On-Line Appendix

Model Structure

A decision tree model, programmed in Excel, similar to that presented in a previous analysis,[1] was developed to examine the cost-effectiveness of the use of CTP over the course of the patient's hospital stay. The decision tree for this analysis is presented in On-line Fig 1. This model considers patients who exhibit stroke symptoms and subsequently seek care through entry to a hospital emergency department. These patients enter the decision tree model at stroke onset after which they proceed to the emergency department. At or on the way to the hospital, a patient history is obtained. Standard acute stroke work-up, which includes an unenhanced CT scan of the head, is administered on arrival at the hospital. CT scans are then interpreted to identify hemorrhage. If hemorrhagic stroke is identified on the CT scan, patients are assumed to be treated according to standard clinical practice for hemorrhagic stroke. If there is no evidence of hemorrhagic stroke and there are no contraindications for IV tPA treatment, patients become candidates for IV tPA. At this time, either patients are treated via the usual care or further assessment via the administration of CTP is performed to assist in determining the appropriate treatment.

Patients in the usual care with no CTP arm are treated with IV tPA as appropriate on the basis of patient history thus far. Patients in the usual care with CTP arm are assessed for tolerance of CTP. Patients who are deemed able to tolerate CTP by the attending clinician receive diagnostic scanning via CTP. Scans are then interpreted for the presence of penumbra (ie, perfusion lesion volume greater than diffusion lesion volume by ≥20%). If scans are not interpretable, the patients are treated with the usual care on the basis of the unenhanced CT and patient history (which may include treatment with IV tPA if the patient is deemed eligible). If scans are interpretable and penumbra is found, patients may be treated with IV tPA up to 6 hours after the onset of stroke. If scans are interpretable and penumbra is not found, patients are treated with other standard treatment.

At the point of treatment (whether it be with IV tPA or other standard treatments), patients are monitored for adverse events and stroke outcome. Specifically, patients receiving CTP are monitored for contrast-induced nephropathy, and patients receiving IV tPA are monitored for secondary hemorrhagic transformation (ie, SICH) while in the hospital.

Input Parameters

Clinical Efficacy. It is routine to assess stroke outcome in both observational studies and clinical trials as an mRS score of 0–6. Even though clinical outcome of the index event on discharge and during the course of a 12-month period after occurrence of the index stroke event may vary, 90-day mRS was selected to represent patient status because it is the most common measurement of functional outcome after treatment of an acute event.

Adverse Events. In ECASS III, patients treated with IV tPA within 3.0–4.5 hours experienced significantly more SICHs (odds ratio, 9.85; 95% CI, 1.26–77.32; P value = .008) than patients treated with placebo.[2] The authors noted that this incidence was similar to the incidence reported in other studies.

Imaging. If penumbra exists in patients, we assumed that one could determine the presence and extent of penumbra in all cases in which MR imaging was the technique of choice. On the basis of a clinical study performed by Darby et al,[3] patterns of penumbra, defined as PWI>DWI by ≥20%, were found in 61.7% of images obtained within 24 hours of the onset of stroke in patients with nonhemorrhagic stroke and with no preexisting nonischemic neurologic deficits or history of prior stroke that would hamper interpretation of clinical and radiologic data.

The probability of interpreting the presence and extent of penumbra was reduced, to account for differences in the sensitivity, specificity, and accuracy of determining the presence and extent of penumbra via CTP versus MR imaging. Specifically, Wintermark et al[4] reported that CTP is 92.7% accurate in predicting core and 96.2% accurate in predicting penumbra compared with MR imaging perfusion and diffusion as the criterion standard. Thus, the model estimates that CTP is 89.2% (92.7% × 96.2%) accurate in imaging the presence and extent of core and penumbra.

Additional assumptions around imaging performed via CT and CTP have been made within this analysis. Specifically, we assume that all patients undergo unenhanced CT first to rule out any hemorrhagic stroke, even those who later undergo CTP. In addition, we assume that an unenhanced CT scan cannot depict disturbances in blood flow.

Timing Data. The total time from onset of stroke to acute stroke treatment was estimated by summing average times from stroke onset to arrival in the emergency department, time from arrival in emergency department to determination of acute stroke treatment, and additional time due to administration and interpretation of CTP as reported in the published literature. Specifically, the time from symptom onset to arrival in the emergency department of 324.0 minutes (range, 290.7–357.3 minutes) was obtained from a large multicenter study designed to investigate the patient delays in seeking care after stroke.[5] The time from arrival in the emergency department to acute stroke treatment of 97.0 minutes (range, 85.7–108.3 minutes) was obtained from Smith et al.[6] On the basis of clinical opinion, administration and interpretation of CTP are assumed to add 15 minutes (range, 5.0–25.0 minutes) to the total time to treatment given the other activities that need to occur and can be done in parallel while the CTP results are being generated (ie, time from onset of stroke symptoms to acute stroke treatment) (personal communication with L.H. Schwamm, MD; September 16, 2009). Given these data, an overall mean and SD around the timing above were estimated. These data were used to estimate the shape and scale of parameters of the γ distribution, which in turn were used to estimate the percentage of patients eligible for treatment within each of the treatment time windows.

Cost. Costs in the model are those that would be incurred by a hospital. Specifically, the cost for the index stroke hospitalization was obtained from an analysis of the Healthcare Utilization Project.[7] ICD-9 codes for ischemic stroke (433.xx and 434.xx) resulted in 554,327 discharges in 2006, whereas ICD-9 codes for hemorrhagic stroke (431.xx) resulted in 65,285 discharges in the same year. The mean cost for ischemic stroke was $9,446, and the mean length of stay was estimated at 4.8 days. The mean cost for hemorrhagic stroke was $16,722, and

the mean length of stay was estimated at 8.1 days. These costs include all those incurred while the patient was in the hospital, such as general ward, intensive care unit, procedures, laboratory services, imaging services (assumed to be a standard CT scan), and other standard hospital expenses.

Cost of the index hospitalization was adjusted for the adverse events of SICH and contrast-induced nephropathy. The additional cost due to SICH was estimated using an approach similar to that taken by Fagan et al.[8] Specifically, the cost per hospital day for patients with ICH was estimated from the Healthcare Cost and Utilization Project.[7] This cost was then multiplied by the additional length of stay in the hospital incurred by patients with ICH to estimate an additional hospitalization cost for symptomatic ICH of $6,811 (=[$16,722 / 8.1 days] × [8.2 − 4.8 days]) expected for patients with ischemic stroke.

The expected cost of contrast-induced nephropathy was estimated and added to that of those who received CTP. Contrast-induced nephropathy was estimated to occur in 0.5% of patients receiving contrast medium.[9] These patients were assumed to increase their length of stay in the hospital by 5.2 days (=10 days for patients with contrast-induced nephropathy[10] − 4.8 days for ischemic stroke) at a cost of $1988 per day.[7] In addition, 6 of 7 patients with acute renal failure are assumed to need 5 days of dialysis[10,11] at a 1992 cost of $250 per dialysis treatment.[12] As a result, the additional cost of contrast-induced nephropathy was estimated at $11,409 (= $1,988 × 5.2 days + [7,8] × $250 × 5 days).

The base-case analysis considers the cost of the hospitalization for only the index event. However, patients surviving the index event are at higher risk for recurrent stroke (especially if the index event was their first one).[13] In scenario analyses in which the time horizon of the model analysis is extended beyond the initial hospitalization, we account for the potential cost of recurrent stroke hospitalizations. Fagan et al[8] reported a 5.2% annual probability of recurrence following an ischemic stroke. Hill et al[14] reported a 1-year probability of ischemic and hemorrhagic stroke following primary hemorrhagic stroke of 3% and 2.4%, respectively. We assume that patients having a recurrent stroke will incur the cost of the primary hospitalization as noted above.

Because the inpatient costs are estimated from hospital discharge data from 2006 and earlier, it was assumed that these costs did not include those associated with the administration and interpretation of CTP to select patients for IV tPA treatment. The cost of the administration and interpretation of CTP was obtained using the current procedural terminology (CPT) code 70460 (CT, head or brain with contrast material). The administration and interpretation cost of CTP was estimated at $296 from the Medicare reimbursement schedules, which consider physician work, practice expense, and malpractice,[15,16] and the cost of 100 mL of contrast medium[2] was $115 (Red Book NDC: 00407-2223-02) for a total cost of $411.[17] Because CT tends to be readily available in hospitals, we assumed that CTP capability would exist for all patients and that it could be performed 24 hours, 7 days a week, at no additional cost to the facility. As a result, the costs of additional staff to administer CTP to provide uninterrupted coverage were not added to this analysis. As a result, the additional cost of contract-induced nephropathy was estimated at $707 (= $296 + $411).

IV tPA drug costs were estimated from the wholesale acquisition price,[17] using a dose of 0.9 mg/kg.[18] Average patient weight was assumed to be 70 kg; therefore, a 100-mg vial was used for each dose.[17] As a result, the cost of IV tPA per administration was estimated at $3442. Costs of administration and physician time for monitoring administration were obtained from the Medicare reimbursement schedule.[16] Administration cost was based on the CPT code 37195 at $294,[15,16] and monitoring cost was estimated at $610 based on CPT codes 99291 and 99292 and an average monitoring time of 2.6 hours as obtained from Kleindorfer et al.[15,16,19] As a result, the cost per administration of IV tPA was estimated at $5,322 (= $3,442 + $294 + $610 × 2.6 hours).

Utility Weights. Utility weights allow an objective measurement of the desirability of a health state in a cost-utility analysis. A utility of 1.0 represents perfect health, whereas a value of 0.0 represents death. When combined with life-years, utilities produce QALYs.

Due to the uncertainty around the base values, sensitivity analysis was performed around a broad range of values derived from several published studies.[20-22]

Model Calculations. The incremental cost-effectiveness ratio (ICER) was used to compare the cost-effectiveness of treatment regimens and was calculated as follows:

$$\text{ICER} = (C_1 - C_2) \div (E_1 - E_2),$$

where C_1 is the total cost incurred by patients in the usual care plus CTP arm, C_2 is the total cost incurred by patients in the usual care, E_1 is the total measure of effectiveness (eg, QALY) accrued by patients in the usual care plus CTP, and E_2 is the total measure of effectiveness accrued by patients in the usual care. The incremental cost per QALY in this analysis is compared with the commonly accepted threshold of $50,000 in the United States even though recent studies support the use of a higher cost-effectiveness threshold.[23]

Sensitivity Analysis. To test the robustness of the assumptions and specific parameters of the model, we examined the effect of changing several parameters in 1-way, scenario, and probabilistic analyses. Parameters analyzed included the distribution of patients by functional outcome for patients receiving no CTP and treated with IV tPA and other standard treatments within 4.5 and after 4.5 hours, odds of favorable outcome for patients receiving CTP imaging and IV tPA≤3.0 hours, odds of favorable outcome for patients receiving CTP imaging and IV tPA>3.0 hours, incidence of SICH, incidence of and mortality due to SICH, incidence of contrast-induced nephropathy, incidence of ischemic stroke, incidence of IV tPA contraindications, presence of penumbra, incidence of recurrent stroke, timing (ie, from stroke onset to emergency department, from emergency department to CTP, and CTP to treatment), costs, utilities, and mortality.

Scenario analyses include examining the impact of changes in several parameters. The first scenario is examining the impact of allowing treatment with IV tPA in patients in whom penumbra is not examined within the current allowable indication (ie, treatment with IV tPA within 3 hours of stroke onset) rather than within the expanded time window of 4.5 hours. Other scenario analyses include changes in discount

rates, availability of CTP, cost of enabling CTP to be available, and time horizons of 1 and 5 years to account for impact of recurrent stroke.

In addition to 1-way and scenario analyses, we also performed a probabilistic sensitivity analysis (second-order Monte Carlo simulation) in which all parameters were varied simultaneously.[24] The parameters that we varied in these analyses included the distribution of patients by functional outcome for patients receiving no CTP and treated with IV tPA and other standard treatments within 4.5 and after 4.5 hours, which was assumed to follow a Dirichlet distribution. The odds of favorable outcome for patients receiving CTP and IV tPA, timing data, and costs were assumed to follow a γ distribution, where the shape and scale of parameters were estimated via means and SDs based on the defined 95% CIs. Incidence of SICH, incidence of and mortality due to SICH, incidence of contrast-induced nephropathy, incidence of ischemic stroke, incidence of IV tPA contraindications, presence of penumbra, incidence of recurrent stroke, and utilities were all varied assuming a β distribution. The α parameters for each β distribution were approximated by the number of cases and the population complement.

Results

When extending the time horizon of the analysis from 90 days to 1 and 5 years, we would observe greater benefit because the true benefit of CTP selection and IV tPA to patients extends beyond the time horizon of the index hospitalization. At the 1-year time horizon, we would observe penumbra-based selection with CTP to produce a greater difference in life-years (0.6816 versus 0.6804) and QALYs (0.4054 versus 0.4039). Costs for patients receiving CTP were lower than those for the usual care ($12,813 versus $12,897). At the 5-year time horizon, we would observe CTP producing a greater difference in life-years (2.8661 versus 2.8603) and QALYs (1.7251 versus 1.7184). Costs for patients receiving CTP were lower than those for the usual care ($14,298 versus $14,379). Thus, CTP remains a cost-saving strategy at both the 1- and 5-year time horizon.

In a secondary analysis, when we compared CTP selection with the usual care, in which IV tPA is administered only within the indicated 3 hours, hospitals may still expect to treat fewer patients with IV tPA. Specifically, 21.7% of patients with ischemic stroke receive IV tPA within 0–3 hours using standard criteria versus 20.9% of patients selected via CTP. Although patients would be treated, CTP improves the percentage of patients achieving a favorable outcome by 0.62%. Life-years and QALYs are improved by 0.0005 and 0.0015 years respectively. Costs are slightly higher for CTP-selected patients by $159 because fewer patients in the usual care arm receive IV tPA and the cost of the CTP is not offset as much. As a result, the addition of CTP in the 0- to 3-hour timeframe results in similar costs and outcomes compared with the usual care.

Discussion

From the available literature, we assumed CTP accuracy to be 89.2%; however, this information is limited, so we tested a wide range of CTP accuracy in sensitivity analysis and found that even at an accuracy of only 80%, penumbra-based CTP is still cost-saving.

The ability to tolerate CTP was assumed to the 100%. Thus, we observed that CTP is cost-effective for patients eligible for CTP. However, in clinical practice, a number of patients will have contraindications for CTP. Overall when examining the impact of these parameters in sensitivity analysis, we observed that the impact was small. Overall, it will be important to perform further research to more accurately estimate these parameters so that we may refine this research in the future.

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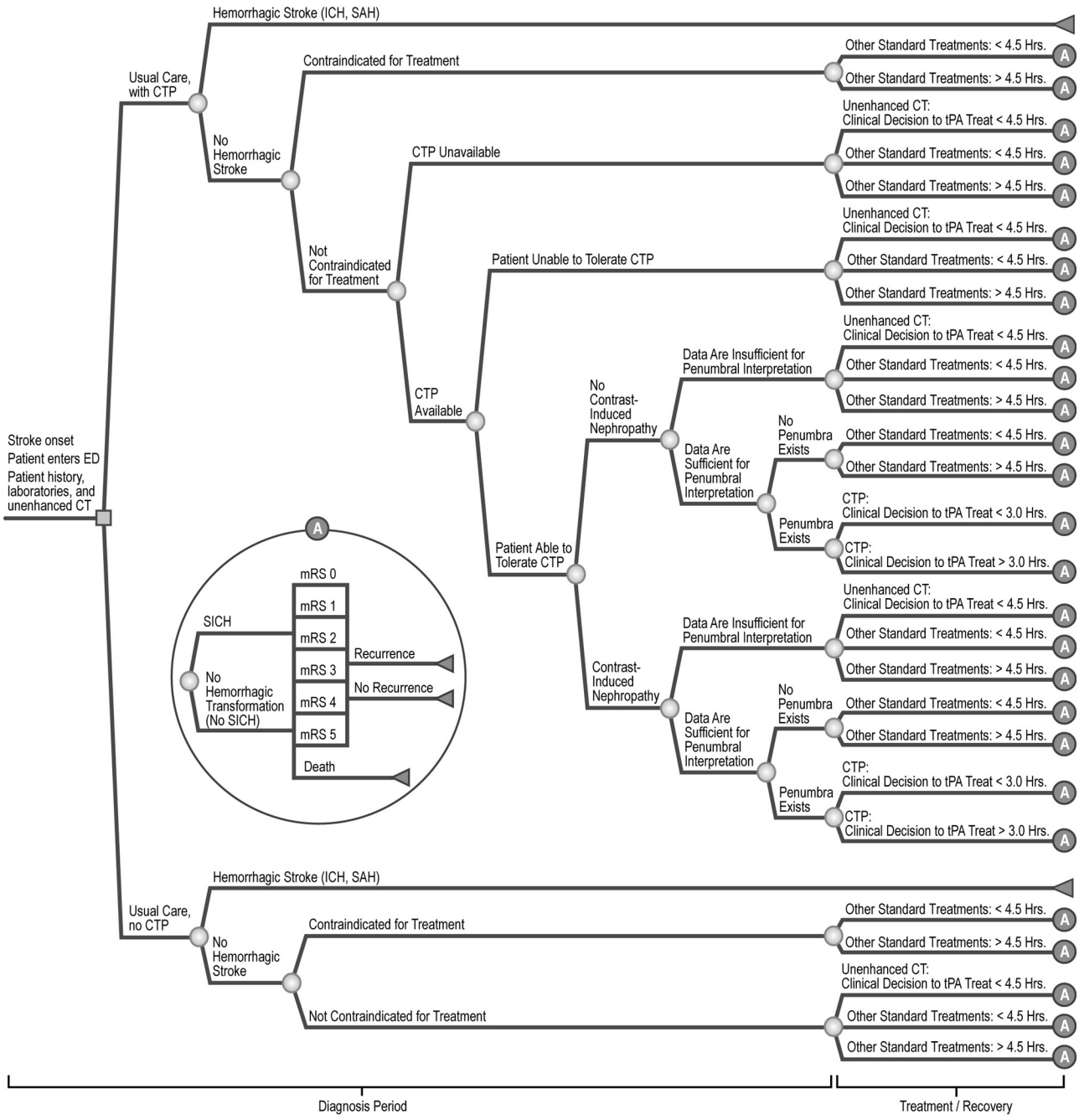

On-line Fig 1. Model structure.

On-line Table 1: Distribution of 90-day mRS and incidence of contrast-induced nephropathy and SICH when treating with IV tPA and other standard treatments within each time window

Model Parameter	Other Standard Treatments ≤4.5 Hours	Other Standard Treatments >4.5 Hours	CT IV tPA ≤4.5 Hours	CTP IV tPA ≤ 3.0 Hours	CTP IV tPA >3.0 Hours
Efficacy (90-day disease severity by mRS score)					
mRS 0	17.5%	14.8%	24.1%	23.8%	29.1%
mRS 1	19.1%	21.1%	25.0%	28.6%	34.9%
mRS 2	13.5%	13.0%	11.1%	7.4%	5.1%
mRS 3	13.5%	14.0%	12.3%	13.8%	9.5%
mRS 4	17.1%	19.1%	11.0%	11.4%	7.9%
mRS 5	6.3%	8.1%	7.8%	6.8%	4.7%
mRS 6	13.0%	10.0%	8.7%	8.3%	8.8%
Incidence of contrast-induced nephropathy (plausible range)	0.0%	0.0%	0.0%	0.5% (0.0–2.0%)	0.5% (0.0–2.0%)
Mortality due to symptomatic ICH	46.7% (40.3–53.1%)	46.7% (40.3–53.1%)	62.2% (61.1–63.4%)	62.2% (61.1–63.4%)	62.2% (61.1–63.4%)
Treatment windows					
		<1.5 Hours	1.5–3 Hours	3–4.5 Hours	4.5–6 Hours
Placebo		0.0% (95% CI, not applicable)	1.0% (95% CI, 0.4–2.0%)	1.7% (95% CI, 1.0–2.9%)	1.0% (95% CI, 0.5–1.8%)
IV tPA		3.1% (95% CI, 1.6–5.6%)	5.6% (95% CI, 3.9–7.9%)	5.9% (95% CI, 4.3–8.0%)	6.9% (95% CI, 5.3- 87%)

On-line Table 2: Base-case values and ranges of plausible values

Model Parameter	Base-Case Value	Plausible Range	Source
% of stroke that is ischemic	87.0%	±20%	Lloyd-Jones et al[20]
% of ischemic stroke within 3 hours with IV tPA contraindications	43.2%	42.20–44.19%	Katzan et al[10]
Death hazard ratios			Samsa et al[19]
mRS 0	1	1.0–1.2	
mRS 1	1	1.0–1.2	
mRS 2	1.11	1.0–1.2	
mRS 3	1.27	1.2–1.4	
mRS 4	1.71	1.3–2.0	
mRS 5	2.37	1.5–4.0	
ICH remaining life expectancy (in years)	6.12	±20%	Earnshaw et al[17]
ICH remaining QALYs (in years)	2.80	±20%	Earnshaw et al[17]
Costs			
Inpatient, ischemic stroke	$9,446	±20%	Nationwide Inpatient Sample[21]
Inpatient, hemorrhagic stroke	$16,722	±20%	Nationwide Inpatient Sample[21]
Additional inpatient cost due to SICH	$6,811	±20%	Nationwide Inpatient Sample[21], Fagan et al[22]
Contrast-induced nephropathy	$11,409	±20%	Nationwide Inpatient Sample[21], Aspelin et al[23], Gleeson and Bulugahapitiya[24], Shield et al[25]
Inpatient-recurrent stroke	$9,446	±20%	Nationwide Inpatient Sample[21]
CTP (per scan)	$707	±20%	Beebe et al[26], Ingenix[27], Red Book For Windows[28]
IV tPA (per administration)	$5,322	±20%	Beebe et al[26], Ingenix[27], Red Book for Windows[28]
Utility values and range[a,b]			Earnshaw et al[7], Samsa et al[19]
mRS 0	0.80	0.80–1.00	
mRS 1	0.80	0.80–0.95	
mRS 2	0.65	0.68–0.90	
mRS 3	0.50	0.45–0.65	
mRS 4	0.35	0.10–0.40	
mRS 5	0.20	0.00–0.32	
mRS 6	0.00	0.00–0.00	

[a] Baseline utility values were obtained from Samsa et al.[19]
[b] Plausible range is based on upper and lower bounds on mRS-specific utility values found in the published literature.[7]