4.0%, multimodal CT was the dominant strategy (figure e-3).

DISCUSSION With the increasing availability of multimodal CT and IA procedures, we examined the cost-effectiveness of multimodal CT compared to NCCT with the option for conventional angiography. Multimodal CT for subjects presenting with symptoms of an acute stroke severe enough to warrant consideration of IV tPA had lower costs and greater QALYs than NCCT, making multimodal CT cost-saving over the 3-month poststroke phase and over the lifetime of the cohort.

An alternative model evaluated a cohort with more severe symptoms and a higher prevalence of thrombus. In this alternative model, multimodal CT was cost-effective at 3 months, but NCCT became the dominant strategy over the lifetime of the cohort. With the increased prevalence of thrombus, the detection of thrombus by multimodal CT became an extra screening test in those who ultimately needed conventional angiography combined with IA procedures. Outcomes after IA procedures were based on recent studies which did not incorporate CTP-guided treatment, thus our base case analysis did not include the sensitivity and specificity of perfusion maps to identify viable parenchyma. If CTP maps can improve patient selection for IA procedures and subsequent outcomes, multimodal imaging would be more effective.

We tested the ability of perfusion-guided IA procedures to improve outcomes using a relative risk term in a 1-way sensitivity analysis. Assuming that an improvement in the percentage of mRS of 0–2 reflects greater discriminating power of CTP, then only a small change (4%) in favorable outcomes would make multimodal CT dominant for a cohort with a high prevalence of thrombus. Two small cohort studies reported that 16 of 34 patients (47%) and 12 of 27 patients (44%) had favorable outcomes following CTP-guided procedures.[26,27] The probabilities of 44–47% for mRS of 0–2 following CTP-guided procedures compared to 41% from the sample weighted data suggest that a relative improvement of 7%, let alone 4%, is possible.

Our model assumed immediate access to multimodal imaging, that physical capabilities for multimodal CT were already in place, and that no cost was incurred for setup. We excluded sequential NCCT, with or without IV tPA, followed by multimodal CT prior to IA procedures as an alternative imaging strategy. First, it is convenient to proceed with the entire multimodal CT protocol once the person is in the CT scanner rather than arranging a return trip to the CT suite. Second, the angiographic suite can be pre-

pared based on the multimodal CT data while IV tPA is administered. Finally, sequential NCCT with multimodal CT prior to angiography would only reduce costs compared to the multimodal CT branch. QALYs would be equivalent between sequential NCCT and multimodal CT.

Price per QALY boundaries in the NE and SW quadrants may not be the same. That is, the 2008 USD saved for a QALY loss in the SW quadrant may not have the same relative value as 2008 USD spent for QALY gains in the NE quadrant.[25,28] Though we presented a threshold of $100,000/QALY as a point of reference, we also presented data over a wide range of ICERs because there is no accepted US economic value for a QALY.[24] This presentation style also allows for evaluation of other prices for a QALY (e.g., $40,000/QALY), which vary by payer or by country.

A previous study examined the cost-effectiveness of mechanical thrombectomy.[29] Mechanical thrombectomy itself was cost-effective compared to no other IA therapy. Imaging modalities to qualify someone for IA treatment were not clearly outlined nor was a probabilistic sensitivity analysis conducted. Our study differs by also addressing imaging modalities, a necessary component prior to thrombectomy, and by simultaneously sampling multiple variables.

Our model has several limitations. Only 1 acute event was allowed, such that after the initial acute ischemic stroke, no future events, other than death, were allowed. This assumption allowed us to address the cost-effectiveness of multimodal CT as a diagnostic tool for IA procedures in a group of subjects with an immediate life-threatening condition and immediate payoffs. Risks of exacerbating renal disease or a contrast reaction were not included in our model (although both multimodal CT and catheter angiography involve ionizing radiation and contrast administration). The prevalence of clot was a weighted estimate (8.6%) from recent trials (range 1.5%–16.1%).[7,8,10,11] This expected value was reasonable because it did not exceed the clot burden reported in Multi-MERCI and was near the midpoint of the prevalence range. Randomized data were not available for outcomes after IA procedures or for multimodal imaging. Our sample weighted outcome estimates after IA procedures may be subject to unknown confounding factors.

Multimodal CT is a cost-effective screening tool for individuals presenting with an acute stroke who would be considered for IV tPA or IA procedures. This assessment of imaging screening strategies with the potential for acute thrombectomy or thrombolysis suggested that multimodal CT would be the imaging modality of choice 90.1% of the time for a WTP of $100,000/QALY over a lifetime. For a cohort with a high prevalence of clot, improving outcomes following multimodal CT guided IA procedures by 4% (e.g., by incorporating CTP data in patient selection) would enhance the cost-effectiveness of multimodal CT. While the hypothesis of improvements with CTP-guided IA procedures cannot be directly tested yet, increasing evidence points to the utility of CTP in determining salvageable penumbra in stroke patients, and such patients may fare better following revascularization.[2,3,26,27] Future models should incorporate new data with longer follow-up from such cohorts.

AUTHOR CONTRIBUTIONS

Markov analysis was conducted by Dr. Kate Young.

DISCLOSURE

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