Cost effectiveness of patient selection based on advanced imaging for patient with acute ischemic stroke.

By

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Abstract

Background

Since 1996, the treatment of acute ischemic stroke with Alteplase (rt-PA) has been based on time after an acute ischemic event. In 2015, thrombectomy procedures were re-introduced to treat strokes with time remaining the principal factor in the decision to treat. More recently, studies have increased the time of treatment with the assistance of advanced imaging, but time continues to be the most important aspect of the determination to treat. As advanced imaging provides significant data on the patient's current condition, this research was designed to evaluate the cost effectiveness of treating acute ischemic stroke relying on advanced imaging as the primary determinant of patient treatment in comparison to the standard of care designated by the American Heart Association (AHA)/American Stroke Association (ASA) which relies primarily on time.

Methods

A decision tree model was built using TreeAge Pro (TreeAge Pro software (Version: 2017; Build-Id: 17.1.1.0-v20170211)) to evaluate the cost effectiveness of treating acute ischemic stroke. The standard of care for acute ischemic stroke is based on the AHA/ASA guidelines and an algorithm that was developed using advanced imaging to determine treatment instead of time was compared. The data were taken from previous studies associated with the treatment of acute ischemic stroke for outcomes and utilities and from the Centers for Medicare and Medicaid Services for the treatment cost of acute

ischemic stroke. After the completion of the base case scenario, a Probability Sensitivity Analysis with Triangular distribution was performed**.**

Results

Although the incremental cost per patient utilizing the scenario of advanced imaging (CT/CTA/CTP) is $17,049.00 more than utilizing the scenario of time (CT), the increase in effectiveness is 0.58 Life Years, the incremental cost-effectiveness ratio (ICER) of $29,149.00, the Net Monetary Benefit (NMB) of $277,873.00, and the cost per unit effectiveness (C/E) of $5,946.00 favoring the scenario of advanced imaging (CT/CTA/CTP) over the scenario of time (CT), making the scenario of advanced imaging (CT/CTA/CTP) more cost-effective than the scenario of time (CT). The probability sensitivity analysis with 10,000 iterations and a Willingness-to-Pay threshold of $50,000.00 was performed reporting an incremental cost-effectiveness ratio (ICER) proportion of 73.48% in favor of the reference or base case which favored the scenario of advanced imaging (CT/CTA/CTP).

Conclusion

It is cost effective to select patients for stroke intervention based on advanced imaging versus time.

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DEDICATION

This dissertation is dedicated to my family. My wife Marie Barone and my two children Nicolas and Vincent who are my life, love, and inspiration. My parents Mario and Christiana Barone for all their love and support throughout my life. My brother and sister Mario III and Kris Ann for always being there for me.

This dissertation is also dedicated to the many individuals that have molded me in to the professional that I am today, they include (in order as they appeared in my life) Gregor Byer; Susan Stupenski; James "Jeep" Sabo EdD, AT-C; Wayne England PhD; Janet Lozar PhD, AT-C; Scott Urquhart PA-C; Peter Carmel MD, Dsc; Michael Schulder MD; Alan Maniker MD; Robert Heary MD; C. David Hunt MD; Theodore Schwartz MD, Michael Nosko MD, PhD; Richard Lehman MD; Sun Ho Lee MD, PhD; Scott Shepard MD; Rachana Tyagi MD; Shabbar Danish MD; Ronald Benitez MD; Jack Knightly MD; David Wells-Roth MD; Kyle Chapple MD; Paul Saphier MD; and Pinakin Jethwa MD. A special thanks to Michael Nosko MD, PhD and Pinakin Jethwa MD, for all their teaching, mentoring, guidance, and friendship over the years.

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CHAPTER I

INTRODUCTION

In the literature review, treatment for acute ischemic stroke was reviewed. Current standards of care for treating acute ischemic stroke are based on the time from the onset of symptoms. This research is designed to evaluate the treatment of acute ischemic stroke as it is currently performed and determine if clinicians can provide cost-effective stroke treatment relying on advanced imaging based on pooled data for the use of rt-PA and the use of mechanical thrombectomy. To determine if clinicians are currently providing cost-effective acute ischemic stroke treatment and if improvements could be made utilizing advanced imaging, a decision-making model will be developed for the intervals associated with the treatment of acute ischemic stroke on time versus advanced imaging. Along with the decision-making model, data will be extracted from multiple studies to provide cost, utility, and clinical outcomes at each step of the decision-making process.

1.1 Research Objectives:

a. Determine if it is cost-effective to treat a patient with an acute ischemic stroke based on advanced imaging and not on the time the symptoms first appeared

b. Determine if a patient with an acute ischemic stroke will have an increase in quality-adjusted life years (QALY) if treated based on advanced imaging instead of the time the symptoms appeared.

1.2 Statement of Problem

Acute ischemic stroke is one of the United States' leading causes of morbidity and mortality. [1] There are multiple risk factors associated with the cause of acute ischemic stroke, with hypertension being the leading and most controllable risk factor. Acute ischemic stroke treatment is a relatively recent phenomenon, with Alteplase currently proving to be superior to other thrombolytic therapy medications. [2] The hallmark study investigating the treatment of acute ischemic stroke with Alteplase was the 1995 NINDS trial, Tissue Plasminogen Activator for Acute Ischemic Stroke trial. [3] There were multiple studies following the NINDS trial to support the use of Alteplase for acute ischemic stroke occurring within 3 hours of symptom onset, including ATLANTIS A, B, ECASS I, II, III, and EPITHET. [4-9] The ECASS III trial showed efficacy and safety with increasing the timing of treatment from 3 to 4.5 hours after the onset of symptoms in a selected acute ischemic stroke population. [8] Prior to 2015, the utilization of mechanical thrombolytic therapy was not proven to be beneficial. [10-12] In 2015, after the development of newer generation devices utilized to extract the thrombus from the vessel during an acute ischemic stroke, the MR CLEAN trial yielded superior results of treating acute ischemic stroke with Alteplase and the mechanical thrombectomy devices compared to Alteplase alone, especially in first order, large vessels of the anterior circulation. [13] Multiple subsequent studies supported the MR CLEAN trial, including the ESCAPE, REVASCAT, EXTEND-IA, THERAPY, and SWIFT PRIME. [14-17] Since the prominent trials for acute ischemic

stroke care were published, algorithms of acute ischemic stroke treatment have been developed. These algorithms are all based on the time from the onset of acute ischemic stroke symptoms and do not utilize the inherently valuable information available from current brain imaging modalities as the primary decision tool to treat patients. With the availability of advanced imaging modalities visualizing cerebral vasculature and acute ischemic stroke damage such as CTA and CTP, would not the use of this valuable information in the clinical decision-making process allow clinicians to provide better, more cost-effective care for patients instead of time as the determining factor?

1.3 Significance of Research

This research seeks to determine if it is more cost-effective to treat acute ischemic stroke using advance imaging versus treatment based on the time of onset of symptoms, the current standard of care. The research can benefit the acute ischemic stroke patient by increasing the efficiency of treating the patients based on their physiology using advance imaging instead of depending on the time since their symptoms first appeared. The use of advanced imaging will increase the number of patients that can be treated for acute ischemic stroke because they will not be confined to treatment based on time. This will also enhance the patient's functional status, leaving them with less disability and a longer life. Currently, the treatment of acute ischemic stroke is based on time and if a patient does not fall within the treatment window, medications or surgical interventions are not performed to reduce the functional burden of the acute ischemic stroke. More recent research is guiding the treatment of acute ischemic stroke to use advanced imaging instead of time of symptom onset to care for the stroke patient. The changing landscape of the treatment of acute ischemic stroke is at the forefront of medicine; this research will support

the theory of treating acute ischemic stroke based on advanced imaging from a cost-effective perspective.

This research is significant to the field of biomedical informatics because it uses a clinical decision-making model to determine the most cost-effective strategy for treating stroke. It employs a meta-analysis approach with a decision tree analysis to aid in clinical decision-making for improving patient care and outcomes. This research relies on previous and currently published information to conduct the decision tree analysis.

1.4 Hypothesis

(1) H1 It is cost effective to select patients for stroke intervention based on advanced imaging versus time.

H0: It is not cost effective to select patients for stroke intervention based on advanced imaging versus time.

(2) H1: There is improvement in patient outcomes with the treatment decision of stroke using advanced imaging versus time-based treatment.

H0: There is no improvement in patient outcomes with the treatment decision of stroke with advanced imaging versus time-based treatment.

CHAPTER II

LITERATURE REVIEW

2.1 Introduction

The following is a literature review discussing cost-effectiveness analysis, incidence and prevalence of stroke, the cerebrovascular anatomy, the natural history and pathophysiology of acute ischemic stroke, a detailed review of the major studies of acute ischemic stroke treatment since the mid 1990's, and the current algorithm used to treat acute ischemic stroke.

2.2 Cost-effectiveness Analysis

A cost-effectiveness analysis a type of decision analysis that is a systemic approach to support decision making with conditions of uncertainty. It is a mathematic tool to provide providers and policy makers with a useful approach to complex decision making. It is a, "..quantitative techniques that provide a systematic approach to integrating evidence within the context of a specific decision problem." [18] A decision tree is a diagrammatic representation of performing decision analysis. The decision tree has, "A *decision node*, typically represented by a square, is a point where several alternatives are possible. A *chance node,* typically represented by a circle, is point in a decision tree where chances determines which event will occur. The sum of probabilities for all branches emanating from a chance node must equal 1.0, because one of the events must occur.

The value of each decision alternative is obtained by multiplying the value or each outcome by its respective probability. These results can be added at the previous chance node on a decision tree, also known as, "folding back the tree.". [18] Multiple types of outcomes can be used in decision analysis, in this decision analysis of cost-effectiveness, quality adjusted life years (QALYs) was used. The QALYs require a value or utility represent the level desired for each outcome, in this case the modified Rankin scale score is used, 0 is for perfect health and 6 for death. "The quality-adjusted life year (QALY) was developed in an effort to combine the attributes of length and quality of life into a single numeric measure. The U.S. Panel on Cost-Effectiveness in Health and Medicine recommended QALYs as the most desirable effectiveness measure for economic analysis of health interventions [19]. Health outcomes or "states" are assigned a value on a scale anchored at zero, representing worst imaginable health or death, and one, representing best imaginable health or perfect health. The length of time in each health state is weighted according to its "health state value." By definition, one year of perfect health is worth one QALY and one year of less than perfect health is worth less than 1 QALY. [20]". [18] A limitation of cost-effectiveness analysis it that it can over-simplify a complex decision process. It also requires accurate and valid data on the likelihood of outcomes.

Sensitivity analysis is part of a cost-effectiveness analysis. A benefit of a formal cost-effectiveness decision analysis is the ability to vary the model probabilities and values within the tree to assess how sensitive the decision alternative is, in this case advanced imaging is the decision alternative. "A sensitivity analysis is performed by varying model parameters to determine which assumptions in the model are fundamental and how changing utilities or probabilities will affect the decision." [18]

Cost-effectiveness analysis is used to assess the expected cost of a decision alternative. It is to evaluate cost associated with health care considering resources are increasingly becoming scarce and policy makers must decide between health outcomes and costs associated with health care. The obvious goal for health care providers and policy makers is to balance a budget while trying to attain maximal health benefits. Cost-effectiveness analysis is a comparison of two or more care alternatives in which one is costlier but offers improved health outcomes and determines if this alternative is worth the added costs. Within the cost-effectiveness analysis the incremental cost-effectiveness ratio (ICER) will be measured. The incremental cost-effectiveness ratio is a primary outcome measure of a cost-effectiveness analysis and is the ratio of the incremental cost of an intervention to the change in the health outcome of an intervention compared to the accepted or defined alternative. The numerator of the incremental cost-effectiveness ratio is the cost in the chosen denomination such as US dollars and the denominator is in the health improvement related to the intervention in an outcome measure such as QALYs. When interpreting the incremental cost-effectiveness ratio, if the new intervention is more effective and less expected than it is considered, “dominant”, making the choice clear the new intervention is the best choice compared to the accepted or defined alternative. If the new intervention is less effective and more expensive the choice is again clear the accepted or defined alternative is the best choice compared to the new intervention. But if the new intervention is more effective but also more expensive or conversely less effective but less expensive the incremental cost-effectiveness ratio quantifies the difference between the added cost and the QALY gained. If the intervention, new or the accepted or defined alternative incremental ratio is less than a defined cost per QALY gained, $50,000.00 is a

common dollar amount used and will be discussed later, than it is usually considered, "cost-effective". To determine the cost per QALY gained, the incremental cost of the intervention, $$$, divided by the incremental effectiveness, QALY.

Cost per QALY gained= $$$/QALY. [18]

2.3 Incidence of Stroke

Acute ischemic stroke is one of the United States' leading causes of death. It is the fifth leading cause of death with one in every twenty deaths being caused by stroke. [1,21] Eighty-five percent of strokes are acute ischemic stokes, the remaining 15% are hemorrhagic or subarachnoid hemorrhages. [1,21] Approximately 795,000 people per year have a stroke of which 75% are new strokes and 25% are recurrent. [1,21] Approximately, every forty seconds a stroke occurs in the Unites States. [1,21] According to the Framingham Heart Study [22], the incidence of first-time stroke has declined since the 1950's. In the data of three periods, 1950–1977, 1978–1989, and 1990–2004, the age-adjusted incidence of first-time stroke per 1000 person-years was 7.6, 6.2, and 5.3 respectively in men and 6.2, 5.8, and 5.1 respectively in women. Carandang et al. [23] also reported that the lifetime risk for the incidence of stroke at age 65 decreased from 19.5% to 14.5% in men and 18% to 16.1% in women when comparing the 1950's period to the 1990's period. Similar findings were reported by Fang et al. [24] who utilized data from hospitalized Medicare beneficiaries, sampling 20% of this population, and reported that the rate of first stroke in patients older than 65 decreased by approximately 40% since 1998 with acute ischemic strokes showing the most significant decline of all stroke types. It was noted during the study, that patients during the time period of 1992–2008, the use of statin medications in the general

population increased from 4% to 41% and that of anti-hypertensive medication increased from 53% to 74%.

Ethnic disparities in stroke incidence continue to exist. The African-American population is impacted more by stroke than any other racial group in the United States.[1] The age-adjusted incidence of first acute ischemic stroke per 1000 of the population was 0.88, 1.49, and 1.91 in whites, Hispanics, and African-Americans respectively from 1993–1997 as reported in the Northern Manhattan Study of The National Institute of Neurological Disorders and Stroke. [25] In this study, they compared whites to blacks as well as to Hispanics (primarily Cuban and Puerto Rican), and it was shown in the BASIC Project from 2000 through 2010 [26] that ethnic disparities in stroke rates persisted in all age groups. They reported a decline in acute ischemic stroke rates in patients equal to or greater than age 60 and no significant change in patients in the age range of 45 to 59 years old. The National Institutes of Neurological Disorders and Stroke's BASIC Project also reported that the rates of decline did not significantly differ for non-Hispanic whites and Mexican Americans in any age group with a crude (2000–2002) three-year cumulative incidence of 13.6/1000 in non-Hispanic Whites and 16.8/1000 in Mexican Americans. [27] The Greater Cincinnati/Northern Kentucky Stroke Study data showed that in the1990's, compared to 2005, the incidence of ischemic stroke decreased in whites but not in blacks, and the incidence of hemorrhagic strokes did not change for either ethnic group.[28]. The REsons for Geographic and Racial Differences in Stroke (REGARDS) cohort [29] showed similar trends as the Greater Cincinnati/Northern Kentucky Stroke study with respect to the decrease in blacks' and whites' stroke incidence rate ratio with age. The cohort, taken between 2003–2010 and encompassing 27,744 participants with a four-year follow-up, showed the overall

age- and sex-adjusted black/white incidence rate ratio of 1.51. In the ages 45 to 54 years, the stroke incidence was 4.02 and in those greater than 85 years, it was 0.86. In contrast to the Greater Cincinnati/Northern Kentucky Stroke study, the Atherosclerosis Risk in Communities study [30] showed a decrease in stroke incidence and mortality from 1987 to 2011 in black and white adults, but the decreases varied across age groups. However, across groupings of sex and age, the incidence and mortality were similar. With respect to ethnicity, specifically focusing on Native Americans, the Strong Heart Study involving 4,507 participants who had not suffered prior stroke between 1989 to 1992 along with the age and sex adjusted, the incidence of stroke through 2004 was 6.79 per 100 person-years with 86% of the strokes being ischemic.

2.4 Prevalence of Stroke

Utilizing the data from the National Health and Nutrition Examination Survey, the AHA 2016 statistics[1] estimated the overall prevalence of stoke from 2009–2012 to be 2.6%. In 2013, the Behavioral Risk Factor Surveillance System, part of the CDC, [31] reported 2.7% of both men and women 18 years or older to have had a history of stroke. 2.5% of Non-Hispanic whites, 4.0% of Non-Hispanic blacks, 1.3% Asian/Pacific Islanders, 2.3% of all Hispanics, and 4.6% of American Indian/Alaskan Natives and other races or multiracial people had a history of stroke. The Behavioral Risk Factor Surveillance System reported from 2006 to 2010 that self-reported stroke prevalence was unchanged and that adults in lower socio-economic groups and those with lower education, blacks, and people living in the Southeastern United States had higher stroke prevalence rates. [32] Silent strokes are estimated at a prevalence of 6 to 28% and are more common in the older population. [33-35]

First-time stroke-related symptoms had a relatively high prevalence as demonstrated in a national cohort study involving 18,642 participants. 17.8% of the cohort with age greater than 45 had at least one symptom. Furthermore, this cohort demonstrated that it was more likely to occur in blacks, those in lower socio-economic and poorly educated groups, and those with fair to poor health status, and the symptoms were more likely to have a higher Framingham Stroke Risk Score. [36] (see Table 1). Future prevalence of stroke is estimated at 3.4 million for people age greater than 18 by 2030 and a 20.5% increase in prevalence from 2012 with the highest increase seen in Hispanic males of approximately 29%. [37] Women however show an increased rate of stroke survival, especially the elderly women.[38]

Table 1. The Framingham Stroke Score. [22]

Men: Probability of Stroke Within 10 Years

Points							
		0	**+1**	**+2**	**+3**	**+4**	**+5**
Age, y		54–56	57–59	60–62	63–65	66–68	69–72
Untreated SBP, mmHg		97–105	106–115	116–125	126–135	136–145	146–155
Treated SBP, mmHg		97–105	106–112	113–117	118–123	124–129	130–135
Diabetes		No		Yes			
Cigs		No			Yes		
CVD		No				Yes	
AF		No				Yes	
LVH		No					Yes

Points						
	+6	**+7**	**+8**	**+9**	**+10**
Age,y	73–75	76–78	79–81	82–84	85

Untreated SBP, mmHg	156–165	166–175	176–185	186–195	196–205
Treated SBP, mmHg	136–142	143–150	151–161	162–176	177–205
Diabetes					
Cigs					
CVD					
AF					
LVH					

Points	**10-Year Probability, %**	**Points**	**10-Year Probability, %**	**Points**	**10-Year Probability, %**
1	3	11	11	21	42
2	3	12	13	22	47
3	4	13	15	23	52
4	4	14	17	24	57
5	5	15	20	25	63
6	5	16	22	26	68
7	6	17	26	27	74
8	7	18	29	28	79

9	8	19	33	29	84
10	10	20	37	30	88

Variables were defined as follows: SBP, systolic blood pressure; Diabetes, history of diabetes; Cigs, smokes cigarettes; CVD (cardiovascular disease), history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure; AF, history of atrial fibrillation; LVH, left ventricular hypertrophy on electrocardiogram.

Women: Probability of Stroke Within 10 Years

Points							
		0	**+1**	**+2**	**+3**	**+4**	**+5**
Age,y		54–56	57–59	60–62	63–64	65–67	68–70
Untreated SBP, mmHg			95–106	107–118	119–130	131–143	144–155
Treated SBP, mmHg			95–106	107–113	114–119	120–125	126–131
Diabetes		No			Yes		
Cigs		No			Yes		
CVD		No		Yes			

AF	No				
LVH	No			Yes	Yes
Points					
	+6	**+7**	**+8**	**+9**	**+10**
Age,y	71–73	74–76	77–78	79–81	82–84
Untreated SBP, mmHg	156–167	168–180	181–192	193–204	205–216
Treated SBP, mmHg	132–139	140–148	149–160	161–204	205–216
Diabetes					
Cigs					
CVD					
AF	Yes				
LVH					

Points	**10-Year Probability, %**	**Points**	**10-Year Probability, %**	**Points**	**10-Year Probability, %**
1	1	11	8	21	43
2	1	12	9	22	50
3	2	13	11	23	57

4	2	14	13	24	64
5	2	15	16	25	71
6	3	16	19	26	78
7	4	17	23	27	84
8	4	18	27		
9	5	19	32		
10	6	20	37		

2.5 Cost of Stroke

In the United States of America, health expenditures are 17.9% of the Gross National Product (GNP). [39] According to TRADINGECONOMICS.com/U.S. Bureau of Economic Analysis, [40] in the second quarter of 2018, the GNP rose to 18,766.40 billion US dollars, making healthcare expenditures $3,359.19 billion US dollars. Besides being the leading cause of long-term disability, stroke costs 34 billion dollars a year which, 30% the cost health care services, medicines, and missed days of work. [41] It is one of the top ten chronic diseases affecting health care payers along with cardiovascular disease and cancer.[42]

2.6 Cerebral Blood Flow

The brain weights approximately 2 pounds per every100 pounds of body weight and consumes 20% of the cardiac output and total body oxygen. [43,44] This significant amount of blood and energy is required to accommodate the brain's high metabolic requirements. The metabolic requirements include synthesis and transportation of macromolecules and substrates such as neuro-transmitters, maintaining the integrity of cellular and the support structures, the osmotic compartmentalization of cells and structures, and the creation and maintenance of heat to allow biochemical reactions for enzymatic functions. [44] For the brain to function metabolically normal, it requires a steady flow of oxygen and substrates provided by the cerebral blood flow via circulation. [43,44] Ischemia is defined as a, "…insufficient supply of blood to an organ, usually due to a

blocked artery." [45] Infarction is defined as, "… a localization area of ischemic necrosis produced by anoxia following occlusion of the arterial supply or the venous drainage of the tissue, organ, or part." [46] Ischemia can be incomplete from insufficient blood flow or complete from the absence of blood flow. It can be global, affecting the whole brain, or focal, affecting a particular section or vascular territory. Regional cerebral blood flow or rCBF is expressed in mL/100g/min. Typical rCBF is between 50–60 mL/100g/min. The gray matter receives a greater flow than the white matter which is further increased during the functional activation of the region.

Ischemic thresholds have been studied in humans as well as other primates and higher mammals. [44,47] Jones showed that if the rCBF exceeds 20–25 mL/100g/min, the cellular structure remains intact and functions are maintained. Below this threshold, the cellular function decreases, and if the flow is below 5–10 mL/100g/min, cellular structures are damaged. Functional impairment was demonstrated utilizing an electroencephalogram (EEG) which showed a slowing and a decrease in waveform amplitudes. Moreover, there was a disruption of evoked cortical responses along with degradation of clinical function in the adjacent/related region of the brain that was ischemic. The amount of flow is not the only factor that determines if cellular structures are damaged – time is also a factor. The longer the tissue suffers from even a mild decrease in cerebral blood (10–20 mL/100g/min), the higher the risk of infarction. [47] This aspect is best illustrated in patients who suffer a transient ischemic attack (TIA) in which the patient has an episode of decreased function for a short period of time with no radiographic sign of infarct.

As mentioned previously, ischemia or infarct can be global or focal. Global infarct commonly occurs when there is cessation of blood to the entire brain, for example in cases

of cardiac arrest. Focal ischemia or infarct can occur from multiple mechanisms which include, cardioembolic, atheroembolic (from artery to artery), or atherosclerotic arteries. The pathophysiology of focal ischemia will be discussed later in the paper.

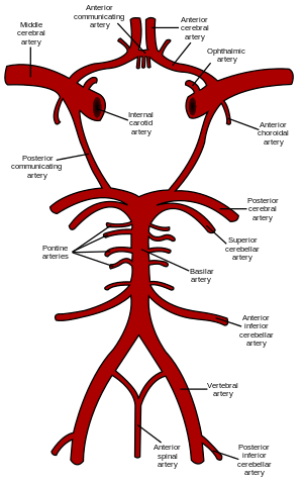
2.7 Cerebral Vascular Anatomy

To only investigate the aspects of the circulatory system most relevant to acute ischemic stroke, discussions will focus on the left side of the heart along with the carotid/vertebral arteries, and the Circle of Willis of the cerebral vasculature. As the blood returns from the lungs via the pulmonary artery, it enters the left atrium. As the left atrium contracts, blood passes through the mitral valve into the left ventricle. The left ventricle contracts and the blood is expelled through the aortic valve into the aorta. As the blood passes through the aorta, approximately 20% to 30% of the blood volume flows into the carotid-vertebral arterial system. The blood enters the left carotid system by passing directly into the left common carotid artery and then into the left internal carotid artery (which leads to the brain) or the left external carotid artery (which leads to the face and scalp). The blood enters the right carotid system by going into the brachiocephalic artery and then into the right common carotid artery. From the right common carotid artery, it leads into the right internal carotid artery (which leads to the brain) or the right external carotid artery (which leads to the face). The blood enters the vertebral artery system on the left by first entering the left subclavian artery and subsequently the left vertebral artery. The blood enters the right vertebral artery by first entering the right subclavian artery and subsequently the right vertebral artery.

Once the blood is in the internal carotid artery, it courses through the skull and into the cranial vault. The vertebral artery travels through the vertebral foramina of the spine till the level of C2 (the second vertebrae below the skull). The vertebral artery at the level of C2 leaves the vertebral foramina and trails around the lateral posterior edge of the C1 ring (vertebral artery groove) and into the cranial vault.

After the internal carotid arteries enter the cranial vault, each carotid artery divides into three vessels. The first division is the Posterior Communicating Artery (PComm) which connects the posterior circulation to the anterior circulation (see posterior circulation below for details). The internal carotid artery then progresses distally for approximately a millimeter or two and divides into the Anterior Cerebral Artery (ACA) and the Middle Cerebral Artery (MCA). The bilateral ACAs continue to extend toward the midline and eventually join to form the Anterior Communicating Artery (AComm). The posterior circulation begins in the vertebral artery. The bilateral vertebral arteries extend into the cranial vault and combine to make one artery, the basilar artery. The basilar artery has tributary arteries going to the cerebellum and at the top divides into the bilateral Posterior Cerebral Arteries (PCA). The PCAs branch off to the PComms and distal to the branching continue as the PCA. The attachment of the PComm to the PCA and the attachment of the ACA at the AComm allow for the intracranial vasculature to form a complete circle, the Circle of Willis. (Figure 1.) The benefit of a complete Circle of Willis, which only occurs in approximately 20–25% of the population [48] is that if one major artery is occluded, blood can still be supplied to the region unless the perfusion pressure/cerebral blood flow is too low, in this case cerebral ischemia and possibly cerebral infarct will occur.

Figure 1. Picture of the Circle of Willis[49]



2.8 Risk Factors for First Ischemic Stroke

Risk Factors, as discussed by Sacco, et al. in a 1997 publication, can be broken up into five categories: modifiable risk factors, potentially modifiable risk factors, less well-documented risk factors which are potentially modifiable, genetic and acquired risk factors, and non-modifiable risk factors.

The modifiable risk factors include elevated blood pressure, atrial fibrillation (heart rhythm disorders), cardiac disease, infective endocarditis, mitral valve stenosis, recent large myocardial infarction, sickle cell disease, transient ischemic attacks, asymptomatic carotid stenosis, tobacco, physical inactivity, and unhealthy diet (nutrition).

Potentially modifiable risk factors are hyperhomocysteinemia and left ventricular hypertrophy.

The less well-documented, potentially modifiable risk factors are elevated blood cholesterol and lipids, cardiac disease, cardiomyopathy, segmental cardiac wall motion

abnormalities, non-bacterial endocarditis, mitral annular calcification, mitral valve prolapse, valve strands, spontaneous echocardiographic contrast, aortic stenosis, patent foramen ovale, atrial septal aneurysm, use of oral contraceptives, excessive alcohol consumption, use of illicit drugs, physical inactivity, obesity, elevated hematocrit, dietary factors, hyperinsulinemia and insulin resistance, acute triggers (stress), migraine, hypercoagulability, inflammation, fibrin formation and fibrinolysis, fibrinogen, and anti-cardiolipin antibodies.

Genetic and acquired risk factors include subclinical diseases, intimal-medial thickness, aortic atheroma, ankle-brachial blood pressure ratio, infarct such as lesion on MRI, and socioeconomic features.

The non-modifiable risk factors are age, gender, heredity/family, race/ethnicity, geographic location, season, and climate. [50] Discussing all these diseases or disorders is beyond the scope of this paper; however, a few of the more significant risk factors associated with stroke will be considered. The actual pathophysiology of stroke and how these risk factors are associated will be discussed in the section covering pathophysiology.

2.8.1 High Blood Pressure

Hypertension (high blood pressure) is a major risk factor associated with ischemic stroke. If there is one modifiable risk factor that is considered the single most influential one, it is hypertension. [21,50] The definition, according to the Joint National Committee V of Hypertension, is the condition in which a person's blood pressure is greater than 140/90 mmHg or a patient with previously diagnosed hypertension and is on anti-hypertensive medications. The AHA defines stage 1 hypertension as a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg. A patient with stage 2

hypertension has a systolic blood pressure of greater than or equal to140 mmHg or a diastolic blood pressure of equal or greater than 90. [51] The prevalence of hypertension, utilizing the definition provided by Crim et al. for adults in the United States aged more than 20 was approximately 32.6% per the National Health and Nutrition Examination Survey. [21] This survey also showed that a higher percentage of men than women had hypertension until the age of 45. After the age of 45, until the age 64, men and women were showed equal prevalence, and after the age of 64, women had a higher percentage. [21] The National Health and Nutrition Examination Survey data from 2011–2012 indicated that 17.2% of United States adults with hypertension were unaware that they had hypertension.[52] In multiple surveys, it was determined that between 27.8% to 30.7% of adults in the United States had been informed they had hypertension. [53] The age-adjusted prevalence of hypertension in 2009 to 2012 was 44.9% for non-Hispanic black men and 46.1% for non-Hispanic black women, 32.9% for non-Hispanic white men and 30.1% for non-Hispanic white women, and 29.6% for Hispanic men and 29.9% for Hispanic women. The prevalence increased between 1998–1994, 1999–2006 and 2007–2012 for all groups except Mexican American men.[21]

The treatment of hypertension with anti-hypertensive medications has been well documented in clinical trials.

> "In a summary of 17 treatment trials of hypertension throughout the world involving nearly 50,000 patients, there was a 38% reduction in all stroke and 40% reduction in fatal stroke favoring systematic treatment of hypertension. This effect was true in whites and blacks and at all ages. Treatment was also effective in preventing stroke in elderly persons with isolated systolic hypertension (Systolic Hypertension in the Elderly Program [SHEP]), the most prevalent form of hypertension in persons older than 65. Importantly, there was no less impact on stroke prevention above age 80, with incidence reduced by 40%".[50]

2.8.2 Diabetes Mellitus

The effect of diabetes mellitus on the vascular wall is not specifically discussed in the Pathophysiology of Stroke section. This brief discussion describes how diabetes mellitus plays a role in vascular disease. This pathophysiology and subsequently discussing the general pathophysiology of plaque formation in the Pathophysiology of Stroke section, will provide the reader a clearer understanding of the link between diabetes mellitus and stroke; however, it is noteworthy that this is a general discussion, and a detailed pathophysiology of this topic is outside the scope of this paper. Diabetes Mellitus causes atherosclerosis which forms a deposit in the arterial vessel wall called, "plaque". The plaque develops from a defect in the endothelial cells lining the blood vessel. The blood vessel is also affected by depressed fatty acid synthase arising from the lack of insulin or insulin resistance. This interferes with the coordination of the vessel wall's nutritional status and tissue repair mechanism, and reduces the level of nitric oxide, which all contribute to vascular injury/disease.[54,55]. The inflammation and reduction of nitric oxide (which allows the blood vessel wall to relax) that occurs in the blood vessel wall is partly due to these processes as well as multiple other biochemical processes associated with diabetes, causing a build-up of free radicals, apoptosis, and inflammation which all lead to atherosclerosis deposition. See the Pathophysiology or Stroke section for more details on plaque formation.

Type 2 diabetes is significantly more common than type 1 diabetes and accounts for approximately 90–95% of all diagnosed cases in adults. [21,56]. A person diagnosed with diabetes,or having a hemoglobin A1c of equal or greater than 6.5, is more prevalent in minorities. Non-Hispanic blacks had two times higher prevalence than whites, while

Mexican Americans had a 35% higher prevalence than whites.[21,57] The prevalence in adults 65 or older in 2010 was 26.9% with more than 20 million considered pre-diabetic. This information along with the data from the National Health and Nutritional Examination Survey of 2005 to 2006 showed that 46% of people 65 or older were undiagnosed diabetics.[21,58] The incidence of diabetes in the adult population of the United States was approximately 1.7 million new cases among Americans 20 years or older in 2012. [21,59] The data from the FHS shows that the incidence over the past 30 years has doubled. [21,60]

> "FHS/NHLBI data showed that having DM significantly increased the risk of developing CVD (HR 2.5 for women and 2.4 for men) and of dying when CVD was present (HR 2.2 for women and 1.7 for men). Men and women greater than or equal 50 years of age with DM lived an average of 7.5 and 8.2 years less than their counterparts without DM. The differences in life expectancy free of CVD were 7.8 and 8.4 years respectively."[21]

2.8.3 Hypercholesterolemia

Hypercholesterolemia is considered a major risk factor for stroke.[21,61] The AHA considers untreated total cholesterol for adults as less than 200 mg/dl ideal for cardiovascular health. [21,62] According to the National Center for Health Statistics and National Health and Nutrition Examination Survey (2009 through 2012), approximately thirty million adults equal aged 20 or older in the United States have total cholesterol levels of approximately 240 mg/dL with a prevalence of 13.1%. Non-Hispanic black adults had a lower percentage of high cholesterol than non-Hispanic white adults, that being 9.8% and 13.5% respectively. [21] The utilization of statin medications caused a precipitous decline in the total cholesterol levels from 206 mg/dL in 1998–1994 to 196 mg/dl in 2007–2010. [21] The guidelines for treatment with statin medications was revised in 2013 by the American College of Cardiology and the American Heart Association. Prior to this revision, treatment

with statin medications was based on a patient's risk category. The new guideline for statin treatment is for the following:

> "(1) people with clinical atherosclerotic cardiovascular disease, (2) those with primary elevations in Low Density Lipoprotein-Cholesterol >190 mg/dL, (3) people age 40 to 75 years who have diabetes mellitus with Low Density Lipoprotein-Cholesterol 70-189 mg/dL and without clinical atherosclerotic cardiovascular disease, and (4) those without clinical atherosclerotic cardiovascular disease or diabetes mellitus with Low Density Lipoprotein-Cholesterol 70-189 mg/dL and estimated 10-year atherosclerotic cardiovascular disease risk greater 7.5%."[21]

Hypercholesterolemia and the effects on the blood vessel will be detailed in the section Pathophysiology of Stroke; however, the Pathophysiology of Stroke section provides a brief discussion and does not detail all the types of cholesterol and their effects on the blood vessel. Such details are beyond the scope of this discussion.

2.8.4 Heart Rhythm Disorders

"In atrial fibrillation, the regular impulses produced by the sinus node to provide rhythmic contraction of the heart are overwhelmed by the rapid randomly generated electrical discharges produced by larger areas of triggering atrial tissue."[63] In atrial fibrillation, the heart's atria fibrillate causing a stagnation of blood in the chamber. This blood stagnation in the chamber coagulates and forms a clot known as a thrombus. The thrombus can break apart into an embolus which can be ejected into the cerebral vasculature. Atrial fibrillation affects approximately 2.2 million people a year, is the leading risk factor for stroke, and is detected in approximately 15% of patients with stroke.[64] See Pathophysiology of Stoke for further details.

2.8.5 Other Risk Factors

Other risk factors include tobacco use, poor nutrition, and physical inactivity. It is obvious, based on advertising in media and on the cigarette packaging, that the use of tobacco products has a deleterious effect on all vasculature. In regard to poor nutrition and physical inactivity, they not only have a significant deleterious effect on the vasculature but also cause or worsen the previous disease processes discussed.

2.9 Pathophysiology of Stroke

Ischemic strokes occur from either stable plaques (stenosis), unstable plaques (thromboembolic strokes), or a thrombo-embolus formed in the heart (cardio thromboembolic strokes). Plaques are formed in the blood vessel and become thrombus or embolus. In the heart, a thrombus is formed leading to an embolus. Prior to discussing stable versus unstable plaques or cardio thromboembolic strokes, it is important to discuss how plaques and the thromboembolisms are formed.

2.9.1 Arterial Plaque Formation

Atherosclerosis is an atheroma in the arterial lumen caused by plaques containing lipids, inflammatory cells, smooth muscle cells, and connective tissue. Atherosclerosis affects primarily large and medium-sized arteries in the entire body. The pathophysiology of atherosclerosis in general will be discussed in this section. Previously, the researcher discussed some of the individual risk factors and their association with atherosclerosis which leads to stroke. The following paragraph is a general description of the formation of atherosclerosis.

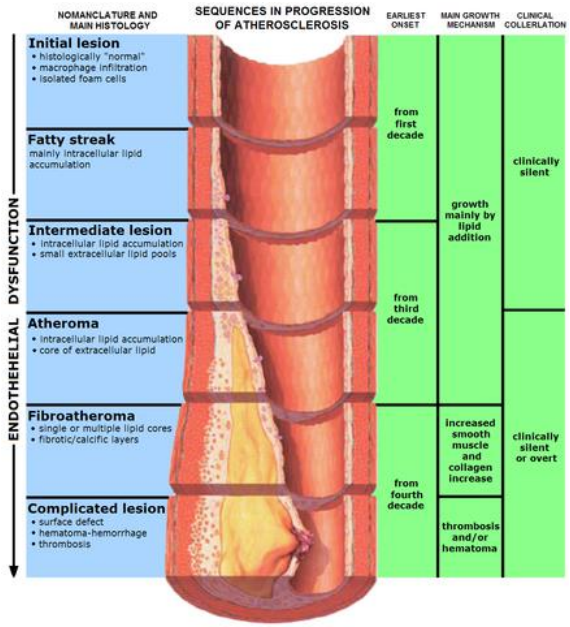
The earliest form of atherosclerosis is a fatty streak. Fatty streaks are an accumulation of lipid-laden foam cells in the intimal layer of the artery. The tunica intima or the intimal layer is the inner layer of the blood vessel wall. The fatty streak is comprising three major components – lipids, inflammatory and smooth muscle cells, and connective tissue. These components are intermixed with thrombus in various stages of organization and incorporated with calcium deposits. Regardless of the stage of the fatty streak or true plaque formation or even complications of the plaque, it is considered an inflammatory response to injury mediated by cytokines. The area of the vasculature commonly affected is an area of turbulent flow, usually occurring at the bifurcation of the blood vessel into two blood vessels. Secondary to the high turbulent, forceful flow on the vessel, the endothelium (inner-most portion of the intima tunica) is injured and dysfunctions. The dysfunction inhibits the endothelial production of nitric oxide. Nitric oxide is a vasodilator and anti-inflammatory molecule that supports healing and vascular wall relaxation. This endothelial dysfunction stimulates the production of adhesion molecules, pro-inflammatory cytokines, chemotactic proteins, and vasoconstrictors. These molecules cause the binding of monocytes and T cells in the sub-endothelial space (the middle-portion of the tunica intima layer), which initiates a local vascular inflammatory response. In the sub-endothelium, monocytes transform into macrophages. The cholesterol in the blood, particularly the lipids, LDL (low-density lipoproteins) and VLDL (very-low-density lipoproteins) bind to the endothelial cells and oxidize in the sub-endothelium. The oxidized lipids are taken up and transformed into lipid-laden foam cells, forming fatty streaks via macrophage transformation. Stimulation of multiple promoting factors along with macrophages' pro-inflammatory cytokines recruit smooth muscle cell migration from the

media, which interacts with and stimulates further growth of macrophages, resulting in the formation of a dense extracellular matrix. The resultant factor of this process produces a fibrous plaque with a cap made of intimal smooth muscle cells surrounded by connective tissue and intra-cellular and extra-cellular lipids. The calcification within the plaque is a process similar to the formation of bone. [65].

2.9.2 Arterial Plaque Source of Stroke

As discussed in the previous section, a thrombus can be formed from an unstable plaque that has eroded or erupted through the inner most lining of the blood vessel wall, the endothelial lining portion of the intima tunica. When the plaque breaks through the endothelial lining, a thrombus is formed from aggregation of platelets in the body's effort to heal the injury. The thrombus can break apart, forming an embolus from the high velocity blood passing by the thrombus. Another possibility is that the vessel can become completely occluded from an already severely stenotic artery caused by plaque formation in the intima. When the intimal tunica is fractured, platelet aggregation occurs as it does in thrombus formation; however, as the vessel was already stenotic, the lumen of the vessel becomes blocked or causes a damming effect at that level. In the cases associated with an embolus, the clot travels along the vasculature until the volume and diameter of the clot is greater than the diameter of the vessel lumen, causing an acute blockage and preventing blood flow distal to the clot. (Figure 2)

Figure 2. Picture of How Atherosclerotic Plaque Forms and Becomes Unstable.[66]



2.9.3 Cardio Thromboembolic Source of Stroke

As discussed in the previous section, a thrombus can form which in-turn can cause an embolic event. Inside the cardiac chambers, a thrombus forms from stagnation of blood caused by a dysrhythmia such that the heart is unable to eject the blood out of the chamber. The stagnation of blood allows the blood to coagulate and form a thrombus. As discussed previously, the thrombus occurs allowing for an embolus to be formed, especially if the heart dysrhythmia is not constant and the heart now contracts normally. If the thrombus weakens or the blood flow in the heart has a high enough velocity to fracture the thrombus, an embolus is formed. The embolus can be ejected and might course toward the cerebral vasculature or to any area of the body. In cases such as atrial fibrillation, myocardial infarction, growth on a cardiac valve from infection (endocarditis) or tumor (cardiac

myxoma), a hole in one of the cardiac walls (septal wall defect), or any of the factors mentioned in the section titled, “Risk Factors”, a thrombus/embolus can occur. This embolus causes a stroke in the same way an embolus from arterial plaque can occur. (see section, Arterial Plaque source of Stoke, above).

2.10 Treatment of Stroke

Currently, there are three ways a stroke is treated: either with rt-PA, mechanical thrombectomy, or a combination of both rt-PA and mechanical thrombectomy. A patient with stroke symptoms is treated according to an algorithm to determine which pathway of treatment they will be provided. Each pathway improves the patient’s long-term outcomes. The following sections provides the algorithm for treatment determination, indications and contraindications to each treatment, and a summary of the outcomes.

Emergency Department Algorithm for Treating Stroke

If a patient is identified as having a stroke or stroke-like symptoms, the following algorithm is recommended: [67] (Figure 3.)

Figure 3. Acute Ischemic Stroke Algorithm [67]

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2.10.1 Tissue Plasminogen Activator (rt-PA)

2.10.1.1 The Basic Chemistry of Tissue Plasminogen Activator (rt-PA)

Tissue Plasminogen Activator (rt-PA) has changed the treatment of acute ischemic stroke. Prior to its availability in 1995, the common course for a patient having a stroke was to languish in the emergency room. Expedient evaluation and treatment was not necessary, whether the stroke was hemorrhagic or ischemic was not of consequence, there was no treatment differentiation or available acute treatments.[68] Tissue Plasminogen Activator is a potent thrombolytic agent. There are different forms of rt-PA; Alteplase, Reteplace, and Tenecteplase. Regardless of the preparation, the underlying chemistry is the same. Tissue Plasminogen Activator is a protein, serine protease, which is an enzyme found on the endothelial cells that line the blood vessels. The enzyme's function is to convert plasminogen to plasmin and cause the breakdown of clots. Using recombinant biotechnology techniques, rt-PA was synthetically developed and is used as a potent clot busting agent to prevent or decrease the penumbra of an acute ischemic stroke. [69]

2.10.2 Summary of Tissue Plasminogen Activator Outcome Studies

2.10.2.1 The Basic Indications and Contraindications for rt-TPA

The basic eligibility requirements for rt-PA are threefold: age greater than 18, a clinical diagnosis of ischemic stroke causing neurologic deficits, and a time from the onset of acute ischemic stroke symptoms of less than 4.5 hours. There are several

contraindications besides the timing of onset of symptoms for the utilization of rt-PA; they are as follows:

> "Absolute Contraindications to rt-PA
> Intracranial hemorrhage on CT
> Clinical presentation suggests subarachnoid hemorrhage
> Neurologic surgery, serious head trauma, or previous stroke in past 3 months
> Uncontrolled hypertension (>185 mmHg or >110 mmHg DBP)
> History of intracranial hemorrhage
> Seizure at stroke onset
> Known arteriovenous malformation, neoplasm, or aneurysm
> Active internal bleeding
> Known bleeding diathesis, including:
> Platelet count <100,000
>
> Patient has received heparin within 48 hours and has an elevated aPTT (greater than upper limit of normal for laboratory)
>
> Current use of oral anticoagulants (ex: warfarin) and INR>1.7
> Abnormal blood glucose (<50 or >400 mg/dl)
> Relative Contraindications/Warnings to tPA
> Only minor or rapidly improving stroke symptoms
>
> Patient has had a major surgery or serious trauma excluding head trauma in the previous 14 days
>
> History of gastrointestinal or urinary tract hemorrhage within 21 days
> Recent arterial puncture at a non-compressible site
> Recent lumbar puncture
> Post myocardial infarction pericarditis
> Pregnancy
> Additional Warnings to tPA >3hr Onset
> Age >80 years
> History of prior stroke and diabetes
> Any active anticoagulant use (even with INR <1.7)
> NIHSS>25
> CT shows multilobar infarction (hypodensity >1/3 cerebral hemisphere)." [70]

2.10.3 Mechanical Thrombectomy

Mechanical thrombectomy has been through many generations of technical improvement. The basic premise of all generations is to deploy a catheter into the arterial vasculature at the point of occlusion and remove the thrombus, thus allowing blood to flow through its natural pathway. The initial generations had many complications, with the most

significant being hemorrhage, and they lost favor of being used; however, subsequent generations addressed these issues and became much safer and provided significant improvement in outcomes compared to acute ischemic stroke care without the use of thrombectomy. (See Appendix B. **Summary of Mechanical Thrombectomy Outcomes Studies**) The indications for the procedure are:

Large vessel occlusion

NIH score of greater than 6

Pre-hospital modified Rankin score of less than 2

Infarct volume of less than 70 cc

Mismatch volume on advanced imaging of greater than 2.0.

The contraindication includes the patient not meeting the aforementioned indications.

2.10.4 Advanced Imaging in Stroke Treatment

Advanced imaging on acute ischemic stroke patients is becoming more common. It has been known for many years that ischemia co-exists with infarct and rapid treatment can reduce infarct.

> "Our study in acute human stroke involving MCA occlusion indicates that a severely ischemic core (CBF $\leq$6 $cm^3 \cdot 100\ g^{-1} \cdot min^{-1}$), observed between 1 to 6 hours after stroke onset, corresponds to the cerebral tissue destined to infarction. The ischemic penumbra with flow values between 7 and 20 $cm^3 \cdot 100\ g^{-1} \cdot min^{-1}$ surrounding the ischemic core is very narrow. Therefore, strategies to improve the outcome of many patients with acute MCA occlusion must either include interventions to reverse the ischemic process within a few minutes of onset or increase the cerebral tolerance of ischemia and thereby prolong the potential therapeutic window."[71]

Considering this information, many studies have attempted to evaluate the best way to determine penumbra (ischemia) versus infarct (stroke). MRI for many years was considered the best modality for evaluating stroke, hemorrhagic or ischemic. MRI should

replace CT as the primary neuroimaging technique for the examination of acute ischemic stroke patients.

> "Until now, non-contrast CT has been the routine imaging modality for acute stroke evaluation. The primary advantage of CT has been the ability to detect acute hemorrhage. The detection of hemorrhage can play a critical role in therapeutic decision-making, since hemorrhage is a contraindication for thrombolytic therapies.". [72]

CT is also being utilized to determine an ASPECTS (Alberta Stroke Program Early CT Score) to determine if a patient is eligible for rt-PA.

> "The Alberta stroke program early CT score (ASPECTS) [73] is a 10-point quantitative topographic CT scan score used in patients with middle cerebral artery (MCA) stroke. Segmental assessment of the MCA vascular territory is made, and 1 point deducted from the initial score of 10 for every region involved." [74]

However, multimodal MRI provides substantially greater information about brain ischemic pathophysiology. This information can identify patients with an ischemic penumbra and potentially extend the time window for late therapies. The limiting factor for adoption of MRI for acute ischemic stroke evaluation is the uncertainty about its ability to detect hyperacute hemorrhage. Recent studies, including the Hemorrhage and Early MRI Evaluation (or HEME study) have demonstrated that GRE MRI sequences are, in fact, as accurate as CT for detection of acute hemorrhage and far more accurate for detection of chronic hemorrhage. [75,76]

> "However, physicians might not be familiar with the appearance of hemorrhage on GRE sequences. For multimodal MRI to replace CT for the evaluation of acute stroke patients, an intensive and validated reading skills training program should be undertaken. [77] With these advances in multimodal MR imaging, we now have the capacity to diagnose acute cerebrovascular disease more accurately and rapidly. It is imperative that physicians involved in the evaluation and care of stroke patients learn how to appropriately interpret MRI findings, including GRE evidence of acute hemorrhage." [78]

However more recently other modalities like CT angiography and CT perfusion have shown to be equivalent to MRI in the evaluation of stroke, hemorrhagic and ischemic,

and are more readily available [79,80]. As stated previously, all the trials with positive outcomes regarding thrombectomy needed to prove the occlusion of a large, first order, intracranial vessel prior to the procedure. The most common test utilized was the CT angiography.

2.11 The Modified Rankin Scale

The outcome results are the patient's modified Rankin scale score at three months post stroke. See Table 2. for a description of the modified Rankin score. [81]

Table 2. Modified Rankin Score. [81]

MODIFIED RANKING SCORE

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

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2.12 Summary of Tissue Plasminogen Activator Outcome Studies

In 1998, an open-labeled study published in *Stroke* and conducted at a university hospital and two community hospitals in Houston, Texas reported that approximately 6% of all patients with acute ischemic stroke received rt-PA at the university hospital while only approximately 1.1% received it in the community hospitals. [82] In 2003 to 2011, the number of acute ischemic stroke patients regardless of age or contra-indications receiving rt-PA nearly doubled from 42.6% to 77% in patients arriving in less than or equal to two hours after onset of symptoms and 4.0% to 7.0% in all patients arriving in less than or equal to three hours after the onset of symptoms. [83] In a 2012 study of almost one million hospital admissions, hospitals participating in the Get With The Guidelines-Stroke Program in the United States showed that less than 5% of the patients overall were eligible for rt-PA. [84]

As stated previously, the indicated treatment time window of stroke with rt-PA is less than 4.5 hours after the onset of symptoms. The guideline of door-to-needle time (the time the patient enters the emergency room to the time the patient receives rt-PA) of providing rt-PA to a patient with stroke symptoms is 60 minutes or less according to the Brain Attach Coalition. [85] However, based on the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry and the Get With The Guidelines-Stroke Program Registry, in 2011, it was reported that in 641 hospitals in the United States, treating equal to or greater than 10 stroke patients per institution, only 6.7% of patients were treated with rt-PA. Furthermore, at least half the patients in these registries were treated in the 60-minute time window suggested by the Brain Attach Coalition [86], and the

median door-to-needle times was approximately 70 minutes (65 minutes in the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry and 75 minutes in the Get With The Guidelines-Stroke program). [86,87] Therefore, many patients are not being treated for ischemic stroke based on ischemic stroke recognition and/or eligibility of treating with rt-PA.

There have been multiple significant studies on the use of rt-PA and stroke outcomes that will be discussed in this paper but this discussion is not exhaustive regarding the topic. (See Appendix B. **Summary of rt-PA Outcomes Studies**) Results from the following studies will be pooled for the data source of this study: The Tissue Plasminogen Activator for Acute Ischemic Stroke, National Institute of Neurological Disorders and Stroke (NINDS), The rt-PA (Alteplase) 0-6-Hour Acute Stroke Trial, Part A (A0276g) Results of a Double-Blind, Placebo-Controlled, Multicenter Study, Alteplace ThromboLysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS A), Recombinant Tissue-Type Plasminogen Activator (Alteplase) for Ischemic Stroke 3 to 5 Hours After Symptom Onset, The ATLANTIS Study: A Randomized Controlled Trial (ATLANTIS B), Intravenous Thrombolysis with Recombinant Tissue Plasminogen Activator for Acute Hemispheric Stroke, the European Cooperative Acute Stroke Study (ECASS I), Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous Alteplase in acute ischemic stroke (ECASS II), Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke (ECASS III), and Effects on Alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Trial (EPITHET): a placebo-controlled randomized trial. These papers were chosen to provide a sample of the outcomes because of their well-known status in the world of acute ischemic stroke care.

Initially, there were three large randomized trials to evaluate the use of rt-PA, NINDS, ATLANTIS and ECASS 1. ATLANTIS and ECASS 1 both evaluated the use of rt-PA in acute ischemic stroke presentation in 0–6 hours while NINDS evaluated the use of rt-PA in ischemic stroke presentation in 0–3 hours. NINDS and ATLANTIS were North American trials and ECASS was a European trial. The later trials ATLANTIS B, ECASS II and III, and EPITHET were second and third generation trials based on the results of the former studies.

As detailed above in the NINDS, ATLANTIS A and B, ECASS I, II, and III, and the EPITHET trials' utilization of Alteplase, rt-PA, improves clinical outcomes if utilized within the extended 3 to 4.5 hours of stroke symptom onset.[3-9] In the NINDS trial, the results in Part 1 of the study showed the following:

> "No statistically significant difference were detected between groups in the primary outcome…..However, post hoc comparisons of median NIHSS scores showed improvement in the condition of the patient treated with t-PA as compared to those given placebo in most time strata in parts 1 and 2 and in the combined analysis." [3]

Overall, in this study, when rt-PA was,

> "..compared with the placebo group, there was a 12 percent absolute (32 percent relative) increase in the number of patients with minimal to no disability (a score of 95 or 100 on the Barthel index) in the t-PA group. There was also an 11 percent absolute (55 percent relative) increase in the number of patients with an NIHSS score of 0 to 1 in this group. A similar magnitude of effect was seen with respect to the absolute and relative improvement in the t-PA group with the use of the modified Rankin scale and the Glasgow outcome scale."[3]

The number of patients in Part 1 of the NINDS study who had symptomatic intracranial hemorrhage within 36 hours of treatment was 8 in the rt-PA group and 0 in the placebo group, and Part 2 of the study included 12 (approximately 6%) in the rt-PA group and 2 in the placebo group.

The ATLANITS A trial proved that administering rt-PA in the 0 to 6-hour range was more harmful than beneficial by showing a significant increase in the intracranial hemorrhage rate of 11% in the rt-PA group compared to 0% with placebo. Additionally, patients receiving rt-PA in less than 3 hours (15%) compared to those receiving rt-PA between 5–6 hours (32%) obtained no significant clinical benefit at the 30-day point.

> "The groups were well matched on baseline characteristics, including NIHSS (mean of 13 for both). For the primary end points, a higher percentage of rtPA patients had a 4-point improvement at 24 hours (placebo 21%, rtPA 40%; P=0.02); however, this early effect was reversed by 30 days, with more placebo patients having a 4-point improvement (75%) than patients treated with rtPA (60%, P=0.05). Treatment with rtPA significantly increased the rate of symptomatic intracerebral hemorrhage within 10 days (11% versus 0%, P<0.01) and mortality at 90 days (23% versus 7%, P<0.01)." [4]

The ATLANTIS B trial re-evaluated the data from the Atlantis A trial and attempted to determine if administering rt-PA to patients within 3 to 5 hours of symptoms onset was safe. The authors concluded the following:

> "This study found no significant rt-PA benefit on the 90-day efficacy end points in patients treated between 3 and 5 hours. The risk of symptomatic ICH increased with rt-PA treatment. The results do not support the use of intravenous rt-PA for stroke treatment beyond 3 hours." [6]

The ECASS study treated patients with acute ischemic stroke, with moderate to severe neurologic deficits and no major signs of early infarct on the initial CT scan, with 1.1 mg per kilogram of body weight of rt-PA and not the 0.9 mg per kilogram of body weight previously studied. The study results showed the following:

> "There was no difference in the primary endpoints in the ITT analysis, while the TP analysis revealed a significant difference in the RS in favor of rt-PA-treated patients (P=.035). Of the secondary end points, the combined BI and RS showed a difference in favor of the rt-PA-treated patients in both analysis (P<.001). Neurologic recovery at 90 days was significantly better for the rt-PA-treated patients in the TP (=.03). The speed of neurologic recovery assessed by the SSS was significantly better up to 7 days in the ITT analysis and up to 30 days for the TP in the rt-PA treatment arm in both analyses." [5]

The study stated the following regarding hemorrhage:

> "The overall incidence of intracranial hemorrhagic events was not significantly different between the treatment groups. In the ITT analysis, 247 patients (39.8%) had intracranial hemorrhage of any degree, 134 patients in the rt-PA group and 113 patients in the placebo group. In the TP analysis, 205 patients (40.1%) had hemorrhagic events of any degree, 108 patients in the rt-PA group and 97 patients in the placebo group. In both analyses, HI was more frequent in the placebo-treated groups, while PH was more frequent in the rt-PA-treated groups. Fisher's exact test showed a significant difference in the subtypes of intracranial bleed events in both analyses (P<.001)."[5]

The study further concluded the following:

> "Intravenous thrombolysis in acute ischemic stroke is effective in improving some functional measures and neurologic outcome in a defined subgroup of stroke patients with moderate to severe neurologic deficit and without extended infarct signs on the initial CT scan. However, the identification of this subgroup is difficult and depends on recognition of early major CT signs of early infarction. Therefore, since treating ineligible patients is associated with an unacceptable increase of hemorrhagic complications and death, intravenous thrombolysis cannot currently be recommended for use in an unselected population of acute ischemic stroke patients."[5]

The ECASS II study was developed to evaluate if rt-PA administered in the dose of 0.9 mg/kg bodyweight within 6 hours was efficacious and safe. The study concluded, "The results do not confirm a statistical benefit for Alteplase. However, we believe the trend towards efficacy should be interpreted in the light of evidence from previous trials. Despite the increased risk of intracranial hemorrhage, thrombolysis with Alteplase at a dose of 0.9 mg/kg in selected patients may lead to a clinically relevant improvement in outcome." [7]

The ECASS III study evaluated whether providing Alteplase within 3-4.5 hours was safe and efficacious, considering no previous studies had concluded that providing Alteplase after 3 hours was safe or efficacious. The study concluded:

> "As compared with placebo, intravenous Alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in

patients with acute ischemic stroke; Alteplase was more frequently associated with symptomatic intracranial hemorrhage." [8]

The EPITHET trial was to evaluate if Alteplase is effective within 3 to 6 hours after stroke symptoms and whether it affects reperfusion along with attenuation of infarct growth in patients who have had an MRI with a perfusion mismatch on a perfusion weighted and diffusion weighted MRI. The authors concluded, "Alteplase was non-significantly associated with lower infarct growth and significantly associated with increased reperfusion in patients who had mismatch. Because repercussion was associated with improved clinical outcomes, phase III trials beyond 3 hours after treatment are warranted."[9]

The MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset is a multicentered trial that patients were randomly assigned to receive Alteplase or placebo. For a patient to be eligible, the patient had to have ischemic lesion on diffusion weighted imaging MRI but not on FLAIR MRI sequence in order to indicate the stroke occurred within the last 4.5 hours. Patients were excluded if they were candidates for thrombectomy. The endpoint was for a favorable outcome with a modified Rankin score of 0–1 (scale of 0–6) at 90 days, and secondary outcome was that Alteplase would lead to lower scores on the modified Rankin score compared to placebo.

The study had a matched group of participants with 254 patients in the Alteplase group and 249 in the placebo group. There were favorable outcomes in 131 (53%) versus 102 (41.8%) for the treatment and placebo groups, respectively. Median scores for the Alteplase group was 1 and 2 for the placebo group on modified Rankin scale scores at 90 days, with intracranial hemorrhage and mortalities, 2.0% and 4.1% respectively in the Alteplase group, and 0.4% and 1.2% respectively in the placebo group.[88]

2.13 Summary of Mechanical Thrombectomy Outcome Studies:

Mechanical Thrombectomy is a procedure performed by a neuro-interventional specialist. The procedure starts with performing a carotid-cerebral angiogram and identifying the anatomy that is affected by the thrombus/embolus. After the offending material is identified, a smaller catheter is guided directly to the area and one or more thrombectomy devices are deployed/utilized to remove the clot, allowing for blood flow and brain perfusion distal to the region to be restored. There are several different devices from multiple companies currently on the market. The indication for the devices is for the treatment of acute ischemic strokes with symptom onset of less than eight hours and where either a patient is ineligible for rt-PA or rt-PA has failed. Also, the patient must not have a significant infarct versus ischemia on radiographic studies. If the patient meets the indications, there are no specific contra-indications. Discussing the devices and their design is beyond the scope of this discussion; however, it is appropriate to state that the later/latest generations of these devices have facilitated performance of the procedure more efficaciously and safely than with the previous or initial generations. The early generation devices, 2009–2013, were being utilized at a steadily increasing rate of 1.5% to 3.1% from 2009 through 2012. [89] However, in February 2013, there were multiple concurrent trials presented at the International Stroke Conference (Interventional Management of Stroke III Trial (IMS III), Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and the Local Versus Systemic Thrombolysis for Acute Ischemic Stroke Expansion (SYNTHESIS) trials which revealed that current thrombectomy devices either were of no benefit or that the results were not superior to rt-

PA for treating stroke. [10-12]. As a result of these presentations, the utilization of these devices dropped from 3.1% to 2.5% after 2012, until the third quarter of 2014 when the newer generation of devices were introduced. [89]

The turning point came in late 2014, with the use of newer generation thrombectomy devices, following the results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for acute ischemic stroke in the Netherlands, when the study protocol for a randomized control trial (MR CLEAN trial) became available. As a result, the use of newer generation thrombectomy devices and interventional treatments significantly increased. The MR CLEAN trial and subsequent trials, such as Solitaire[tm] With the Intention for Thrombectomy (SWIFT), Solitaire[tm] With the Intention for Thrombectomy as PRIMary treatment for acute ischemic stroke (SWIFT PRIME), Endovascular treatment for Small Core and Anterior circulation Proximal Occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE), Extending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA), Trevo versus Merci retrievers for thrombectomy Revascularization of large Vessel Occlusions (TREV0-2), and Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptoms Onset (REVASCAT), have all shown positive results. The resurgence of this intervention caused an increase in the usage of the devices with endovascular treatment to 4.7% by the end of the second quarter in 2015. There was a year on year increase of 150% for 2015 compared to 2014, as reported in Neurology Reviews by Anthony S. Kim, MD, Medical Director of the Stroke Center at the University of California, San Francisco and his associates. [89] The

second-generation device study, the MR CLEAN study, is significant because it showed that "If IAT leads to a 10% absolute reduction in poor outcome after stroke, careful implementation of the intervention could save approximately 1% of all new stroke cases from death or disability annually." [90] This study was unique because it was performed in the Netherlands, a socialized medicine system, and in order for expenses incurred in the care of stroke patients to be reimbursable all facilities had to utilize the procedures when appropriate. This allowed for a true comparison of intra-arterial treatment versus non-intra-arterial treatment arms of the study among the entire population of stroke patients. There were 500 patients in the study. The most recent studies, DAWN [91] and DEFUSE III [92], have shown that by using advanced CTA and CTP imaging the time of treatment can be extended based on the physiology of ischemia vs infarct mismatch ratio instead of exclusively by time of stroke onset. (See Appendix B. **Summary of Mechanical Thrombectomy Outcomes Studies**)

2.14 Description of Study Groups

Below are tables with a compilation in weighted averages of the results of the outcomes and hemorrhagic complications from the major studies associated with rt-PA and thrombectomy. The data was broken up into categories associated with the decision tree model that was developed. The categories include: No treatment, Treatment with rt-PA, Treatment with rt-PA and Thrombectomy, Thrombectomy with no rt-PA and Treatment with rt-PA based on advanced imaging (see Data section for the weighted average tables).

Tables 3– Table 7 show the results from studies associated with patients having rt-PA compared to no treatment, and the results associated with patients having no treatment

which is a different category using the same data. These are combined as weighted averages for the data that is input to the decision tree (NINDS, ATLANTIS B, ECASS II, ECASS III, and EPITHET). (see Data section for weighted average tables). Table 8–Table 12 show the results from the studies associated with patients receiving rt-PA and thrombectomy compared to patients with rt-PA alone. These results are combined as weighted averages for the data that is input to the decision tree (MR CLEAN, Extend IA, ESCAPE, REVASCAT, SWIFT-PRIME). (see Data section for weighted average tables). Table 13–Table 15 show the results for patients treated with mechanical thrombectomy utilizing advanced imaging instead of time as the initial factor, compared to patients with no treatment. These results are combined as weighted averages for the data that is input into the decision tree (DAWN, DIFFUSE-III, ESCAPE). (see Data section for weighted average tables). Table 16 shows the results of patients treated with rt-PA utilizing advanced imaging instead of time as the initial factor, compared to no treatment (WAKE-UP). (see Data section for weighted average tables.)

Table 3. NINDS Outcome Results.

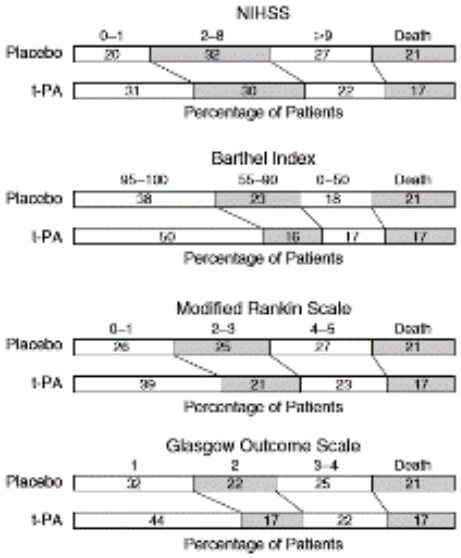


Figure 2. Outcome at Three Months in Part 2 of the Study, According to Treatment.

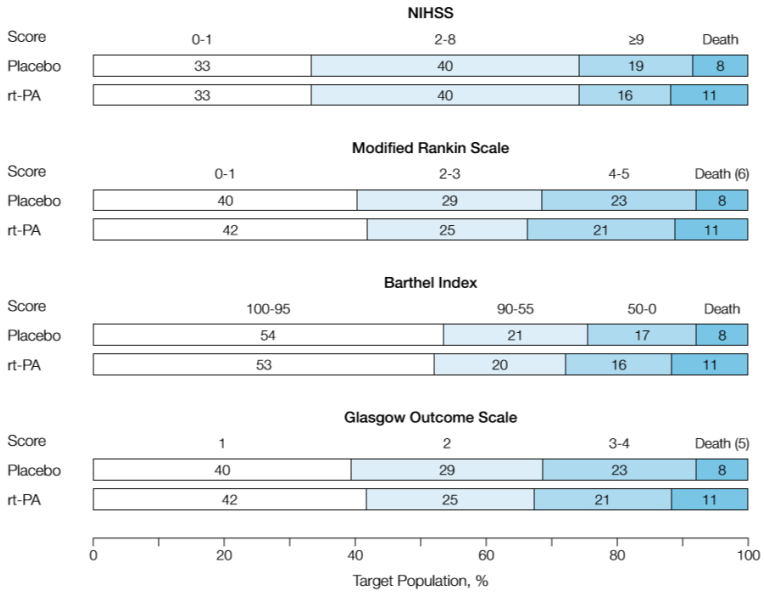
Scores of 0–1 on the NIHSS, 95 or 100 on the Barthel index, 0–1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome. Values do not total 100 percent because of rounding.

Incidence of Intracranial Hemorrhage within 36 Hours of Treatment for Stroke.

TYPE OF INTRACRANIAL HEMORRHAGE	t-PA	PLACEBO
	no. (%)	
Part 1	144	147
Symptomatic	8 (6)	0
Fatal*	4	0
Nonfatal	4	0
Asymptomatic	5 (3)	3 (2)
Part 2	168	165
Symptomatic	12 (7)	2 (1)
Fatal*	5	1
Nonfatal	7	1
Asymptomatic	9 (5)	6 (4)

*Values include all deaths attributed to hemorrhage.

Table 4. ATLANTIS B Outcome Results.



The target population is defined as patients aged 18 through 79 years who presented with a clinical diagnosis of ischemic stroke causing a measurable neurologic deficit and who received the study drug between 3 and 5 hours of definite symptom onset. NIHSS indicates National Institutes of Health Stroke Scale (scores range from 0 to 42); rt-PA, recombinant tissue-type plasminogen activator. Not all sums equal 100% due to rounding. Barthel index scores are given in 5-point increments.

	Intent-to-Treat Population			Target Population†		
Serious Adverse Event	Placebo (n = 306)	rt-PA (n = 307)	*P* Value	Placebo (n = 275)	rt-PA (n = 272)	*P* Value
Asymptomatic ICH	4.2	11.3	.001	4.7	11.4	.004
Symptomatic ICH	1.3	6.7	<.001	1.1	7.0	<.001
Fatal ICH	0.3	2.6	<.001	0.3	3.0	<.001
Death within 90 d	6.9	10.9	.08	6.9	11.0	.09
Death within 30 d	4.2	7.6	.08	4.4	7.0	.18

*rt-PA indicates recombinant tissue-type plasminogen activator; ICH, intracerebral hemorrhage. Data are presented as percentages unless otherwise indicated.
†The target population received treatment as assigned between 3 and 5 hours after symptom onset.

Table 5. ECASS II Outcome Results.

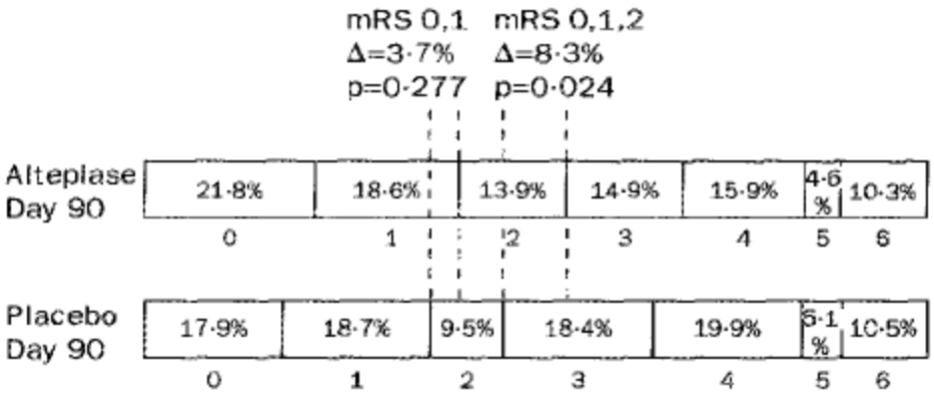


Figure 2: **Distribution of mRS scores at day 90**

CT criterion*	0–3 h		3–6 h		Total (n=793)†	
	Alteplase (n=81)	Placebo (n=77)	Alteplase (n=326)	Placebo (n=309)	Alteplase (n=407)	Placebo (n=386)
Petechial haemorrhage						
PH2	6 (7%)	1 (1%)	27 (8·3%)	2 (0·6%)	33 (8·1%)	3 (0·8%)
PH1	1 (1%)	3 (4%)	14 (4·3%)	6 (1·9%)	15 (3·7%)	9 (2·3%)
Haemorrhagic infarction						
HI2	10 (12%)	12 (16%)	52 (16·0%)	35 (11·3%)	62 (15·2%)	47 (12·2%)
HI1	15 (19%)	22 (29%)	65 (19·9%)	72 (23·3%)	80 (19·6%)	94 (24·3%)
Other	3 (4%)	0	4 (1·2%)	2 (0·6%)	7 (1·7%)	2 (0·5%)
Total	35 (43%)	38 (49%)	162 (49·6%)	117 (37·9%)	197 (48·4%)	155 (40·2%)

*For definitions see methods. †Seven patients were randomised but not treated.

Table 4: **Cases of intracranial haemorrhage up to day 7 in patients who actually received treatment**

Reprinted from The Lancet, Vol 352, Hacke, W. et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous Alteplase in acute ischaemic stroke (ECASS II), 1245–1251. October 17, 1998, with permission from Elsevier.

Table 6. ECASS III Outcome Results

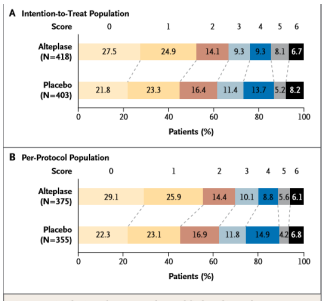


Figure 2. Distribution of Scores on the Modified Rankin Scale.
The distribution of scores is shown for the intention-to-treat population (Panel A) and the per-protocol population (Panel B) at the 3-month visit (90 days plus or minus 14 days). In both the intention-to-treat population and the per-protocol population, stratified analysis of the score distribution showed a significant difference between the study groups (P=0.02 for both comparisons by the Cochran–Mantel–Haenszel test, with adjustment for the baseline score on the National Institutes of Health Stroke Scale and for the interval between the onset of symptoms and the initiation of treatment). In the intention-to-treat population, the number of deaths recorded at the 3-month visit (59) was different from the overall number of deaths (66), since 7 deaths occurred after 90 days. The scores on the modified Rankin scale indicate the following: 0, no symptoms at all; 1, no significant disability despite symptoms (able to carry out all usual duties and activities); 2, slight disability (unable to carry out all previous activities but able to look after own affairs without assistance); 3, moderate disability (requiring some help but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance); 5, severe disability (bedridden, incontinent, and requiring constant nursing care and attention); 6, death.

Adverse Events	Alteplase Group (N=418)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value
	no. (%)			
Prespecified safety end points				
Any ICH	113 (27.0)	71 (17.6)	1.73 (1.24–2.42)	0.001
Symptomatic ICH				
According to ECASS III definition†	10 (2.4)	1 (0.2)	9.85 (1.26–77.32)	0.008
According to ECASS II definition‡	22 (5.3)	9 (2.2)	2.43 (1.11–5.35)	0.02
According to SITS–MOST definition§	8 (1.9)	1 (0.2)	7.84 (0.98–63.00)	0.02
According to NINDS definition¶	33 (7.9)	14 (3.5)	2.38 (1.25–4.52)	0.006
Fatal ICH	3 (0.7)	0	—	—

† The ECASS III definition of symptomatic intracranial hemorrhage was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.
‡ The ECASS II definition was the same as that for ECASS III, except that establishment of a causal relationship between the hemorrhage and clinical deterioration or death was not a requirement.
§ The SITS–MOST definition was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.
¶ In the NINDS definition, a hemorrhage was considered symptomatic if it had not been seen on a previous CT scan but there was subsequently either a suspicion of hemorrhage or any decline in neurologic status. To detect intracranial hemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical findings suggested hemorrhage.

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Table 7. EPITHET Outcome Results

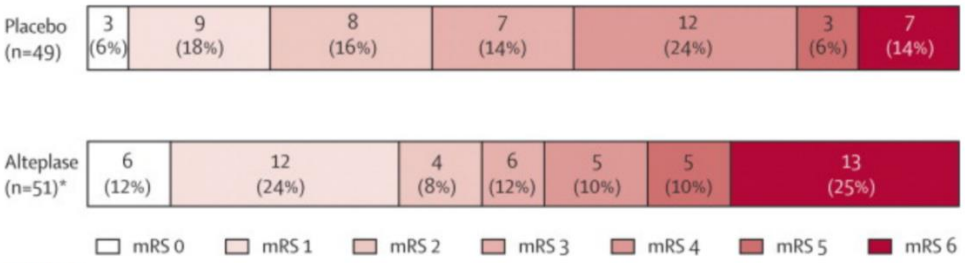

Figure 2

Functional outcome for all patients

Functional outcome (mRS distribution) at day 90 for all patients. Percentages do not total 100% because of rounding. *One patient in the alteplase group declined clinical assessment at day 90.

Reprinted from The Neurology Lancet, Vol 7, Davis et al. Effects of Alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomized trial. 299–309. April 2008, with permission from Elsevier.

Table 8–12. Study results associated with patients having rt-PA and mechanical thrombectomy compared to patients with rt-PA alone.

Table 8. MR CLEAN Outcome Results

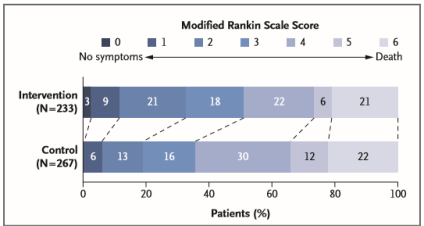

Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.

Shown is the distribution of scores on the modified Rankin scale. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (patient is able to look after own affairs without assistance but is unable to carry out all previous activities), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (patient requires constant nursing care and attention), and 6 death. There was a significant difference between the intervention group and the control group in the overall distribution of scores in an analysis with univariable ordinal regression (common odds ratio, 1.66; 95% CI, 1.21 to 2.28), as well as after adjustment of the treatment effect for age; National Institutes of Health Stroke Scale score at baseline; time from stroke onset to randomization; status with respect to previous stroke, atrial fibrillation, and diabetes mellitus; and occlusion of the internal-carotid-artery terminus (yes vs. no) in an analysis with multivariable regression (adjusted common odds ratio, 1.67; 95% CI, 1.21 to 2.30). In the control group, only 1 patient (0.4%) had a modified Rankin score of 0.

Table 3. Safety Variables and Serious Adverse Events within 90 Days after Randomization.

Variable	Intervention (N=233)	Control (N=267)
	no. of patients (%)	
Safety variables		
Death		
Within 7 days	27 (11.6)	33 (12.4)
Within 30 days	44 (18.9)	49 (18.4)
Hemicraniectomy	14 (6.0)	13 (4.9)
Serious adverse events*		
Any serious adverse event	110 (47.2)	113 (42.3)
Symptomatic intracerebral hemorrhage		
Any type	18 (7.7)	17 (6.4)
Parenchymal hematoma†		
Type 1	0	2 (0.7)
Type 2	14 (6.0)	14 (5.2)
Hemorrhagic infarction‡		
Type 1	1 (0.4)	0
Type 2	1 (0.4)	1 (0.4)
Subarachnoid hemorrhage	2 (0.9)	0
New ischemic stroke in a different vascular territory§	13 (5.6)	1 (0.4)
Progressive ischemic stroke	46 (19.7)	47 (17.6)
Pneumonia	25 (10.7)	41 (15.4)
Other infection	16 (6.9)	9 (3.4)
Cardiac ischemia	1 (0.4)	4 (1.5)
Extracranial hemorrhage	0	2 (0.7)
Allergic reaction	1 (0.4)	0
Other complication	22 (9.4)	33 (12.4)

* Only first events of a type are listed. Patients having multiple events of one type were counted once.
† For parenchymal hematoma, type 1 was defined by one or more blood clots in 30% or less of the infarcted area with a mild space-occupying effect, and type 2 was defined by blood clots in more than 30% of the infarcted area with a clinically significant space-occupying effect.
‡ For hemorrhagic infarction, type 1 was defined by small petechiae along the margins of the infarction, and type 2 was defined by more confluent petechiae within the infarction area.
§ P<0.001.

Table 9. Extend IA Outcome Results

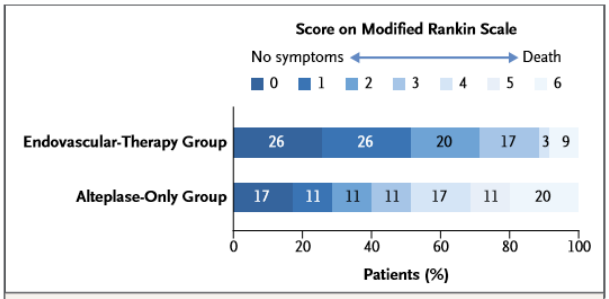

Figure 2. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Shown are the percentages of patients in the endovascular-therapy group and the alteplase-only group with scores from 0 to 6 on the modified Rankin scale as follows: 0, no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (requiring constant nursing care and attention); and 6, death. In the endovascular group, no patients had a score of 5.

Table 3. Study Outcomes.*

Outcome	Alteplase-Only Group (N=35)	Endovascular-Therapy Group (N=35)	Effect Size (95% CI)†			
			Adjusted	P Value	Unadjusted	P Value
Primary outcomes						
Median reperfusion at 24 hr (IQR) — (%)‡	37 (−0.5 to 96)	100 (100 to 100)	4.7 (2.5 to 9.0)	<0.001	4.9 (2.5 to 9.5)	<0.001
Early neurologic improvement — no. (%)§	13 (37)	28 (80)	6.0 (2.0 to 18.0)	0.002	6.8 (2.3 to 20)	<0.001
Secondary outcomes						
Score on the modified Rankin scale at 90 days¶						
Median score (IQR) on ordinal analysis	3 (1 to 5)	1 (0 to 3)	2.0	0.02	2.1 (1.2 to 3.8)	0.006
Independent outcome — no. (%)	14 (40)	25 (71)	4.2 (1.4 to 12)	0.01	3.8 (1.4 to 10.0)	0.009
Excellent outcome — no. (%)	10 (29)	18 (51)	2.4 (0.87 to 6.6)	0.09	2.6 (1.0 to 7.1)	0.05
Safety — no. (%)						
Death	7 (20)	3 (9)	0.45 (0.1 to 2.1)	0.31	0.38 (0.1 to 1.6)	0.18
Symptomatic intracerebral hemorrhage‖	2 (6)	0	NA	NA	−6 (−13 to 2)**	0.49
Parenchymal hematoma	3 (9)	4 (11)	NA	NA	3 (−11 to 17)**	0.99
Tertiary outcomes††						
Reperfusion of >90% at 24 hr without symptomatic intracerebral hemorrhage — no. (%)	12 (34)	31 (89)	27.0 (5.5 to 135.0)	<0.001	15.0 (4.0 to 52.0)	<0.001
Recanalization at 24 hr — no. (%)‡‡	15 (43)	33 (94)	29.0 (5.4 to 155.0)	<0.001	22.0 (4.5 to 106.0)	<0.001
Median infarct growth at 24 hr (IQR) — ml§§	35.3 (6.3 to 73.4)	10.9 (0 to 23.6)	−0.44 (−0.76 to −0.13)‖‖	0.007	NA	NA
Median home time (IQR) — days¶¶	15 (0 to 69)	73 (47 to 86)	64 (28 to 90)‖‖	0.001	58 (17 to 90)‖‖	0.006

* NA denotes not applicable.
† Values are odds ratios unless otherwise indicated. Odds ratios or median differences are for the endovascular-therapy group as compared with the alteplase-only group.
‡ Reperfusion was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and 24-hour imaging. This value can be negative if hypoperfusion becomes more severe over time. This analysis was adjusted for the site of vessel occlusion at baseline. The effect size in this category is the Wilcoxon–Mann–Whitney generalized odds ratio.
§ Early neurologic improvement was defined as a reduction of 8 points or more on the National Institutes of Health Stroke Scale (NIHSS) or a score of 0 or 1 at 3 days. This analysis was adjusted for the NIHSS score and age at baseline.
¶ The initial analysis of the modified Rankin scale was an ordinal analysis that used the full range of the scale from 0 (normal function) to 6 (death) and is expressed as a Wilcoxon–Mann–Whitney generalized odds ratio. The analysis was adjusted for the baseline NIHSS score (≤15 vs. >15) and age (≤70 years vs. >70 years) with the use of a permutation method to accommodate small stratum size. This method does not produce confidence intervals. In addition, scores on the modified Rankin scale were analyzed for an outcome with functional independence (score of 0 to 2) or an excellent outcome (score of 0 or 1), adjusted for the full range of ages and baseline score on the NIHSS.
‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score.
** The effect size in this category is a risk difference, as measured in percentage points for symptomatic intracerebral hemorrhage and parenchymal hematoma.
†† A more detailed list of tertiary outcomes is provided in Table S3 in the Supplementary Appendix.
‡‡ Recanalization was defined as a Thrombolysis in Myocardial Infarction score of 2 or 3 (partial or complete restoration of flow at the site of arterial occlusion).[21] This analysis was adjusted for the site of vessel occlusion at baseline.
§§ Infarct growth was defined as the increase in the ischemic core volume from baseline to 24 hours and was adjusted for the ischemic core volume at baseline.
¶¶ Home time (the number of days spent at home during the first 90 days after the diagnosis of stroke) was adjusted for the NIHSS score and age at baseline.
‖‖ The effect size in this category is the median difference in infarct growth (as measured in milliliters and transformed by an exponent of 0.2 owing to a non-normal distribution) and the median difference in days for home time, as calculated by median regression.

Table 10. ESCAPE Outcome Results (only section A is used for this category)

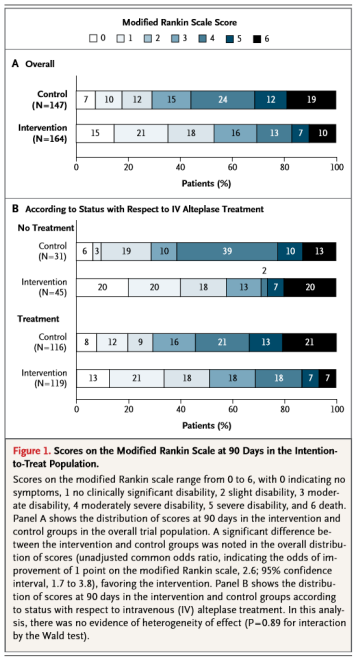

Figure 1. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Panel A shows the distribution of scores at 90 days in the intervention and control groups in the overall trial population. A significant difference between the intervention and control groups was noted in the overall distribution of scores (unadjusted common odds ratio, indicating the odds of improvement of 1 point on the modified Rankin scale, 2.6; 95% confidence interval, 1.7 to 3.8), favoring the intervention. Panel B shows the distribution of scores at 90 days in the intervention and control groups according to status with respect to intravenous (IV) alteplase treatment. In this analysis, there was no evidence of heterogeneity of effect ($P=0.89$ for interaction by the Wald test).

Table 3. Reported Serious Adverse Events.

Event	Intervention (N=165)	Control (N=150)	Difference (95% CI)*	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
Death — no./total no. (%)	17/164 (10.4)	28/147 (19.0)	8.6 (0.8 to 16.6)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)
Large or malignant middle-cerebral-artery stroke — no. (%)‡	8 (4.8)	16 (10.7)	5.8 (0.1 to 11.7)	0.5 (0.2 to 1.0)	0.3 (0.1 to 0.7)
Symptomatic intracerebral hemorrhage — no. (%)‡§	6 (3.6)	4 (2.7)	1.0 (–2.9 to 4.8)	1.4 (0.4 to 4.7)	1.2 (0.3 to 4.6)
Hematoma at access site — no. (%)¶	3 (1.8)	0			
Perforation of the middle cerebral artery — no. (%)	1 (0.6)	0			

* Differences (intervention group – control group) are shown as percentage points.
† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.
‡ Two hemicraniectomy procedures were performed. The indications for hemicraniectomy were malignant middle-cerebral-artery ischemic stroke (one patient in the control group) and symptomatic intracerebral hemorrhage (one patient in the intervention group).
§ Symptomatic intracerebral hemorrhage was clinically determined at the study site.
¶ Hematoma occurred in two participants at the site of groin puncture. Neck hematoma occurred in the single participant in whom direct carotid access was used, after femoral access was unsuccessful.

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Table 11. REVASC Outcome Results

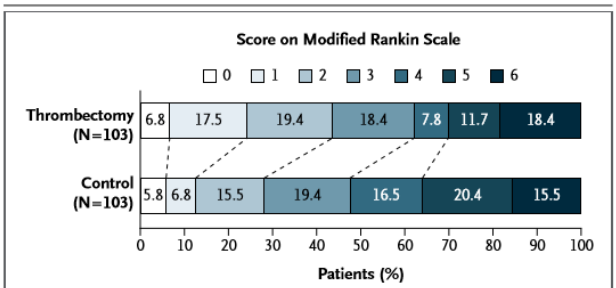

Figure 1. Distribution of Functional Scores at 90 Days (Intention-to-Treat Population).

Shown are scores on the modified Rankin scale for patients in the thrombectomy group and the control group who were evaluated by means of video recording (in 106 patients) and by local investigators (in 65 patients). Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help, but able to walk unassisted; 4, moderately severe disability (unable to attend body needs and unable to walk); 5, severe disability (requiring constant nursing care and attention); and 6, death. Scores of 5 and 6 were combined for the analysis. A significant difference between the thrombectomy group and the control group was noted in the overall distribution of scores (adjusted common odds ratio for improvement of 1 point on the modified Rankin scale, 1.7; 95% confidence interval, 1.05 to 2.8).

Table 4. Serious Adverse Events within 90 Days.*

Variable	Thrombectomy (N=103)	Control (N=103)	Between-Group Difference (95% CI)	Risk Ratio (95% CI)
	no. (%)			
Safety variable				
Death				
At 90 days	19 (18.4)	16 (15.5)	−2.9 (−13.2 to 7.3)	1.2 (0.6 to 2.2)†
At ≤7 days	10 (9.7)	5 (4.9)	−4.8 (−11.9 to 2.2)	2.0 (0.7 to 5.6)
Intracranial hemorrhage				
Symptomatic‡				
SITS-MOST criteria	2 (1.9)	2 (1.9)	0.0 (−3.8 to 3.8)	1.0 (0.1 to 7.0)
ECASS II criteria	5 (4.9)	2 (1.9)	−2.9 (−7.8 to 2.0)	2.5 (0.5 to 12.6)
Asymptomatic§	17 (16.5)	11 (10.7)	−5.8 (−15.2 to 3.5)	1.5 (0.7 to 3.1)
Subarachnoid hemorrhage	5 (4.9)	2 (1.9)	−2.9 (−7.8 to 2.0)	2.5 (0.5 to 12.6)
Parenchymal hematoma¶				
Any	6 (5.8)	6 (5.8)		
Type 1	3 (2.9)	4 (3.9)		
Type 2	3 (2.9)	2 (1.9)		
Other adjudicated serious adverse event				
Neurologic worsening‖	16 (15.5)	13 (12.6)	−2.9 (−12.4 to 6.6)	1.2 (0.6 to 2.4)
Malignant cerebral edema**	11 (10.7)	10 (9.7)	−1.0 (−9.2 to 7.3)	1.1 (0.5 to 2.5)
Recurrent stroke	4 (3.9)	3 (2.9)	−1.0 (−5.9 to 4.0)	1.3 (0.3 to 5.8)
Procedure-related complication††		NA	NA	NA
Distal embolization in a different territory	5 (4.9)			
Arterial dissection	4 (3.9)			
Arterial perforation	5 (4.9)			
Groin hematoma	11 (10.7)			
Groin pseudoaneurysm	1 (1.0)			
Vasospasm requiring treatment‡‡	4 (3.9)			

* Negative values for the between-group difference favor the control group. The risk ratio is for the thrombectomy group as compared with the control group. A complete list of adverse events is provided in Tables S6 and S7 in the Supplementary Appendix.
† The adjusted risk ratio for death at 90 days was 1.1 (95% CI, 0.8 to 1.4).
‡ Symptomatic intracranial hemorrhage was defined as parenchymal hemorrhage type 2 on follow-up imaging and neurologic deterioration of at least 4 points on the NIHSS, according to the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) criteria, or any symptomatic intracranial hemorrhage and neurologic worsening of at least 4 points on the NIHSS, according to the second European–Australasian Acute Stroke Study (ECASS II) criteria.
§ Asymptomatic intracranial hemorrhage was defined as any parenchymal hematoma with no neurologic worsening, as adjudicated by local investigators.
¶ Parenchymal hematomas were graded according to the neuroimaging core laboratory classification.
‖ Neurologic worsening was defined as an increase of at least 4 points on the NIHSS within 5 days after stroke onset that was not attributed to intracranial hemorrhage or malignant cerebral edema.
** Malignant cerebral edema was treated with decompressive hemicraniectomy in 3 patients in the thrombectomy group and in 6 patients in the control group.
†† All procedure-related complications were reported by the clinical events committee.
‡‡ Vasospasm events were reported by local investigators and the angiography core laboratory.

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Table 12. SWIFT-PRIME Outcome Results

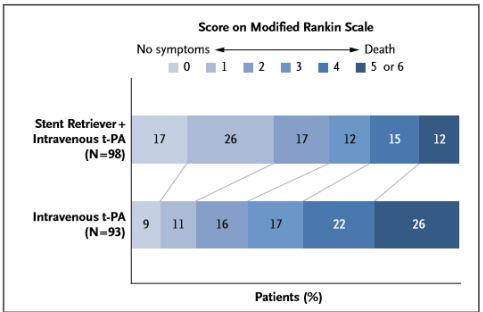

Figure 1. Functional Outcomes at 90 Days, According to the Score on the Modified Rankin Scale.

Shown are the 90-day scores on the modified Rankin scale for the patients in the two treatment groups. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), and 6 death. Persons with a score of 0, 1, or 2 are considered to be independent in daily function. Neurovascular thrombectomy with the use of a stent retriever was associated with a significant shift in the distribution of scores toward lesser disability (P<0.001 by the Cochran–Mantel–Haenszel test), including an absolute increase of 25 percentage points in the proportion of patients who were functionally independent at 90 days (P<0.001). The term t-PA denotes tissue plasminogen activator.

Table 3. Safety Outcomes.*

Outcome	Intravenous t-PA Alone (N=97)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	P Value
	no. of patients (%)			
Primary safety outcomes				
Any serious adverse event at 90 days†	30 (31)	35 (36)	1.15 (0.78–1.72)	0.54
Symptomatic intracranial hemorrhage at 27 hr	3 (3)	0	0.00 (NA)	0.12
Additional safety outcomes at 27 hr				
Parenchymal hematoma	7 (7)	5 (5)	0.71 (0.23–2.15)	0.57
Type 1	3 (3)	4 (4)	1.32 (0.30–5.74)	1.00
Type 2	4 (4)	1 (1)	0.25 (0.03–2.17)	0.21
Subarachnoid hemorrhage	1 (1)	4 (4)	3.96 (0.45–34.79)	0.37

* NA denotes not applicable.
† A serious adverse event was an adverse event that led to death, a life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function, or fetal distress, fetal death or a congenital anomaly or birth defect. Serious adverse events that are classified according to organ system are shown in Table S11 in the Supplementary Appendix. None of the serious adverse events were adjudicated by the clinical-events committee to be device-related. Nonserious adverse events that were deemed to be device-related are shown in Table S12 in the Supplementary Appendix.

Table 13–Table 16. Study results associated with patients treated with mechanical thrombectomy without time as the initial factor, but advanced imaging, compared to patient with no treatment.

Table 13. DAWN Outcome Results

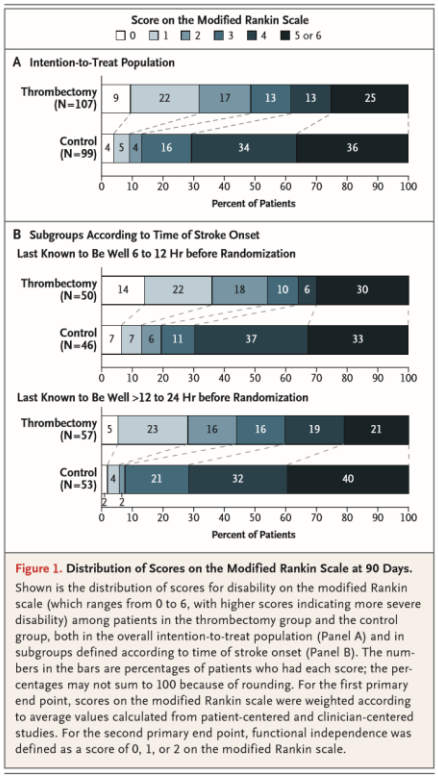

Figure 1. Distribution of Scores on the Modified Rankin Scale at 90 Days.
Shown is the distribution of scores for disability on the modified Rankin scale (which ranges from 0 to 6, with higher scores indicating more severe disability) among patients in the thrombectomy group and the control group, both in the overall intention-to-treat population (Panel A) and in subgroups defined according to time of stroke onset (Panel B). The numbers in the bars are percentages of patients who had each score; the percentages may not sum to 100 because of rounding. For the first primary end point, scores on the modified Rankin scale were weighted according to average values calculated from patient-centered and clinician-centered studies. For the second primary end point, functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale.

Table 3. Safety Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)	Risk Ratio (95% CI)
	no. (%)		*percentage points*	
Stroke-related death at 90 days	17 (16)	18 (18)	−2 (−13 to 8)	1 (1 to 2)
Death from any cause at 90 days	20 (19)	18 (18)	1 (−10 to 11)	1 (1 to 2)
Symptomatic intracranial hemorrhage at 24 hr†	6 (6)	3 (3)	3 (−3 to 8)	2 (1 to 7)
Neurologic deterioration at 24 hr‡	15 (14)	26 (26)	−12 (−23 to −1)	1 (0 to 1)
Procedure-related complications	7 (7)	NA		
Distal embolization in a different territory	4 (4)	NA		
Intramural arterial dissection	2 (2)	NA		
Arterial perforation	0	NA		
Access-site complications leading to intervention	1 (1)	NA		

* There were no significant differences between the two treatment groups with respect to safety outcomes, except for neurologic deterioration (P=0.04). All safety outcomes were adjudicated by an independent clinical-events committee.
† Symptomatic intracranial hemorrhage was defined according to European Cooperative Acute Stroke Study III criteria as the presence of extravascular blood in the cranium that was associated with an increase in the NIHSS score of 4 points or more or death and was judged to be the predominant cause of neurologic deterioration.
‡ Neurologic deterioration was defined as an increase in the NIHSS score of 4 or more points within 5 days after stroke that was not attributed to intracranial hemorrhage or malignant cerebral edema.

Table 14. DEFUSE III Outcome Results

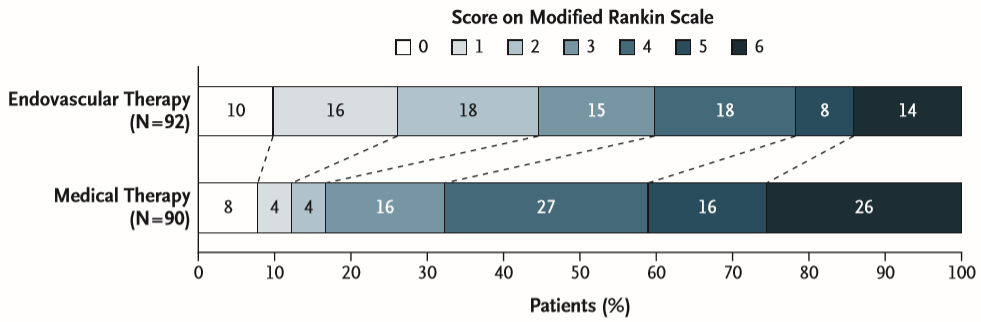

Figure 2. Scores on the Modified Rankin Scale at 90 Days.

Patients in the endovascular-therapy group received endovascular therapy plus standard medical therapy. Patients in the medical-therapy group received standard medical therapy alone. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. There was a significant difference favoring the endovascular-therapy group over the medical-therapy group in the overall distribution of scores (unadjusted common odds ratio, 2.77; 95% CI, 1.63 to 4.70; P<0.001).

Table 2. Clinical and Imaging Outcomes.

Outcome	Endovascular Therapy (N=92)*	Medical Therapy (N=90)	Odds Ratio or Risk Ratio (95% CI)†	P Value
Primary efficacy outcome: median score on modified Rankin scale at 90 days (IQR)‡	3 (1–4)	4 (3–6)	2.77 (1.63–4.70)§	<0.001
Secondary efficacy outcome: functional independence at 90 days — no. (%)¶	41 (45)	15 (17)	2.67 (1.60–4.48)	<0.001
Safety outcomes — no. (%)				
Death at 90 days	13 (14)	23 (26)	0.55 (0.30–1.02)	0.05
Symptomatic intracranial hemorrhage‖	6 (7)	4 (4)	1.47 (0.40–6.55)	0.75
Early neurologic deterioration	8 (9)	11 (12)	0.71 (0.30–1.69)	0.44
Parenchymal hematoma type 2	8 (9)	3 (3)	2.61 (0.73–14.69)	0.21
Imaging outcomes**				
Median infarct volume at 24 hr (IQR) — ml	35 (18–82)	41 (25–106)	—	0.19
Median infarct growth at 24 hr (IQR) — ml	23 (10–75)	33 (18–75)	—	0.08
Reperfusion >90% at 24 hr — no./total no. (%)	59/75 (79)	12/67 (18)	4.39 (2.60–7.43)	<0.001
Complete recanalization at 24 hr — no./total no. (%)	65/83 (78)	14/77 (18)	4.31 (2.65–7.01)	<0.001
TICI score of 2b or 3 — no./total no. (%)	69/91 (76)	—	—	

* An intervention was attempted in 90 patients (98%), of whom 88 had an attempted mechanical thrombectomy and 2 had carotid stenting alone. In one of these two cases, the interventionalist elected not to perform a thrombectomy. The other patient did not have an occlusion on the baseline angiogram but was treated with carotid stenting for presumed dissection. The 2 patients with no intervention had carotid-artery occlusions, one in the common carotid and the other in the internal carotid, and the interventionalist decided that treatment was not feasible. Revascularization of the carotid artery with angioplasty, stenting, or both was performed in 13 patients (14%).

† The odds ratio is shown for the primary efficacy outcome, and risk ratio is shown for the other outcomes.

‡ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability. The protocol required the score to be assessed by a person who was not aware of the trial-group assignments. However, three patients in the endovascular-therapy group and one patient in the medical-therapy group had an assessor who was aware of the trial-group assignments.

§ Shown is the unadjusted common odds ratio. The odds ratio with adjustment for stratification factors is 3.36 (95% CI, 1.96 to 5.77; P<0.001). The proportional-odds assumption was not met when core volume was included in the fully adjusted model; without core volume included, the adjusted odds ratio is 3.24 (95% CI, 1.89 to 5.55).

¶ Functional independence was defined as a score on the modified Rankin scale of 0 to 2.

‖ Among the patients with symptomatic intracranial hemorrhage, the hemorrhage was rated as parenchymal hematoma type 2 (dense blood clot exceeding 30% of the infarct volume with substantial space-occupying effect; in two patients in the endovascular-therapy group and three patients in the medical-therapy group), parenchymal hematoma type 1 (blood clot not exceeding 30% of the infarcted area with some mild space-occupying effect; in one patient in the endovascular-therapy group), hemorrhagic infarction type 2 (confluent petechiae within the infarcted area, but without space-occupying effect; in three patients in the endovascular-therapy group), or hemorrhagic infarction type 1 (small petechiae along the margins of the infarct; in one patient in the medical-therapy group).

** Infarct volume at 24 hours was assessed on diffusion-weighted MRI (or CT if MRI was not feasible). Infarct volume and infarct growth at 24 hours were assessed in 90 patients in the endovascular-therapy group and 89 patients in the medical-therapy group (2 patients in the endovascular-therapy group and 1 patient in the medical-therapy group died before imaging).

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Table 15. ESCAPE Outcome Results (only section B is used for this category)

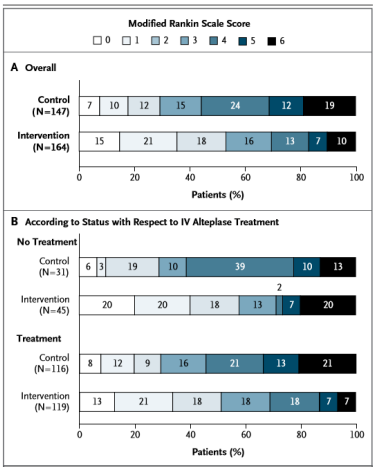


Figure 1. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Panel A shows the distribution of scores at 90 days in the intervention and control groups in the overall trial population. A significant difference between the intervention and control groups was noted in the overall distribution of scores (unadjusted common odds ratio, indicating the odds of improvement of 1 point on the modified Rankin scale, 2.6; 95% confidence interval, 1.7 to 3.8), favoring the intervention. Panel B shows the distribution of scores at 90 days in the intervention and control groups according to status with respect to intravenous (IV) alteplase treatment. In this analysis, there was no evidence of heterogeneity of effect (P=0.89 for interaction by the Wald test).

Table 3. Reported Serious Adverse Events.

Event	Intervention (N=165)	Control (N=150)	Difference (95% CI)*	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
Death — no./total no. (%)	17/164 (10.4)	28/147 (19.0)	8.6 (0.8 to 16.6)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)
Large or malignant middle-cerebral-artery stroke — no. (%)‡	8 (4.8)	16 (10.7)	5.8 (0.1 to 11.7)	0.5 (0.2 to 1.0)	0.3 (0.1 to 0.7)
Symptomatic intracerebral hemorrhage — no. (%)‡§	6 (3.6)	4 (2.7)	1.0 (–2.9 to 4.8)	1.4 (0.4 to 4.7)	1.2 (0.3 to 4.6)
Hematoma at access site — no. (%)¶	3 (1.8)	0			
Perforation of the middle cerebral artery — no. (%)	1 (0.6)	0			

* Differences (intervention group – control group) are shown as percentage points.
† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.
‡ Two hemicraniectomy procedures were performed. The indications for hemicraniectomy were malignant middle-cerebral-artery ischemic stroke (one patient in the control group) and symptomatic intracerebral hemorrhage (one patient in the intervention group).
§ Symptomatic intracerebral hemorrhage was clinically determined at the study site.
¶ Hematoma occurred in two participants at the site of groin puncture. Neck hematoma occurred in the single participant in whom direct carotid access was used, after femoral access was unsuccessful.

Table 16. Study Results Associated with Patients Treated with rt-PA Without Time as the Initial Factor, but with Advanced Imaging, Compared to No Treatment

Table 16. WAKE UP OUTCOME RESULTS

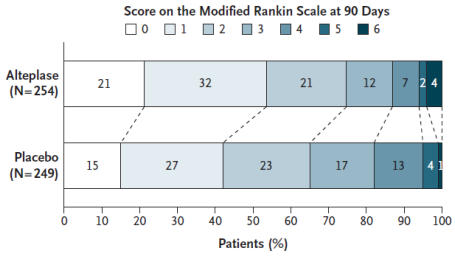


Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

Shown are the differences in the scores on the modified Rankin scale among patients in the alteplase group and the placebo group at 90 days. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Numbers indicate rounded proportions. There was a significant difference favoring the alteplase group over the placebo group in the overall distribution of scores (adjusted common odds ratio, 1.62; 95% confidence interval, 1.17 to 2.23; P=0.003).

Table 3. Safety Outcomes.

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Adjusted Odds Ratio (95% CI)*	P Value
	no. (%)			
Primary†				
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39–1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.2)	3.38 (0.92–12.52)	0.07
Secondary				
Symptomatic intracranial hemorrhage				
As defined in SITS-MOST‡	5 (2.0)	1 (0.4)	4.95 (0.57–42.87)	0.15
As defined in ECASS II§	7 (2.8)	3 (1.2)	2.40 (0.60–9.53)	0.21
As defined in ECASS III¶	6 (2.4)	1 (0.4)	6.04 (0.72–50.87)	0.10
As defined in NINDS‖	20 (8.0)	12 (4.9)	1.78 (0.84–3.71)	0.13
Parenchymal hemorrhage type 2**	10 (4.0)	1 (0.4)	10.46 (1.32–82.77)	0.03
Other††				
Space-occupying brain infarction or edema with clinical deterioration	6 (2.4)	2 (0.8)		
Recurrent ischemic stroke				
Asymptomatic‡‡	58 (23.1)	55 (22.5)		
Symptomatic	17 (6.8)	8 (3.3)		
Major extracranial bleeding	3 (1.2)	0		
Severe anaphylactic reaction	0	1 (0.4)		

* Odds ratios were adjusted for the stratification factors (i.e., age and symptom severity) at randomization.
† The primary safety outcome was analyzed in 244 patients in the alteplase group and in 241 in the placebo group because of loss to follow-up.
‡ The definition of symptomatic intracranial hemorrhage according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS–MOST) was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.
§ The definition according to the European Cooperative Acute Stroke Study (ECASS) II was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death.
¶ The definition according to ECASS III was the same as that in ECASS II, plus the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.
‖ The definition according to the National Institute of Neurological Disorders and Stroke (NINDS) was any new hemorrhage associated with any neurologic deterioration.
** Parenchymal hemorrhage type 2 was defined as an intracerebral hemorrhage that involved more than 30% of the infarcted area with a substantial space-occupying effect or that was remote from the original infarcted area.
†† Other safety outcomes were determined by the safety adjudication committee on the basis of the evaluation of clinical and imaging information. Odds ratios and P values were not calculated for these comparisons.
‡‡ Asymptomatic recurrent stroke was defined as any new lesion on follow-up MRI that was not considered to be a growth of the original stroke lesion.

In summary, the treatment of stroke has improved since 1995, first with the utilization of Alteplase and then with the use of Alteplase and intra-arterial mechanical thrombectomy devices. Currently, the standard of care for treating a stroke is based on time of symptom onset. Despite the literature suggesting that patients with first order, large, intracranial arterial thrombus are best treated with Alteplase and intra-arterial mechanical thrombectomy, the algorithm relating to the standard of care in treating an acute ischemic stroke patient based on timing has not changed despite the advent and utilization of advanced imaging. In using time as the primary factor in the decision of treating acute ischemic stroke, rather than using the available advanced imaging modalities to determine the care of acute ischemic stroke, are clinical practitioners providing the most efficient, cost-effective pathway for treatment of acute ischemic stroke?

Chapter III

METHODS

The decision-making model was built using TreeAge Pro software (Version: 2017; Build-Id: 17.1.1.0-v20170211; I Copyright 1988-2017 TreeAge Software, Inc. All rights reserved.). At each decision-point, which is based on the current algorithm of stroke treatment, [67] outcomes data was inputted based on the major studies associated with treating acute ischemic stroke. The major studies that the outcomes data was taken from are the NINDS trial, the ATLANTIS A and B trials, the ECASS I, II, and III trials, the EPITHET trial, MR CLEAN trial, the EXTEND IA trial, the ESCAPE trial, the REVASCAT trial, and the SWIFT-PRIME trial for the branches associated with the decision to perform CT. For the branches associated with the decision to perform CT/CTA/CTP, the ESCAPE trial, the DAWN trial, DEFUSE III trial, the EXTEND IA TNK, and the WAKE-UP trial was used. The outcome measure for each of the studies was the modified Rankin scale score. Because each study is weighted differently, the weighted averages of the modified Rankin scale score from each of the studies listed above were placed in the decision group (see Data Section for tables). Weighted averages instead of simple averages were used, because each study has a different number of patients and by using the weighted averages each group was not counted equally, preventing the results from being skewed. [93] To arrive at the weighted average the product of each value was

multiplied times its weight; these products were summed; and the sum divided by the weightings ((value 1 * weight 1) + (value 2 * weight 2) + (value 3 * weight 3)….) / (sum of weights)).

The utilities were taken from the most recent study assigning a weight to the modified Rankin scale score [94] and then multiplied by 10 to create the QALYs. The costs associated with each branch of the tree, in both the decision to treat based on CT or the branch for CT/CTA/CTP, were taken from the Centers for Medicare and Medicaid Services 2017 pay fee schedule. Along with the decision-making model, a chart was developed detailing the data inputted into the decision tree. The chart (see Data section) included the costs associated with stroke treatment, the probability of each decision, the outcomes associated with each decision, and the utility assigned for the outcomes reflected in QALYs. After the decision-making model was completed, a cost-effectiveness analysis was performed to determine which decision branch scenario, CT or CT/CTA/CTP, was most cost effective.

3.1 Method of Building the Decision Tree

The decision tree model structure is as follows: The root node is "Stroke", with a decision node of "CT" or "CT/CTA/CTP". The decision node of CT branches into chance nodes following the current standard of care for evaluation and treatment of acute ischemic stroke, which is based on time. [51] The decision node of CT/CTA/CTP branches into chance nodes that are not based on time but are based on evaluation and treatment of patients using advanced imaging. The chance nodes in each decision had probabilities assigned based on historical data of the major stroke trials' weighted averages as previously discussed. (see

Data section for tables of major trials' weighted averages) The cost associated with each chance node was based on the physician fees schedule published by the Centers for Medicare and Medicaid Services. The chance nodes terminated, and at each terminal node there was an accumulated cost of evaluation and treatment, outcomes of functional status at three months with the modified Rankin scale score assigned in the major stroke trials, and a utility in QALY that was based on the published weight of the modified Rankin scale score as previously discussed and multiplied by 10 years of life. (See Outcome section for description of the modified Rankin scale score)

3.2 Outline of the Decision Tree

The following is an outline of the decision tree:

** Note that "c_To"t= the total cost incurred up to that point in the branch.
** Note that " # "is the remainder of patients left over from previous probability totaling 100 (if 15% of patients have hemorrhage, then # is 85% who do not have hemorrhage (ischemic stroke).
** Note that "()" is the moniker used in the decision tree

STROKE

CT Head
Hemorrhage Cannot treat

- probability of hemorrhage on CT (p_Hemorrhage_CT)
- cost (c_Tot + c_HemorrhagicStroke); probability of a modified Rankin scale score 0 through 6 (p_Hem_mRs 0-6).
- terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale scores of patients with hemorrhage to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

No Hemorrhage
probability of ischemic stroke (#)
probability of being eligible for TPA (p_Eligible_TPA_)
cost (c_Tot + c_TPA)
Hemorrhage

- probability of hemorrhage (p_hemorrhage_TPA)

- cost (c_Tot + c_HemorrhagicStroke); probability of a modified Rankin scale score 0 through 6 (p_Hem_mRs 0-6).
- terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale scores of patients with hemorrhage to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

No hemorrhage (#)

- NIH 0 to 6 TPA
  - probability of NIH 0 to 6 TPA (#)
  - cost (c_Tot + c_DRGStrokeCareTPA); probability of modified Rankin scale score 0 to 6 (p_TPA_mRs_0-6)
  - terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale scores of patients with No hemorrhage TPA to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))
- NIH 6 to 42 get CTA/CTP
  - probability NIH 6 to 42 get CTA/CTP (p_CTA_CTP)
  - cost CTA/CTP (c_Tot + c_CTA_CTP)
    - Large Vessel Occlusion TPA
      - probability of Large Vessel Occlusion TPA (p_LVO_After_TPA)
      - cost (c_Tot + c__Thrombectomy
        - Hemorrhage
          - probability of hemorrhage (p_hemorrhage_after TPA_embo)
          - cost (c_Tot + c_HemorrhagicStroke)
          - terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale scores of patients with Large Vessel Occlusion and TPA to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

- No Hemorrhage TPA Thrombectomy
  - probability (#)
  - cost (c_Tot + c_DRGStrokeCareEndo)
  - terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale scores of patients with No Hemorrhage TPA and Thrombectomy to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))
- No Large Vessel Occlusion TPA
  - probability (#)
  - cost (c_tot + c_DRGStrokeCareTPA)
  - terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale scores of patients with No Large Vessel Occlusion TPA to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

CT/CTA/CTP

Hemorrhage Cannot treat

- probability (p_Hemorrhage_CT)
- cost (c_Tot + c_HemorrhagicStroke)
- terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale scores of patients with hemorrhage to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

Small Vessel Occlusion with or without ischemia and infarct treated with TPA

1. probability (p_svo_tpa)
2. cost (c_Tot + c_TPA)
   a. Hemorrhage
      i. probability (p_hemorrhage_TPA)
      ii. cost (c_Tot + c_HemorrhagicStroke)
      iii. terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale score of

patients with hemorrhage to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

b. No Hemorrhage
    i. probability (#)
    ii. cost (c_Tot + c_DRGStrokeCareTPA)
    iii. terminate with total cost (c_Tot) and a utility (u_mRs_0-6) associated with modified Rankin scale score of patients with Small Vessel Occlusion treated with TPA to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

Large Vessel Occlusion with ischemia and infarct treated with Tenecteplase and Angiogram

1. probability (p_LVO_tenectaplace)
2. cost (c_Tot + c_tenectaplace + c_thrombectomy)
    a. Hemorrhage
        i. probability (p_hemorrhage_afterTPA_embo
        ii. cost (c_Tot + c_HemorrhagicStroke)
        iii. terminate with total cost (c_Tot) and a utility score of patients with hemorrhage to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))
    b. No Hemorrhage Tenecteplace Thrombectomy
        i. probability (#)
        ii. cost (c_Tot + c_DRGStrokeCareEndo)
        iii. terminate with total cost (c_Tot) and a utility score of patients treated with Tenecteplase and thrombectomy to give a total in Life Years (LY). (total cost/outcomes in Life Years (LY))

(see the Data section for a chart with descriptors used in the tree, the probabilities, cost and utilities, along with bibliography associated with the data)

3.3 Important Decision Tree Points

Important points on the decision tree are as follows:

1. As previously stated, all the modified Rankin scores (mRs) (see Outcomes section for description of modified Rankin scale score) were weighted averages of the multiple studies associated with outcomes. Certain conditions such as hemorrhage have worse outcomes (higher modified Rankin scale scores) than patients treated successfully with rt-

PA or thrombectomy (lower modified Rankin scale scores). The tables in the Data section show the data from each of the studies and their weighted averages for the groups associated with those studies. (see Study Groups for list of studies associated with the different groups and see Tables 17-22 for the weighted averages)

i. Within these tables, it is important to note that for studies with combined modified Rankin scores, such as the NINDS, ATLANTIS, and DAWN trials, the scores were divided by two and distributed appropriately. For example, if the modified Rankin score of 0-1 was 12, then mRs 0 was allocated as a 6, and mRs 1 was allocated as a 6.

ii. The ATLANTIS A trial that was stopped early did not use modified Rankin scores, but the ATLANTIS B trial which combined the ATLANTIS A and B data did use modified Rankin scores.

iii. There are 2 types of stroke that occur, Hemorrhagic (15%) and Ischemic (85%). [1] The initial diagnosis is based on the radiographic studies. Hemorrhagic strokes have worse outcomes than ischemic strokes, with a much higher percentage of patients having higher modified Rankin scale scores. Patients who do not initially have hemorrhagic strokes and have stroke symptoms are considered ischemic strokes. Patients that undergo treatment for ischemic stroke, whether rt-PA or thrombectomy, are at risk of the ischemic stroke converting into a hemorrhagic stroke. If the patient has a

conversion from ischemic stroke to hemorrhagic stroke and it is considered symptomatic, the patient's outcomes, modified Rankin scale score, and cost of care are then considered the same as if the patient had a hemorrhagic stroke initially. Therefore, in the decision tree there is a branch for hemorrhagic stroke where the patient initially presents with a hemorrhagic stroke on radiographic studies with the outcomes, cost, and utilities associated with hemorrhagic stroke. If the patient has an ischemic stroke initially and then has a conversion to a hemorrhagic stroke, there is a branch after each treatment to signify the percentage of people who had hemorrhagic conversion from their ischemic stroke, with the outcomes, cost and utilities then reverting to be the same as if they had a hemorrhagic stroke initially. Each study published the hemorrhage rates associated with the treatments. In all the studies, all hemorrhages were reported, whether or not the patient had worse symptoms from the hemorrhage, but only the patients that had worsened symptoms were considered in the definition of symptomatic hemorrhage associated with the medication or procedure. Only the symptomatic hemorrhage rates were used in the tables and decision tree. Symptomatic hemorrhage is defined as, "any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and

that was identified as the predominant cause of the neurologic deterioration." [8] The NIHSS score is utilized to evaluate patients with stroke to determine the severity, and predict the outcomes associated with stroke. [70] The patient receives a score of 0–42 that quantifies stroke severity. To be eligible for thrombectomy, a patient must have an NIHSS score greater than 6 indicating a Large Vessel Occlusion. The higher the NIHSS score is the more the brain is affected, and it is also associated with larger vessel strokes or larger hemorrhages.

iv. Once all the data was imported, the normalization function in TreeAge Pro (Version: 2017; Build-Id: 17.1.1.0-v20170211; I Copyright 1988-2017 TreeAge Software, Inc. All rights reserved.) to normalize the probabilities was utilized to equalize all nodes to 1.0 (100%). In none of the studies which the modified Rankin scale scores were taken from did the totals equal 1.0 (100%), because of rounding, and therefore normalization was necessary. The normalization ranged from 0.003 to 0.1 in each section. The normalization function equally distributes the range between all the scores within the group. For example, if there were 7 possible scores (modified Rankin scale score 0 through 6) and the node was equal to 0.9, the remaining 0.1 to equal a total of 1.0 was distributed equally between the 7 scores, i.e., 0.014 was added to each score.

2. In the decision tree node “thrombectomy with no rt-PA” of the current algorithm stroke care (CT branch), it was only the data from the ESCAPE trial that tended towards a low number. This low number could affect the validity of that particular branch.
3. Triangular distributions were allocated as stated previously for: probability of patients eligible for rt-PA (Min: 2%, Likeliest: 11%, Max: 20%, and Override mean: 11%); probability of patients with large vessel occlusion after rt-PA (Min: 1%, Likeliest: 8%, Max: 20%, and Override mean: 8%); probability of patients with Small Vessel Occlusion getting rt-PA (Min: 45%, Likeliest: 60%, Max: 75%, and Override mean: 60%); and probability of patients with large vessel occlusion receiving Tenecteplase (Min: 5%, Likeliest: 25%, Max: 50%, and Override mean: 25%)

3.4 Method for Cost-effectiveness Configuration

A table showing cost effectiveness has been produced (see Results section, Table 24. Cost-Effectiveness Rankings). The definitions relating to the graph are as follows:

1. Category- Undominated means there are only 2 strategies. If there were more than 2 strategies, there would be a dominated strategy that costs more and is least effective.
2. Strategy- The two strategies are CT and CT/CTA/CTP.
3. Cost- This is calculated using the expected value, the weight of the cost for the probability of that outcome occurring. It is the expected value of the cost of

each strategy. The formula for expected value is the summation of all cost multiplied by summation of all the probabilities. In this study, for example if patient has a hemorrhage, EV= (cost of CT + treatment for hemorrhagic stroke care) * (probability of hemorrhage + probability of a modified Rankin scale score of 1)

4. Incremental Cost- The difference between the expected values of CT/CTA/CTP strategy and CT strategy.
5. Effectiveness- The expected value of each strategy is in Life Years (LY).
6. Incremental Effectiveness- The difference in effectiveness of CT/CTA/CTP strategy and the CT strategy.
7. Incremental Cost-Effectiveness Ratio- "An incremental cost-effectiveness ratio is a summary measure representing the economic value of an intervention, compared with an alternative (comparator). It is usually the main output or result of an economic evaluation. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' – for the more expensive therapy vs the alternative. In the UK the QALY is most frequently used as the measure of health effect, enabling ICERs to be compared across disease areas, but in other healthcare systems other measures of health effect may be used. In decision-making, ICERs are most useful when the new intervention is costlier but generates improved health effect. ICERs reported by economic evaluations are compared with a pre-determined threshold (see cost-effectiveness threshold) in

order to decide whether choosing the new intervention is an efficient use of resources." [95] The ICER can be estimated as: ICER= (C1-C0)/(E1-E0), where

C1 and E1 are the cost and effectiveness in the intervention group (CT/CTA/CTP) and C0 and E0 are the cost and effectiveness in the control care group (CT).

8. Net Monetary Benefit- The net monetary benefit (NMB) is,

   "Net monetary benefit (NMB) is a summary statistic that represents the value of an intervention in monetary terms when a willingness-to-pay threshold for a unit of benefit (for example a measure of health outcome or QALY) is known. The use of NMB scales both health outcomes and use of resources to costs, with the result that comparisons without the use of ratios (such as in ICER). NMB is calculated as (incremental benefit x threshold) – incremental cost. Incremental NMB measures the difference in NMB between alternative interventions, a positive incremental NMB indicating that the intervention is cost-effective compared with the alterative at the given willingness-to-pay threshold. In this case the cost to derive the benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit. It is calculated as follows: Net monetary benefit= (E * WTP) – C (E=effectiveness; WTP=willingness-to-pay threshold; C=cost." [96]

9. C/E (Cost divided by the effectiveness)- The average cost-effectiveness for the strategy of cost divided by the effectiveness.

3.5 Method for Monte Carlo Simulation

Following the Cost-effectiveness analysis, a Monte Carlo Simulation (Probabilistic Sensitivity Analysis) was performed. Sensitivity analysis is part of Cost-effectiveness analysis. It determines how the net benefits change if specific parameters deviate from the imputed values, assuming the imputed values are correct. Sensitivity analysis addresses the values that have uncertainty, or if the probability of outcome distributions is not known. The Monte Carlo Simulation (Probabilistic Sensitivity Analysis) was used to perform

10,000 simulation trials, with each trial being independent of the others. Performing these independent simulations allows for a frequency distribution of net benefits. It determines the net present values, the mean and mode, and the net present value range. The net present value is the difference between the present value of cash inflows and the cash outflows over a period. If you have a positive net present value, then the amount of money earned is greater than the amount of money associated with costs. The utility of a Monte Carlo Simulation is associated with the law of large numbers like 10,000 simulations to estimate the mean, median, and range, and will converge on their underlying values. Monte Carlo Simulation was used to show how the variable changes impacted the conclusion.

As previously mentioned, in the Data section of this paper there are tables showing the data that was entered in the decision tree to perform the Cost Effectiveness analysis, and there is also a chart showing Triangular distributions used to perform the Probabilistic Sensitivity Analysis. (See Tables 23) These distributions allow for parameters of minimum, likeliest, and maximum percentages of the variables of uncertainty to be analyzed (Also, see below important points in the decision tree #3 for information about the range in the distribution).

Triangular distributions were used in the Monte Carlo (Probabilistic Sensitivity Analysis) to allow for ranges of probabilities for the following nodes: probability of patients eligible for rt-PA, probability of patients with large vessel occlusion after rt-PA, probability of patients with Small Vessel Occlusion getting rt-PA, and probability of patients with large vessel occlusion receiving Tenecteplase. A triangular distribution is a continuous probability distribution made up of continuous variables or an infinite number of values with lower limits, upper limits, and a mode. The lower limit is less than the upper

limit, and the lower limit is lower than or equal to the mode, while the mode is lower than or equal to the upper limit. The benefit of Triangular distribution is its utility when interpreting three values. Triangular distributions are commonly used as a subjective population description when the relationship of the variables is known but the data is limited. For example, there is uncertainty as to what percentage of patients having large vessel occlusion would be eligible for thrombectomy. There is literature stating between 20% and 33%, but there are few studies which suggest such a population. [88,97] Using Triangular distribution allows one to determine the lower and upper limits of the variable to see how they would impact the conclusion, instead of relying on just a weighted average of the most likely scenario. Beta distributions, the most common distribution used, use a weighted average with most weight given to the most likely scenario, producing a curve that is the mode between the minimum and maximum. Although Beta distributions are considered more accurate than a Triangular distribution, a model with more estimates of the maximum and minimum values and likely outcomes with no specific mean or standard deviation makes the Triangular distributions more useful than using a Beta analysis with a specific mean and standard deviation.[98,99] However, because Beta distribution is considered more accurate a second Monte Carlo Simulation was performed using a Beta distribution with a mean of 0.5 and standard deviation of 0.2 for the same nodes.

In building a decision tree, configuration parameters are imputed prior to building the tree. There are multiple types of calculation methods that can be chosen when developing a decision tree. The calculation method for this decision tree is a Cost-effectiveness calculation. When selecting a Cost-effectiveness calculation, the assignment of cost payoff and effectiveness payoff are designated. Further parameters are assigned

when performing a Cost-effectiveness calculation. Willingness-to-Pay is a parameter that is determined by the author of the decision tree. In this case, the Willingness-to-Pay threshold was set at $50,000.00. This amount was chosen from a historical background. The earliest Willingness-to-Pay dates to the 1970s, when Medicare set the dollar amount of $50,000.00/QALY for patients with end stage renal disease because this was the estimated cost-effectiveness ratio of a patient on dialysis. However, $50,000.00/QALY was not widely used until the 1990s, when multiple publications used multiple ranges from $20,000.00 to $100,000.00/QALY for defining cost-effective care. $50,000.00 eventually became the most common dollar amount used, and because it was used often and was a round number it became the standard amount to use in cost-effective studies. [100] There are many studies suggesting that a higher cost is more suitable based on inflation and especially when the discussion relates to surgical procedures being performed. There is no specific consensus, though, on the dollar amount to be used. In order to be conservative, therefore, and in keeping with the most widely used dollar amount, $50,000.00 was used in this decision tree.

Global discounting is a configuration parameter that can be used in many Cost-effectiveness models. Global discounting was not used in this model because it is most useful when costs are incurred in the present time and the benefit occurs in the distant future, for example vaccinations. [101] The model used here is that the cost is incurred in the present to achieve short-term benefit for the patient. For example, when the patient has an acute ischemic stroke, the cost of acute ischemic stroke evaluation and treatment is incurred at that moment in time. The benefit is improved patient functional status at that time and not in the distant future.

After configuring the parameters, numeric formatting should be performed. Numeric formatting is at the discretion of the configuring author. This model used numeric formatting for the cost with comma separators at the thousands place, with exact numbers, and the currency unit in US dollars, whereas for effectiveness it had exact numbers with two decimal places and trailing zeros, and LY as the units. For example, cost will look like $1,234,567 and effectiveness will look like 1234567.89 LY.

A second analysis was performed to evaluate the modified Rankin scale scores. Because the modified Rankin scale score is the measure used when evaluating the success of treatments associated with stroke and a cost effectiveness model uses QALY (QALY was based on the utility of the individual modified Rankin scale scores multiplied by 10) to determine Life Years, the model was reconfigured, and a second analysis was performed. Instead of using Life Years the model was reconfigured to show not only the cost effectiveness but also the modified Rankin scale scores to determine if there were differences in the individual scores of each scenario time, CT, and advanced imaging, CT/CTA/CTP.

3.6 Data

As mentioned at the beginning of the previous (Methods) section, the weighted averages of the major studies associated with stroke care are given below as Tables 17 to 21. The categories are weighted averages of: Table 17. No treatment; Table 18. Treatment with rt-PA; Table 19. Thrombectomy with rt-PA; Table 20. Thrombectomy with no rt-PA; Table 21. Treatment with rt-PA based on advanced imaging; Table 22. Showing all the data input into the tree with annotation and the distributions; Table 23. Showing the Monte

Carlo distributions (Probability Sensitivity Analysis); and Figure 4. is a picture of the decision tree.

Table 17. Weighted Averages of “No Treatment”.

			modified Rankin scale score																
			0		1		2		3		4		5		6		Total		
		PTs	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	Pt %	Pt Count	Bleed
	NINDS	160	13.0%	20.80	13.0%	20.80	12.5%	20.00	12.5%	20.00	13.5%	21.60	13.5%	21.60	21.0%	33.60	99.0%	158.40	0.6%
	ECASSII	391	17.9%	69.99	18.7%	73.12	9.5%	37.15	18.4%	71.94	19.9%	77.81	5.1%	19.94	10.5%	41.06	100.0%	391.00	3.4%
	ECASSII	355	22.3%	79.17	23.1%	82.01	16.9%	60.00	11.8%	41.89	14.9%	52.90	4.2%	14.91	6.8%	24.14	100.0%	355.00	0.2%
	EPITHET	49	6.0%	2.94	18.0%	8.82	16.0%	7.84	14.0%	6.86	24.0%	11.76	6.0%	2.94	7.0%	3.43	91.0%	44.59	0.0%
	ATL B	275	20.0%	55.00	20.0%	55.00	14.5%	39.88	14.5%	39.88	11.5%	31.63	11.5%	31.63	8.0%	22.00	100.0%	275.00	1.1%
	Total	1230	18.5%	227.89	19.5%	239.74	13.4%	164.86	14.7%	180.57	15.9%	195.69	7.4%	91.02	10.1%	124.23	99.5%	1,223.99	1.5%

No treatment

Table 18. Weighted Averages of “Treatment with rt-PA”.

			modified Rankin scale score																
			0		1		2		3		4		5		6		Total		
		PTs	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	Pt %	Pt Count	Bleed
	NINDS	160	19.5%	31.20	19.5%	31.20	10.5%	16.80	10.5%	16.80	11.5%	18.40	11.5%	18.40	17.0%	27.20	100.0%	160.00	6.4%
	ECASSII	409	21.8%	89.16	18.6%	76.07	13.9%	56.85	14.9%	60.94	15.9%	65.03	4.6%	18.81	10.3%	42.13	100.0%	409.00	8.8%
	ECASSIII	375	29.1%	109.13	25.9%	97.13	14.4%	54.00	10.1%	37.88	8.8%	33.00	5.6%	21.00	6.1%	22.88	100.0%	375.00	2.4%
	EPITHET	51	12.0%	6.12	24.0%	12.24	8.0%	4.08	12.0%	6.12	10.0%	5.10	10.0%	5.10	25.0%	12.75	101.0%	51.51	7.7%
	ATL A/B	272	21.0%	57.12	21.0%	57.12	12.5%	34.00	12.5%	34.00	10.5%	28.56	10.5%	28.56	11.0%	29.92	99.0%	269.28	7.0%
	Total	1267	23.1%	292.73	21.6%	273.76	13.1%	165.73	12.3%	155.74	11.8%	150.09	7.3%	91.87	10.6%	134.87	99.8%	1,264.79	6.2%

Treatment with rt-PA

Table 19. Weight Averages of “Thrombectomy with rt-PA”.

			modified Rankin scale score																
			0		1		2		3		4		5		6		Total		
		PTs	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	Pt %	Pt Count	Bleed
	MR CLEAN	231	3.0%	6.93	9.0%	20.79	21.0%	48.51	18.0%	41.58	22.0%	50.82	6.0%	13.86	21.0%	48.51	100.0%	231.00	7.7%
	Extend IA	35	26.0%	9.10	26.0%	9.10	20.0%	7.00	17.0%	5.95	3.0%	1.05	0.0%	-	9.0%	3.15	101.0%	35.35	0.0%
	Escape	164	15.0%	24.60	21.0%	34.44	18.0%	29.52	16.0%	26.24	13.0%	21.32	7.0%	11.48	10.0%	16.40	100.0%	164.00	3.6%
	Revascat	103	6.8%	7.00	17.5%	18.03	19.4%	19.98	18.4%	18.95	7.8%	8.03	11.7%	12.05	18.4%	18.95	100.0%	103.00	1.9%
	Swift-Prim	98	17.0%	16.66	26.0%	25.48	17.0%	16.66	12.0%	11.76	15.0%	14.70	12.0%	11.76	0.0%	-	99.0%	97.02	0.0%
	Total	631	10.2%	64.29	17.1%	107.84	19.3%	121.67	16.6%	104.48	15.2%	95.92	7.8%	49.15	13.8%	87.01	99.9%	630.37	4.1%

Thrombectomy with rt-PA

Table 20. Weighted Averages of “Thrombectomy with no rt-PA”.

			modified Rankin scale score																
			0		1		2		3		4		5		6		Total		
		PTs	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	Pt %	Pt Count	Bleed
	Escape	45	20.0%	9.00	20.0%	9.00	18.0%	8.10	13.0%	5.85	2.0%	0.90	7.0%	3.15	20.0%	9.00	100.0%	45.00	0.0%
	DAWN	107	9.0%	9.63	22.0%	23.54	17.0%	18.19	13.0%	13.91	13.0%	13.91	12.5%	13.38	12.5%	13.38	99.0%	105.93	6.0%
	DEFUSE 3	92	10.0%	9.20	16.0%	14.72	18.0%	16.56	15.0%	13.80	18.0%	16.56	8.0%	7.36	14.0%	12.88	99.0%	91.08	7.0%
	Total	244	11.4%	27.83	19.4%	47.26	17.6%	42.85	13.8%	33.56	12.9%	31.37	9.8%	23.89	14.4%	35.26	99.2%	242.01	5.3%

Thrombectomy with no rt-PA

Table 21. Treatment with rt-PA based on Advanced Imaging.

			modified Rankin scale score																
			0		1		2		3		4		5		6		Total		
		PTs	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	% of PT	Pt Count	Pt %	Pt Count	Bleed
	Wake Up	251	21.0%		32.0%		21.0%		12.0%		7.0%		2.0%		4.0%				10.0%

Treatment with rt-PA based on Advanced Imaging

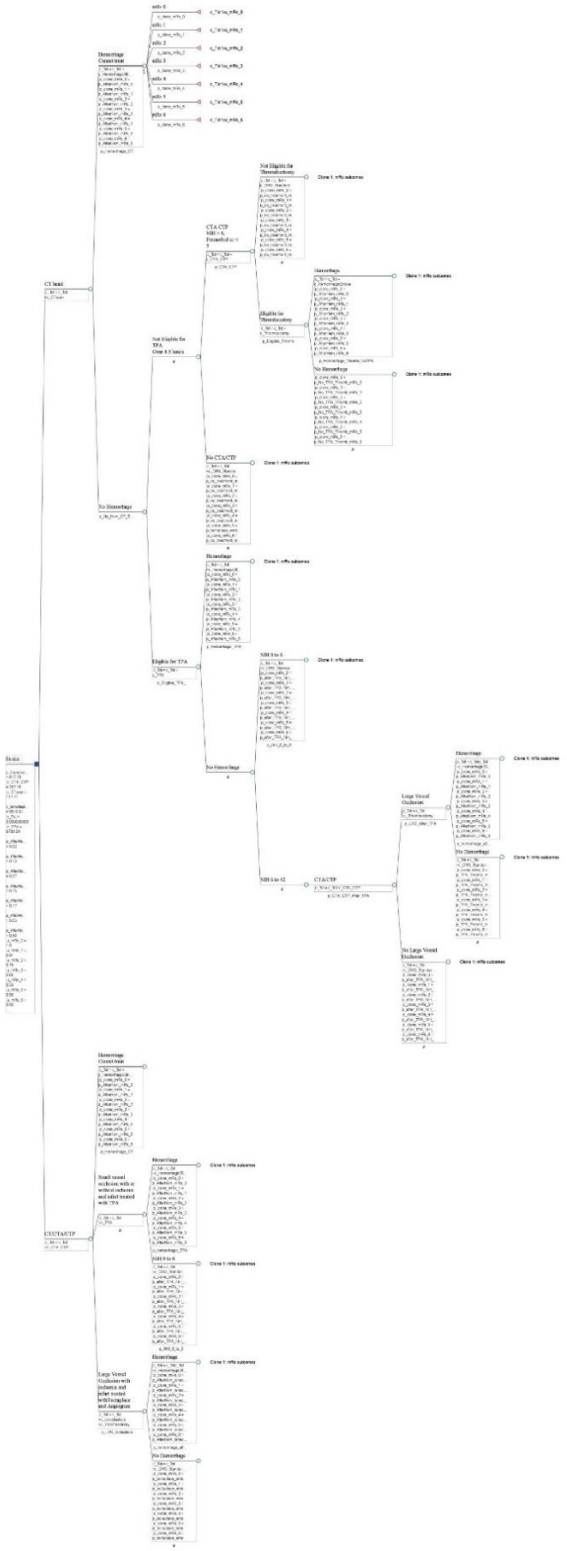
Table 22. Data with Bibliographic Annotation and Distributions.

Name in tree	Description	Comment	Cost or Probability
c_CTA_CTP	cost of CTA/CTP	(Centers for Medicare and Medicaid Services, 2018)	$1192.32
c_CTscan	cost of CT	(Centers for Medicare and Medicaid Services, 2018)	$236.16
c_DRGStrokeCareEndo	how much a hospital will receive for treating a stroke with thrombectomy	(Centers for Medicare and Medicaid Services, 2017)	$35539.00
c_DRGStrokeCareNoTx	how much a hosptial will receive for treating a stroke with no treatment	(Centers for Medicare and Medicaid Services, 2017)	$8082.00
c_DRGStrokeCareTPA	how much a hospital will receive for treating a stroke with rt-PA	(Centers for Medicare and Medicaid Services, 2017)	$14761.00
c_HemorrhagicStroke	cost of treating a hemorrhagic stroke	(Centers for Medicare and Medicaid Services, 2017)	$68903.00
c_tenectaplace	cost of tenectaplase	Pharmacy Department at Jersey Shore University Medical Center, Neptune, NJ 07753	$5516.61
c_Thrombectomy	cost of thrombectomy	(Centers for Medicare and Medicaid Services, 2018)	$1634.38
c_Tot	additditive cost to this point in the current branch		$0
c_TPA	cost or rt-PA	Pharmacy Department at Jersey Shore University Medical Center, Neptune, NJ 07753	$6700.00
p_Cerebral_Angiogram	probability of having a cerebral angiogram	(Quintiles QI, 2015)	8%
p_clone_mRs_0	payoffs and utilities	clone of the payoff and utilities	
p_clone_mRs_1	payoffs and utilities	clone of the payoff and utilities	
p_clone_mRs_2	payoffs and utilities	clone of the payoff and utilities	
p_clone_mRs_3	payoffs and utilities	clone of the payoff and utilities	
p_clone_mRs_4	payoffs and utilities	clone of the payoff and utilities	
p_clone_mRs_5	payoffs and utilities	clone of the payoff and utilities	
p_clone_mRs_6	payoffs and utilities	clone of the payoff and utilities	
p_CTA_CTP	probability of having a CTA/CTP	(Beumer & et al., 2016)	30%
p_Eligible_Thromb	probability of being eligible for thrombectomy	(Quintiles QI, 2015)	13%
p_Eligible_TPA_	probability of being eligible for rt-PA	(Quintiles QI, 2015)	dist_p_Eligible_TPA
p_Hem_mRs_0	probability of a modified Rankin scale score 0 if there was a hemorrhage	(Hemphill, Farrant, & Neill, 2009)	2%
p_Hem_mRs_1	probability of a modified Rankin scale score 1 if there was a hemorrhage	(Hemphill, Farrant, & Neill, 2009)	12%
p_Hem_mRs_2	probability of a modified Rankin scale score 2 if there was a hemorrhage	(Hemphill, Farrant, & Neill, 2009)	7%
p_Hem_mRs_3	probability of a modified Rankin scale score 3 if there was a hemorrhage	(Hemphill, Farrant, & Neill, 2009)	13%
p_Hem_mRs_4	probability of a modified Rankin scale score 4 if there was a hemorrhage	(Hemphill, Farrant, & Neill, 2009)	17%
p_Hem_mRs_5	probability of a modified Rankin scale score 5 if there was a hemorrhage	(Hemphill, Farrant, & Neill, 2009)	3%
p_Hem_mRs_6	probability of a modified Rankin scale score 6 if there was a hemorrhage	(Hemphill, Farrant, & Neill, 2009)	46%
p_hemorrhage_afterTPA_embo	probability of a hemorrhage after having rt-PA and thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	4.1%
p_Hemorrhage_CT	probability of having a hemorrhage on CT	(Quintiles QI, 2015)	15.41%
p_hemorrhage_Tenecteplace_Thromb	probability of having a hemorrhage with Tenecteplase and thrombectomy	(Campbell et al., 2018)	6%
p_Hemorrhage_Thromb_NoTPA	probability of having a hemorrhage with Tenecteplase and notpaectomy	(Goyal et al., 2015)	0.99%
p_hemorrhagic_TPA	probability of having a hemorrhage with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	6%
p_LVO_After_TPA	probability of having a large vessel occlusion with rt-PA	(Quintiles QI, 2015)	dist_p_LVO_After_TPA
p_LVO_tectaplace	probability of having a large vessel occlusion with Tenecteplase	(Thomalla et al., 2018)	dis_LVO_tenect
p_No_Hem_CT_StandardStrokeCare	probability of not having hemorrhage on CT scan	(Quintiles QI, 2015)	75%
p_no_treatment_mRs_0	probability of a modified Rankin scale score 0 if there was no treatment	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	18.4%
p_no_treatment_mRs_1	probability of a modified Rankin scale score 1 if there was no treatment	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	19.4%
p_no_treatment_mRs_2	probability of a modified Rankin scale score 2 if there was no treatment	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	13.3%
p_no_treatment_mRs_3	probability of a modified Rankin scale score 3 if there was no treatment	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	14.6%
p_no_treatment_mRs_4	probability of a modified Rankin scale score 4 if there was no treatment	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	15.9%
p_no_treatment_mRs_5	probability of a modified Rankin scale score 5 if there was no treatment	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	08.3%
p_no_treatment_mRs_6	probability of a modified Rankin scale score 6 if there was no treatment	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	10.1%
p_NoTPA_Thromb_mRs_0	probability of a modified Rankin scale score 0 if no rt-PA and with thrombectomy	(Goyal et al., 2015)	20%
p_NoTPA_Thromb_mRs_1	probability of a modified Rankin scale score 1 if no rt-PA and with thrombectomy	(Goyal et al., 2015)	20%
p_NoTPA_Thromb_mRs_2	probability of a modified Rankin scale score 2 if no rt-PA and with thrombectomy	(Goyal et al., 2015)	18%
p_NoTPA_Thromb_mRs_3	probability of a modified Rankin scale score 3 if no rt-PA and with thrombectomy	(Goyal et al., 2015)	13%
p_NoTPA_Thromb_mRs_4	probability of a modified Rankin scale score 4 if no rt-PA and with thrombectomy	(Goyal et al., 2015)	2%
p_NoTPA_Thromb_mRs_5	probability of a modified Rankin scale score 5 if no rt-PA and with thrombectomy	(Goyal et al., 2015)	7%
p_NoTPA_Thromb_mRs_6	probability of a modified Rankin scale score 6 if no rt-PA and with thrombectomy	(Goyal et al., 2015)	20%
p_svo_tpa	probability of having a small vessel occlusion and having rt-PA		dis_svo_tpa
p_SVO_with_ischemia_infarct	probability of having a small vessel occlusion and having infarct	(Beumer & et al., 2016; Thomalla et al., 2018)	75%
p_tenectaplace_embo_mRs_0	probability of a modified Rankin scale score 0 with tenecteplase and thrombectomy	(Campbell et al., 2018)	26%
p_tenectaplace_embo_mRs_1	probability of a modified Rankin scale score 1 with tenecteplase and thrombectomy	(Campbell et al., 2018)	21%
p_tenectaplace_embo_mRs_2	probability of a modified Rankin scale score 2 with tenecteplase and thrombectomy	(Campbell et al., 2018)	14%
p_tenectaplace_embo_mRs_3	probability of a modified Rankin scale score 3 with tenecteplase and thrombectomy	(Campbell et al., 2018)	14%
p_tenectaplace_embo_mRs_4	probability of a modified Rankin scale score 4 with tenecteplase and thrombectomy	(Campbell et al., 2018)	8%
p_tenectaplace_embo_mRs_5	probability of a modified Rankin scale score 5 with tenecteplase and thrombectomy	(Campbell et al., 2018)	6%
p_tenectaplace_embo_mRs_6	probability of a modified Rankin scale score 6 with tenecteplase and thrombectomy	(Campbell et al., 2018)	10%
p_TPA_mRs_0	probability of a modified Rankin scale score 0 with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	23.8%
p_TPA_mRs_1	probability of a modified Rankin scale score 1 with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	22.3%
p_TPA_mRs_2	probability of a modified Rankin scale score 2 with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	13.5%
p_TPA_mRs_3	probability of a modified Rankin scale score 3 with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	12.7%
p_TPA_mRs_4_	probability of a modified Rankin scale score 4 with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	12.2%
p_TPA_mRs_5	probability of a modified Rankin scale score 5 with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	7.5%
p_TPA_mRs_6	probability of a modified Rankin scale score 6 with rt-PA	(Clark et al., 1999; Davis et al., 2008; Hacke et al., 1998; Hacke et al., 2008; NINDS tPA Study Group, 1995)	1.1%
p_TPA_Thromb_mRs_0	probability of a modified Rankin scale score 0 with thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	10.2%
p_TPA_Thromb_mRs_1	probability of a modified Rankin scale score 1 with thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	17.1%
p_TPA_Thromb_mRs_2	probability of a modified Rankin scale score 2 with thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	19.3%
p_TPA_Thromb_mRs_3	probability of a modified Rankin scale score 3 with thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	16.6%
p_TPA_Thromb_mRs_4	probability of a modified Rankin scale score 4 with thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	15.2%
p_TPA_Thromb_mRs_5	probability of a modified Rankin scale score 5 with thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	7.8%
p_TPA_Thromb_mRs_6	probability of a modified Rankin scale score 6 with thrombectomy	(Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Jovin et al., 2015; Saver et al., 2015)	13.8%
u_mRs_0	utility of modified Rankin scale score 0	(Chaisinanunkul et al., 2015)	1.0*10
u_mRs_1	utility of modified Rankin scale score 1	(Chaisinanunkul et al., 2015)	.91*10
u_mRs_2	utility of modified Rankin scale score 2	(Chaisinanunkul et al., 2015)	.76*10
u_mRs_3	utility of modified Rankin scale score 3	(Chaisinanunkul et al., 2015)	.65*10
u_mRs_4	utility of modified Rankin scale score 4	(Chaisinanunkul et al., 2015)	.33*10
u_mRs_5	utility of modified Rankin scale score 5	(Chaisinanunkul et al., 2015)	0.00*10
u_mRs_6	utility of modified Rankin scale score 6	(Chaisinanunkul et al., 2015)	0.00*10

Index	Type	Name	Description	Minimum	Likeliest	Maximum
1	Triangular	dis_LVO_tenect	Probability of Large Vessel Occlusion with tenecteplace	5%	25%	50%
2	Triangular	dis_svo_tpa	Probability of Small Vessel Occlusion with TPA	45%	60%	75%
3	Triangular	dist_p_Eligible_TPA	Probability of Patients Eligible for TPA	2%	11%	20%
4	Triangular	dist_p_LVO_After_TPA	Probability of Patients with Large Vessel Occlusion after TPA	1%	8%	20%

Index	Type	Sampling Ra...	Name
1	Beta	EV	dis_LVO_tenect
2	Beta	EV	dis_svo_tpa
3	Beta	EV	dist_p_Eligibl...
4	Beta	EV	dist_p_LVO_A...

Figure 4. Decision Tree

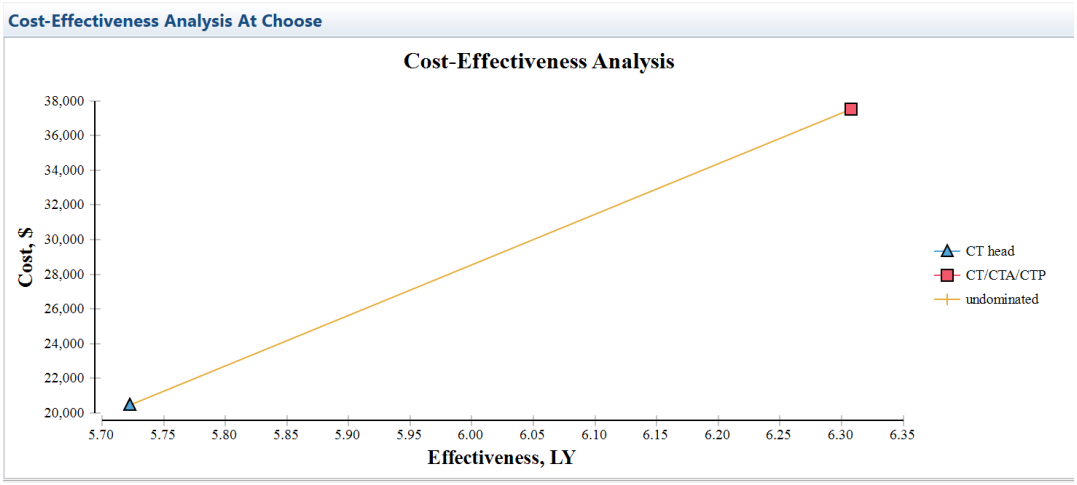


Chapter IV

RESULTS

4.1 The Cost-effectiveness Analysis with Triangular Distribution

The cost-effectiveness analysis as depicted below in Graph 1 shows the cost-effectiveness frontier as the yellow line, with the, CT head, (blue triangle) being the scenario based on time, where cost is less and the effectiveness also is less compared to the other scenario. The CT/CTA/CTP (red square) is the scenario based on advanced imaging, where cost is increased but effectiveness also is increased compared to the other scenario.



Graph 1. Cost-effectiveness Analysis

4.2 The Cost-effectiveness Ranking with Triangular Distribution

The cost-effectiveness ranking is depicted in Table 23 below. Column 1, **Category**, shows undominated strategies, which means neither of the strategies is more nor less cost effective (dominance occurs only when there are more than two strategies). Column 2, **Strategy**, shows the two strategies—scenario based on time, CT vs the scenario base on advanced imaging, CT/CTA/CTP. Column 3, **Cost**, ($20,452.00 for CT vs $37,502.00 for CT/CTA/CTP) shows the cost of each strategy with the expected value listed in US dollars. Column 4, **Incremental Cost**, ($17,049.00) shows the difference between the two strategies—the scenario based on time, CT vs the scenario based on advanced imaging, CT/CTA/CTP—in US dollars. Column 5, **Effectiveness** (5.72 LY for CT vs 6.31 LY for CT/CTA/CTP), is the expected value in life years. Column 6, **Increase in Effectiveness** (0.58 LY), shows the increase in effectiveness between the two strategies—the scenario based on time CT vs the scenario based on advanced imaging CT/CTA/CTP—in life years. Column 7, **Incremental Cost-Effectiveness Ratio (ICER)** ($29,149.00), shows incremental cost and effectiveness values. It measures how much we pay for each additional unit of effectiveness (Life Years) in order to move to the more effective treatment (increasing cost/increasing effectiveness). Comparing the ICER to the willingness-to-pay ($50,000.00), with the willingness-to-pay being the limit to how much we are willing to pay for an additional unit of effectiveness, the decision can be made as to whether we are willing to pay for the purposed strategy (scenario based on advanced imaging, CT/CTA/CTP). Column 8, **Net Monetary Benefit (NMB)** ($265,677.00 for CT vs $277,873.00 for CT/CTA/CTP), helps to determine which strategy to suggest by showing the calculation of the combination of willingness-to-pay, cost, and effectiveness

into a single measurement. The greater the net monetary benefit, the more cost-effective the strategy. (see **Method for Cost-effectiveness Configuration** section for formula of NMB)

Column 9, **Cost/Effectiveness** ($3,574.00 for CT vs $5,946.00 for CT/CTA/CTP), shows the cost per unit of effectiveness. The higher the C/E the more cost-effective the strategy.

In the table, the ICER is $29,149.00 and is less than the willingness-to-pay ($50,000.00), allowing recommendation of the use of the scenario based on advanced imaging, CT/CTA/CTP, because it is within the willingness-to-pay threshold. In addition, both NMB and C/E are higher, which shows that the strategy is more cost-effective.

Table 23. Cost-Effectiveness Rankings

Cost-Effectiveness Rankings

Category	Strategy	Cost	Incr Cost	Eff	Incr eff	Incr C/E (ICER)	NMB	C/E
Excluding dominated								
undominated	CT head	20,452		5.72			265,677	3574
undominated	CT/CTA/CTP	37,502	17,049	6.31	0.58	29149	277,873	5946
All								
undominated	CT head	20,452		5.72			265,677	3574
undominated	CT/CTA/CTP	37,502	17,049	6.31	0.58	29149	277,873	5946
All referencing common baseline								
undominated	CT head	20,452		5.72			265,677	3574
undominated	CT/CTA/CTP	37,502	17,049	6.31	0.58	29149	277,873	5946
All by Increasing effectiveness								
undominated	CT head	20,452		5.72			265,677	3574
undominated	CT/CTA/CTP	37,502		6.31			277,873	5946

4.3 The Cost-effectiveness Ranking with Beta Distribution

As stated in the method section a second cost effectiveness analysis was performed with a Beta Distribution. There were differences in the results. The Categories and the Strategies remained the same. The Cost for both strategies increased with the scenario based on time, CT and the scenario based on advanced imaging, CT/CTA/CTP in the Beta Distribution compared to the Triangular Distribution models (CT scenario, $26,920.00 in the Beta Distribution compared to $20,452.00 in the Triangular Distribution, and for the CT/CTA/CTP scenario $40,185.00 for the Beta Distribution compared to $37,502.00 for the Triangular Distribution). This caused the Incremental Cost to be $13,265.00 in the Beta Distribution compared to the $17,049.00 in the Triangular Distribution. The Effectiveness increased in the Beta Distribution for the two scenarios (CT scenario, 5.90 in the Beta Distribution compared to 5.72 in the Triangular Distribution, and for the CT/CTA/CTP scenario 6.35 in the Beta Distribution compared to 6.31 in the Triangular Distribution). The Incremental Effectiveness decreased to 0.44 in the Beta Distribution compared to 0.58 in the Triangular Distribution. The Incremental Cost Effectiveness Ratio (ICER) increased in the Beta Distribution, $29,971.00, compared to $29,149.00 in the Triangular Distribution. The Net Monetary Benefit (NMB) increased in the Beta distribution in the CT scenario and decreased in the CT/CTA/CTP scenario (CT scenario, $268,246.00 in the Beta Distribution compared to $265,677.00 in the Triangular Distribution, and for the CT/CTA/CTP scenario $277,111.00 in the Beta Distribution compared to $277,873.00 in the Triangular Distribution). The Cost/Effectiveness increased in the Beta Distribution for both scenarios (CT scenario, $4,560 in the Beta Distribution compared to $3,574.00 in the

Triangular Distribution, and for the CT/CTA/CTP scenario $6,332.00 in the Beta Distribution and $5,946.00 in the Triangular Distribution). (See **Appendix A** for Beta Distribution charts and tables.)

4.4 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was performed. A probabilistic sensitivity analysis was run to measure the overall impact of combined uncertainty on model outcome. Uncertainty related to multiple parameters and analysis of the model under different data scenarios based on different values of the parameters was carried out to see if the recalculations came up with the same conclusion as the primary base case analysis—the more the similarity the greater the confidence. (See Methods section, Important points in decision tree, #4, for details of distribution and areas of uncertainty).

The Monte Carlo Summary Text Report, Table 24 below, shows the statistical analysis data that was used in developing the Acceptability Curves and Scatter Plots.

Table 24. Monte Carlo Summary Text Report.

Monte Carlo Summary Text Report

Attribute	Statistic	CT head	CT/CTA/CTP
Cost	Mean	20,468	39,767
Cost	Std Deviation	506	2,811
Cost	Minimum	19,241	34,519
Cost	2.5%	19,504	36,021
Cost	10%	19,780	36,847
Cost	Median	20,472	39,074
Cost	90%	21,148	43,775
Cost	97.5%	21,425	46,888
Cost	Maximum	21,718	52,240
Cost	Sum	204,676,672	397,672,712
Cost	Size (n)	10,000	10,000
Cost	Variance	255,601	7,901,052
Cost	Variance/Size	26	790
Cost	SQRT[Variance/Size]	5	28
Eff	Mean	5.72	6.19
Eff	Std Deviation	0.02	0.17
Eff	Minimum	5.66	5.08
Eff	2.5%	5.68	5.76
Eff	10%	5.69	5.97
Eff	Median	5.72	6.24
Eff	90%	5.76	6.35
Eff	97.5%	5.77	6.39
Eff	Maximum	5.79	6.43
Eff	Sum	57220.82	61928.71
Eff	Size (n)	10000.00	10000.00
Eff	Variance	0.00	0.03
Eff	Variance/Size	0.00	0.00
Eff	SQRT[Variance/Size]	0.00	0.00
NMB	Mean	265,636	269,876
NMB	Std Deviation	739	10,700
NMB	Minimum	263,870	201,730
NMB	2.5%	264,245	241,876
NMB	10%	264,640	254,931

NMB	Mean	265,636	269,876
NMB	Std Deviation	739	10,700
NMB	Minimum	263,870	201,730
NMB	2.5%	264,245	241,876
NMB	10%	264,640	254,931
NMB	Median	265,638	272,972
NMB	90%	266,631	280,132
NMB	97.5%	267,051	282,035
NMB	Maximum	267,727	284,349
NMB	Sum	2,656,364,351	2,698,762,895
NMB	Size (n)	10,000	10,000
NMB	Variance	545,807	114,494,835
NMB	Variance/Size	55	11,449
NMB	SQRT[Variance/Size]	7	107

4.5 Monte Carlo Simulation Report

The Monte Carlo Simulation Report (Table 25), the CE Acceptability Curve (Graph 2), and the Acceptability at Willingness-to-Pay (Graph 3) show the following results. The Monte Carlo Simulation Report is the raw data for the graphs. The CE Acceptability Curve shows the Willingness-to-Pay (x axis) and Iterations of Cost-Effectiveness (y axis). The curve shows that at a willingness-to-pay of less than $30,000.00, it is more cost effective to use the strategy of the scenario based on time, CT (73.2% CT vs 26.8% CT/CTA/CTP). At $35,000.00, the cost effectiveness starts to change and is close to equal, still favoring the scenario based on time, CT, over the scenario based on advanced imaging, CT/CTA/CTP (53.2% CT vs 46.7% CT/CTA/CTP). At $40,000.00, the cost effectiveness changes to favor the scenario based on advanced imaging, CT/CTA/CTP (41.0% CT vs 59.0%, CT/CTA/CTP). At the willingness-to-Pay threshold of $50,000.00, the scenario based on advanced imaging, CT/CTA/CTP is favored significantly (27.0% CT vs 73.4% CT/CTA/CTP) as seen in the CE Acceptability Curve and the Acceptability at Willingness-to-Pay graphs.

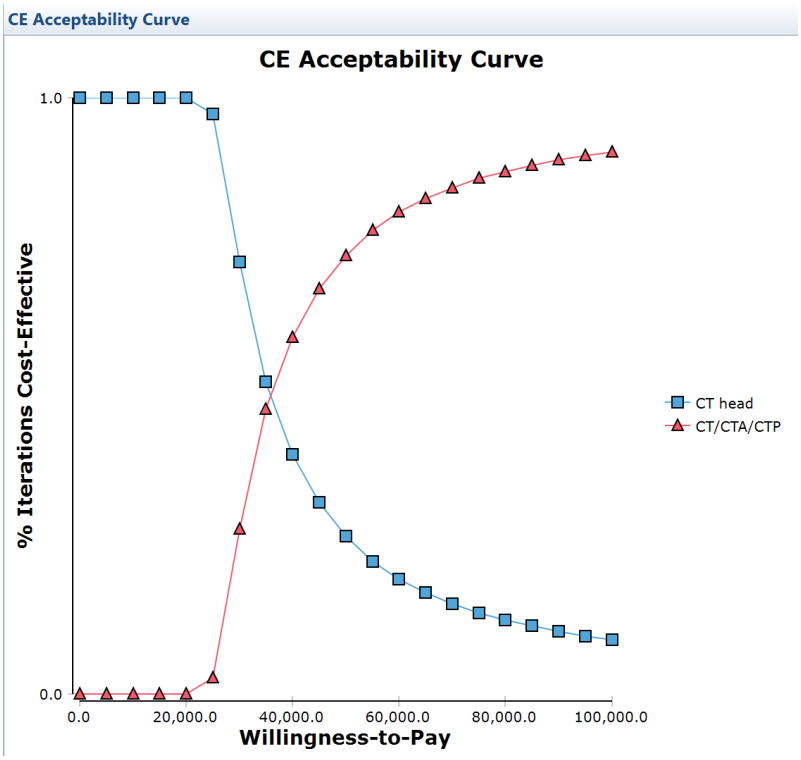
In the Beta Distribution Monte Carlo Simulation Report (See **Appendix A** for charts and tables) the results were very similar. As an example, The Acceptability at Willingness-to-Pay graph again favored the scenario based on advanced imaging, CT/CTA/CTP (21.47% CT vs 78.53%).

Table 25. Monte Carlo Simulation Report.

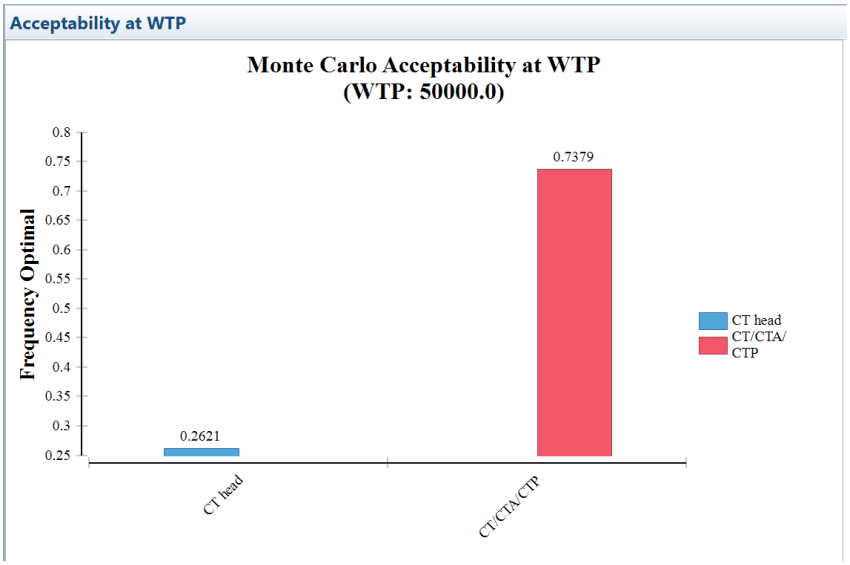
Monte Carlo Simulation Report

WEIGHT	STRATEGY	STRATEGYNAME	ACCEPTABILITY
0	0	CT head	1
0	1	CT/CTA/CTP	0
5000	0	CT head	1
5000	1	CT/CTA/CTP	0
10000	0	CT head	1
10000	1	CT/CTA/CTP	0
15000	0	CT head	1
15000	1	CT/CTA/CTP	0
20000	0	CT head	1
20000	1	CT/CTA/CTP	0
25000	0	CT head	0.9726
25000	1	CT/CTA/CTP	0.0274
30000	0	CT head	0.7321
30000	1	CT/CTA/CTP	0.2679
35000	0	CT head	0.5328
35000	1	CT/CTA/CTP	0.4672
40000	0	CT head	0.4103
40000	1	CT/CTA/CTP	0.5897
45000	0	CT head	0.3247
45000	1	CT/CTA/CTP	0.6753
50000	0	CT head	0.2663
50000	1	CT/CTA/CTP	0.7337
55000	0	CT head	0.2269
55000	1	CT/CTA/CTP	0.7731
60000	0	CT head	0.1939
60000	1	CT/CTA/CTP	0.8061
65000	0	CT head	0.1707
65000	1	CT/CTA/CTP	0.8293
70000	0	CT head	0.1506
70000	1	CT/CTA/CTP	0.8494
75000	0	CT head	0.1362
75000	1	CT/CTA/CTP	0.8638
80000	0	CT head	0.1238
80000	1	CT/CTA/CTP	0.8762
85000	0	CT head	0.1122
85000	1	CT/CTA/CTP	0.8878
90000	0	CT head	0.1037
90000	1	CT/CTA/CTP	0.8963
95000	0	CT head	0.0969
95000	1	CT/CTA/CTP	0.9031
100000	0	CT head	0.0882
100000	1	CT/CTA/CTP	0.9118

Graph 2. CE Acceptability Curve.



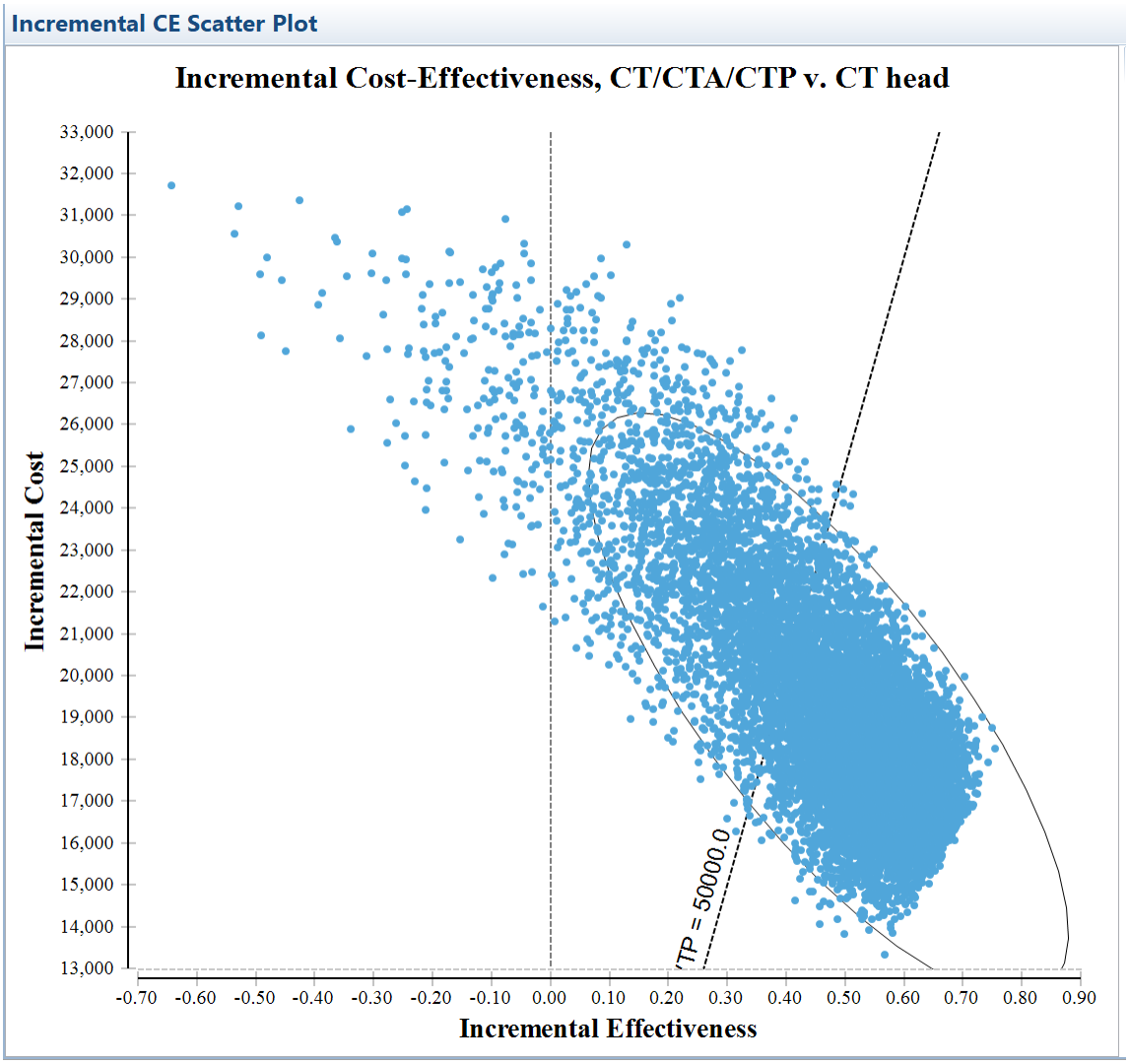
Graph 3. Acceptability at Willingness-to-Pay



4.6 Incremental CE Scatter Plot

The Incremental CE Scatter Plot (Graph 4) shows a Willingness-to-Pay of $50,000 with an iteration range of 1 to 10,000, comparing the scenario based on advanced imaging, CT/CTA/CTP, to the scenario based on time, CT (the more expensive scenario compared to the less expensive scenario). The scatter plot shows that the incremental cost is always positive, because the scenario based on advanced imaging, CT/CTA/CTP, is always more expensive than the scenario based on time, CT. However, it is not always more effective, because some of the iterations (dots) are to the left of the zero-line, showing that the scenario based on time, CT, would be the preferred scenario unlike what is suggested by the result of the reference/base case (the Cost-effectiveness analysis above is considered the base case that shows the scenario based on advanced imaging to be more cost-effective than the scenario based on time). The true dividing line is the Willingness-to-Pay line. All the iterations to the right and below the line have positive ICERs, but are less than the Willingness-to-Pay, favoring the scenario based on advanced imaging, CT/CTA/CTP, and thereby confirming the reference/base case. The iterations to the left of the Willingness-to-Pay line and right of the zero-line have positive ICERS but are less effective and have a high cost, which confirms that the scenario based on time, CT, is better and the reference/base case is not favored.

Graph 4. Incremental CE Scatter Plot.



4.7 Incremental CE Plot Report

The Incremental CE Plot Report (Table 26) shows the data behind the Incremental CE Scatter Plot. The Incremental CE Plot Report shows that the scenario based on advanced imaging, CT/CTA/CTP, is favored because 73.48% of the 10,000 trials had an ICER less than $50,000.00, whereas 24.57% did not favor the scenario based on advanced

imaging, CT/CTA/CTP, because the ICER was greater than $50,000.00, and 1.95% had more effective treatment with the scenario based on time, CT, than the scenario based on advanced imaging, CT/CTA/CTP.

Table 26. Incremental CE Plot Report.

Incremental CE Plot Report

COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	0	0
C2	I	IE>0	IC>0	ICER<50000.0	7,348	0.7348
C3	III	IE<0	IC<0	ICER>50000.0	0	0
C4	I	IE>0	IC>0	ICER>50000.0	2,457	0.2457
C5	III	IE<0	IC<0	ICER<50000.0	0	0
C6	II	IE<0	IC>0	Inferior	195	0.0195
Indiff	origin	IE=0	IC=0	0/0	0	0

4.8 Analysis with modified Rankin scale Scores

The outcome in the results was based on life years (LY). When performing a cost effectiveness model, it represents the increase in the quality-adjusted life years (QALY), a generic measure of the burden of a disease. A second analysis was performed (Table 27) showing the base case using the modified Rankin scale (mRs) for the outcomes instead of life years (LY). This was performed to break down the comparison of the two scenarios, time and advanced imaging, according to the patient's functional status. As is evident from Table 31, the base case shows that the advanced imaging scenario has better outcomes. The patients with outcomes of no or low disability favored the scenario of advanced imaging, CT/CTA/CTP, where patients with an mRs of 0 were found to be higher by 5% in the CT/CTA/CTP scenario (21.4% for CT/CTA/CTP vs 16.4% for CT), and those with mRs of 1 were higher by 2.2% in the advanced imaging scenario, CT/CTA/CTP (20.8% for CT

vs 18.6% for CT/CTA/CTP). The very disabled (bedbound and incontinent) patients with an mRs of 5 also favored the advanced imaging scenario, CT/CTA/CTP, showing a 0.9% difference (6.5% for CT/CTA/CTP and 7.4% for CT), whereas patients that died, mRs 6, favored the scenario for advanced imaging, CT/CTA/CTP, as shown by a difference of 3.2% between the two scenarios (15.4% for CT and 12.2% for CT/CTA/CTP). This shows that patients treated in the CT/CTA/CTP scenario had better functional lives and less mortality. (see Table 2 for a description of mRs definitions.)

Table 27. Cost-effectiveness Rankings with modified Rankin Scale Scores.

Cost-Effectiveness Rankings

Category	Strategy	Cost	Incr Cost	Eff	Incr eff	Incr C/E (ICER)	NMB	C/E	Utility	MRS0	MRS1	MRS2	MRS3	MRS4	MRS5	MRS6
Excluding dominated																
undominated	CT head	20,452		5.72			265,677	3573.943	5.723	0.164	0.186	0.125	0.142	0.154	0.074	0.154
undominated	CT/CTA/CTP	37,502	17,049	6.31	0.58	29149.285	277,873	5945.569	6.307	0.214	0.208	0.129	0.136	0.126	0.065	0.122
All																
undominated	CT head	20,452		5.72			265,677	3573.943	5.723	0.164	0.186	0.125	0.142	0.154	0.074	0.154
undominated	CT/CTA/CTP	37,502	17,049	6.31	0.58	29149.285	277,873	5945.569	6.307	0.214	0.208	0.129	0.136	0.126	0.065	0.122
All referencing common baseline																
undominated	CT head	20,452		5.72			265,677	3573.943	5.723	0.164	0.186	0.125	0.142	0.154	0.074	0.154
undominated	CT/CTA/CTP	37,502	17,049	6.31	0.58	29149.285	277,873	5945.569	6.307	0.214	0.208	0.129	0.136	0.126	0.065	0.122
All by Increasing effectiveness																
undominated	CT head	20,452		5.72			265,677	3573.943	5.723	0.164	0.186	0.125	0.142	0.154	0.074	0.154
undominated	CT/CTA/CTP	37,502		6.31			277,873	5945.569	6.307	0.214	0.208	0.129	0.136	0.126	0.065	0.122

Chapter V

DISCUSSION

The standard of care for the treatment of acute ischemic stroke is based on time. [51] There have been recent studies published expanding the time period, wherein with the use of advanced imaging a patient can be treated with equivalent results to the patients treated using the "time" standard of care. [92,102-104] The trend in treating acute ischemic stroke is leaning towards utilizing advanced imaging to determine the physiology of infarct versus ischemia, rather than treating a patient based on time alone. Patients who are treated by "time" are less likely than those based on physiology to be treated using advanced imaging, with only 6.7% for patients being treated by time [86] and 30% for patients being treated with advanced imaging. [105] Although we are expanding the "time" within which we treat acute ischemic strokes, the original concept of "time is brain" still holds true. The benefit and rationale of expanding the "time" we treat stroke within is not to replace treating the patient using the guidelines, once diagnosed, within 60 minutes for rt-PA or 90 minutes for thrombectomy [51], rather it is to safely increase the number of patients treated outside the current standard time period. Using the standard of care algorithm approved by the American Heart Association, [51] patients with acute ischemic stroke symptoms with a "last known well time" of more than 4.5 hours, or having "no last known well time", are not eligible for rt-PA. Accordingly, if a patient has acute ischemic stroke symptoms and "last

known well time" is 4 hours and 31 minutes, they are not eligible for rt-PA. However, if we treat patients based on physiology associated with advanced imaging, the patient would possibly be eligible up to 9 hours [104], with many providers believing that it is possible to mimic the thrombectomy data of up to 24 hours or even greater.

5.1 Thesis Points of Discussion

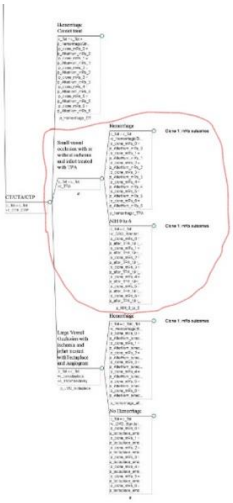
The results answered the questions: "Is it cost effective to select patients for acute ischemic stroke intervention based on advanced imaging versus time?" and "Is there improvement in patient outcomes with treatment of acute ischemic stroke using advanced imaging versus time?" Based on the results, the answer is "yes" to both questions. The significance of the results is that they show that the trend of treating patients based on physiology instead of time is appropriate from a cost-effectiveness perspective, and the results also support the conclusions of the most recent studies for treating acute ischemic stroke with evaluation by advanced imaging [91,92,104,106] with regard to outcomes, with time as the secondary factor. This study has the potential to continue to propel acute ischemic stroke research through pushing the "time" within which we treat stroke, and possibly laying the ground for changes in the standard of care of treating stroke based on advanced imaging and physiology instead of time.

This paper examined the cost-effectiveness of treating patients with the time standard of care, compared to using advanced imaging to determine treatment. The standard of care algorithm was based on the American Heart Association/American Stroke Association guidelines [51], and the advanced imaging algorithm was based on the algorithms associated with advanced imaging studies for treating stroke. [91,92,105]. In the advanced imaging algorithm, the branch titled "Small Vessel Occlusion", (see Figure 5.) the patients'

outcomes were based on the WAKE-UP trial. [105] The study was an advanced imaging trial using MRI/MRP and not CTA/CTP, to show patients who "wake-up" with symptoms of acute ischemic stroke and do not have a known time of symptom onset, with advanced imaging showing that their acute ischemic stroke is consistent with an acute ischemic stroke that occurred within the last 4.5 hours. Such patients were therefore eligible for treatment with rt-PA. In this branch, I did not adjust for the cost of MRI. It was not adjusted because, considering the negligible cost of the MR studies compared to the CT studies, it did not significantly change the results. The liberty of using the WAKE-UP trial in the advanced imaging algorithm even though patients were treated within the radiographic equivalent of 4.5 hours of time was available because the reported but not published results of the EXTEND International trial [104] showing patients treated with rt-PA "9 hours from last known well time", using CTA/CTP to determine if they were good candidates for treatment, had equivalent outcomes to the WAKE-UP trial. [104] Therefore, with increased time to treatment using CTA/CTP and equivalent outcomes it is reasonable to use the cost of CTA/CTP and the outcomes from the WAKE-UP trial, since these results are published.

Figure 4. Picture of the Small Vessel Occlusion Branch. Small Vessel Occlusion

Figure 5. Pictrue of small vessel occlusion branch



5.2 Future Research

The future of stroke care is evolving. Stroke care prior to 1996 was supportive only, and after 1996 the mainstay was treatment based on time. Currently, strides are being made towards basing treatment on physiology, using advanced imaging instead of time as the main factor. This research shows that it is more cost-effective to base treatment on advanced imaging from the initial diagnosis of stroke as against the current standard of care. The next step will be to develop a protocol and perform human trials based on the algorithms compared in this paper. In that study, time will be recorded but treatment will be based on advanced imaging, not time.

Chapter VI

CONCLUSION and SUMMARY

It is cost effective to select patients for acute ischemic stroke intervention based on advanced imaging versus time. There is improvement in patient outcomes with treatment decision of acute ischemic stroke with advanced imaging versus time based treatments.

The use of advanced imaging to evaluate patients having an acute ischemic stroke and determine if they are eligible for treatment instead of using the traditional decision algorithm of treatment based on the time of onset of the patient's acute ischemic stroke symptoms is appropriate from a cost effectiveness perspective. Current clinical research is ongoing in effort to expand the time patients are treated from their symptoms of acute ischemic stroke and have shown positive results in the patient's functional outcome. The current clinical research uses advanced imaging in part to determine if a patient should be treated with time still a major factor. In the future it is expected the standard of care algorithm for treating acute ischemic stroke based on the clinical trials will change, and eventually the advanced imaging will be the determinant of treatment, not associated with time. The results of this study should help propel the change on how patients are evaluated for treatment of their acute ischemic stroke based on a financial/cost effectiveness perspective.

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Glossary

ACA	Anterior Cerebral Artery
AComm	Anterior Communicating Artery
AHA/ASA	American Heart Associate/American Stroke Association
ASPECTS	Alberta Stroke Program Early CT Score
ATLANITS A	The rt-PA (Alteplase) 0-6-Hour Acute Stroke Trial, Part A (A0276g) Results of a Double-Blind, Placebo-Controlled, Multicenter Study, Alteplace ThromboLysis for Acute Non-interventional Therapy in Ischemic Stroke.
ATLANTIS B	Recombinant Tissue-Type Plasminogen Activator (Alteplase) for Ischemic Stroke 3 to 5 Hours After Symptom Onset, The ATLANTIS Study: A Randomized Controlled Trial (ATLANTIS B)
Atheroembolic	pertaining to an embolus from the artery
Atherosclerotic stenosis	pertaining to build-up of plaque on an arterial wall causing arterial
C2	Level of the 2nd vertebra of the cervical spine
C1	Level of the 1st vertebra of the cervical spine
C/E	Cost per unit Effectiveness
Cardioembolic	pertaining to an embolus from the heart
CBF	Cerebral Blood Flow
CT	Computed Tomography Radiographic Study

CTAComputed Tomography Angiography Radiograph Study

CTPComputed Tomography Perfusion Radiography Study

DAWN	Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct trial
DEFUSE III	Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging trial
Thrombectomy	Removal of a Thrombus
ECASS	European Cooperative Acute Stroke Study
EEG	Electroencephalogram
Embolus	A blood clot or any other object than has been carried in the blood stream and lodges in an artery causing an obstruction of the artery
EPITHET	The Echoplanar Imaging Thrombolytic Trial
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times Trial
EXTEND IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial Trial
EXTEND IA TNK	Name of investigator group for the study, "Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke"
GNP	Gross National Product
GRE MRI	Gradient Recalled Echo Magnetic Resonance Imaging
IAT	Intra-Arterial Therapy
ICER	Incremental Cost Effectiveness Ratio
IMS III	Interventional Management of Stroke III trial
Infarct	a localized area of ischemic necrosis produced by anoxia following occlusion of the arterial supply or venous drainage of the tissue, organ, or part
Ischemia	insufficient supply of blood to an organ, usually due to a blocked artery
LY	Life Years
MCA	Middle Cerebral Artery
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Trial
MRI	Magnetic Resonance Imaging

MR RESCUE	The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy trial
mRs	modified Rankin scale score
NIHSS	The National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NMB	Net Monetary Benefit
PCA	Posterior Cerebral Artery
PComm	Posterior Communicating Artery
QALY	Quality-Adjusted Life Years
rCBG	regional Cerebral Blood Flow
REVASCAT	Randomized Trial of Revascularization with Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset
rt-PA	Alteplase
SWIFT	Solitaire with the Intention for Thrombectomy trial
SWIFT PRIME	Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment trial
SYNTHESIS	Name of the investigators group for the study, “Endovascular Treatment for Acute Ischemic Stroke”
TIA	Transient Ischemic Attack
Thrombus	A blood clot formed in the blood vessel within the vascular system decreasing or preventing blood flow
WTP	Willingness-to-Pay

Appendix A

Monte Carlo Probabilistic Sensitivity Analysis with Beta Distribution Results.

In the Monte Carlo probabilistic sensitivity analysis shown in the Methods chapter, the rationale of using a triangular distribution was explained. The triangular distribution was used because it allowed for the variables with uncertainty to have a very wide distribution of 10% or more from the minimum to the maximum in all the categories. Based on the beta distribution being highly accepted, I ran the distribution with the mean of .5 and a standard deviation of .2, again to make the distribution as wide as possible. Tables 28–30 and Graphs 5–7 are the base case results and probabilistic sensitivity analysis results with a beta distribution. As you can see in the tables, the incremental cost per patient was $13,265.00, which is less than the triangular distribution results ($17,049.00), because the triangular distribution is using a preset value in the base case whereas the beta distribution uses weighted averages of the data in the base case.

Table 28. Cost-effectiveness Rankings Beta Distribution.

Cost-Effectiveness Rankings

Category	Strategy	Cost	Incr Cost	Eff	Incr eff	Incr C/E (ICER)	NMB	C/E
Excluding dominated								
undominated	CT head	26,920		5.90			268,246	4560
undominated	CT/CTA/CTP	40,185	13,265	6.35	0.44	29971	277,111	6332
All								
undominated	CT head	26,920		5.90			268,246	4560
undominated	CT/CTA/CTP	40,185	13,265	6.35	0.44	29971	277,111	6332
All referencing common baseline								
undominated	CT head	26,920		5.90			268,246	4560
undominated	CT/CTA/CTP	40,185	13,265	6.35	0.44	29971	277,111	6332
All by Increasing effectiveness								
undominated	CT head	26,920		5.90			268,246	4560
undominated	CT/CTA/CTP	40,185		6.35			277,111	6332

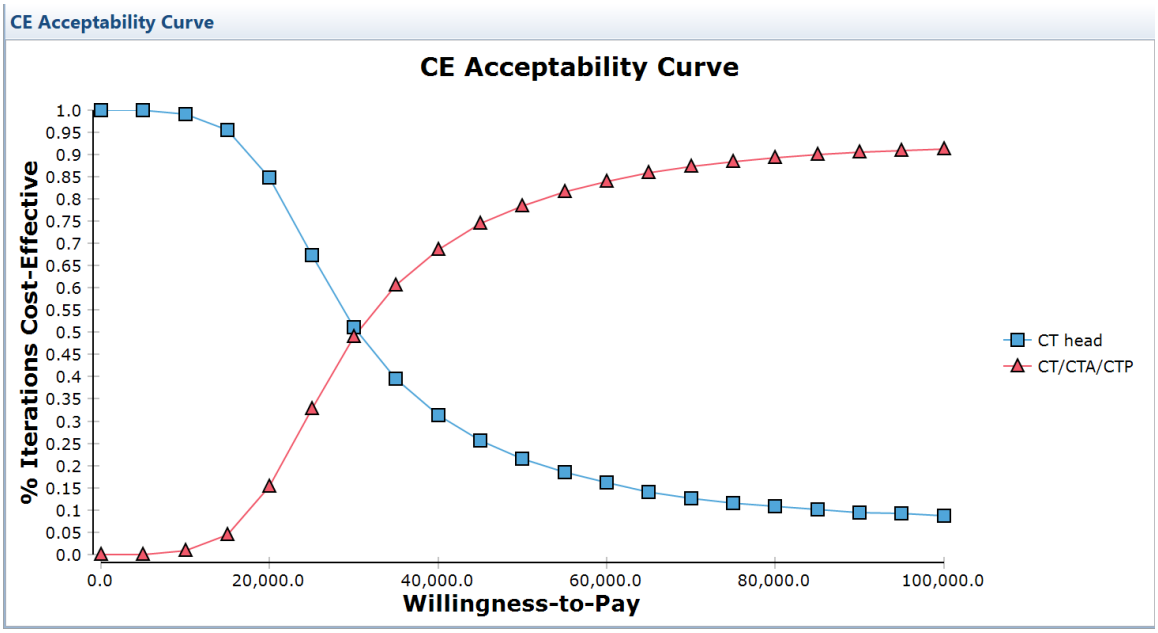
The CE Acceptability Curve and Simulation Report for Beta Distributions shows the Willingness-to-Pay (x axis) and Iterations of Cost-Effectiveness (y axis). The curve shows that at a willingness-to-pay of less than $30,000.00, it is more cost-effective to use the strategy of the scenario based on time, CT (51.11% for CT vs 48.89% for CT/CTA/CTP) in the beta distribution and in the triangular distribution (73.2% for CT vs 26.8% for CT/CTA/CTP). At a willingness-to-pay of $35,000.00, the cost-effectiveness changes to favor the scenario based on advanced imaging, CT/CTA/CTP, over the scenario based on time, CT (39.47% for CT versus 60.53% for CT/CTA/CTP), in the beta distribution. In the triangular distribution, on the other hand, at a willingness-to-pay of $35,000.00 the scenario based on time, CT, is still favored (53.2% for CT vs 46.7% for CT/CTA/CTP). However, at the willingness-to-pay threshold of $50,000.00, the scenario based on advanced imaging, CT/CTA/CTP, is favored in both the beta distribution (18.44% for CT vs 78.44% for CT/CTA/CTP), and in the triangular distribution (27.0% for CT vs 73.4% for CT/CTA/CTP).

Table 29. Monte Carlo Simulation Report Beta Distribution.

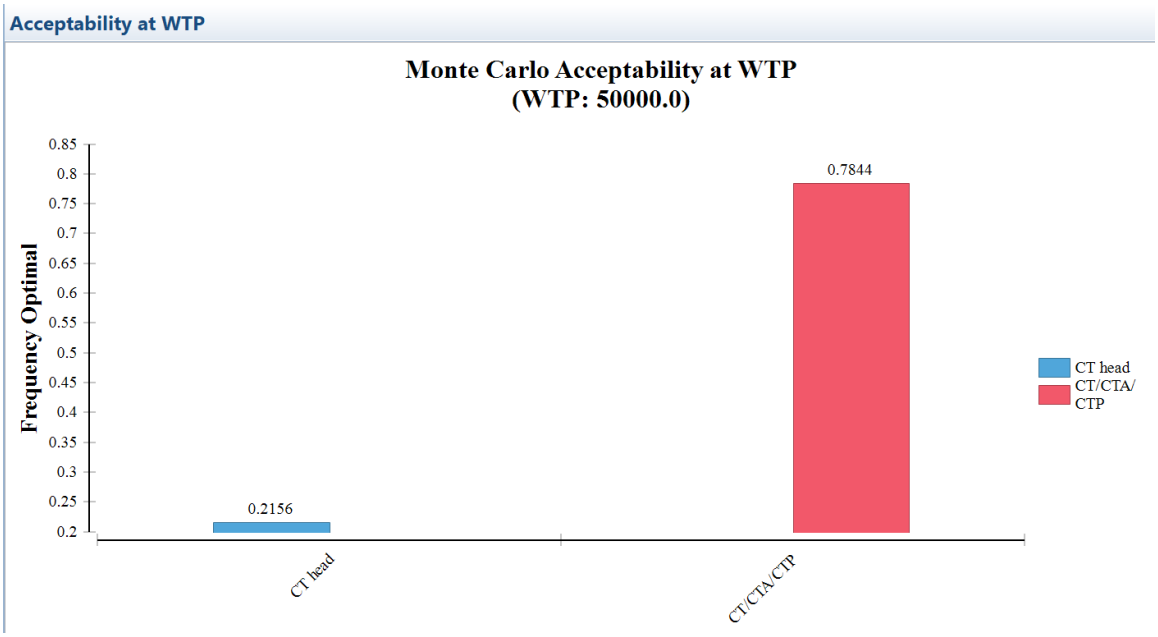
Monte Carlo Simulation Report

WEIGHT	STRATEGY	STRATEGYNAME	ACCEPTABILITY
10000	1	CT/CTA/CTP	0.0092
15000	0	CT head	0.9547
15000	1	CT/CTA/CTP	0.0453
20000	0	CT head	0.8471
20000	1	CT/CTA/CTP	0.1529
25000	0	CT head	0.6724
25000	1	CT/CTA/CTP	0.3276
30000	0	CT head	0.5111
30000	1	CT/CTA/CTP	0.4889
35000	0	CT head	0.3947
35000	1	CT/CTA/CTP	0.6053
40000	0	CT head	0.314
40000	1	CT/CTA/CTP	0.686
45000	0	CT head	0.256
45000	1	CT/CTA/CTP	0.744
50000	0	CT head	0.2156
50000	1	CT/CTA/CTP	0.7844
55000	0	CT head	0.1844
55000	0	CT head	0.1844
55000	1	CT/CTA/CTP	0.8156
60000	0	CT head	0.1617
60000	1	CT/CTA/CTP	0.8383
65000	0	CT head	0.1414
65000	1	CT/CTA/CTP	0.8586
70000	0	CT head	0.1266
70000	1	CT/CTA/CTP	0.8734
75000	0	CT head	0.116
75000	1	CT/CTA/CTP	0.884
80000	0	CT head	0.1078
80000	1	CT/CTA/CTP	0.8922
85000	0	CT head	0.1014
85000	1	CT/CTA/CTP	0.8986
90000	0	CT head	0.0951
90000	1	CT/CTA/CTP	0.9049
95000	0	CT head	0.0921
95000	1	CT/CTA/CTP	0.9079
100000	0	CT head	0.0873
100000	1	CT/CTA/CTP	0.9127

Graph 5. CE Acceptability Curve Beta Distribution.



Graph 6. Acceptability Willingness-to-Pay Beta Distribution.



The Incremental CE Scatter Plot and Report Beta distribution (Graph 7 and Table 30) are like the Triangular distribution Incremental CE Scatter Plot and Report. The graph and table both show that the scenario based on advanced imaging, CT/CTA/CTP, is favored, because 78.53% of the 10,000 trials had an ICER of less than $50,000.00, while

18.38% did not favor the scenario based on advanced imaging, CT/CTA/CTP, because the ICER was greater than $50,000.00, and 3.18% had more effective treatment using the scenario based on time, CT, than the scenario based on advanced imaging, CT/CTA/CTP. In the triangular distribution the results are similar, with an ICER of less than $50,000.00 for 78.43% trials, an ICER of more than $50,000.00 for 24.57%, and 1.95% having more effective treatment with the CT scenario.

Graph 7. Incremental CE Scatter Plot Beta Distribution.

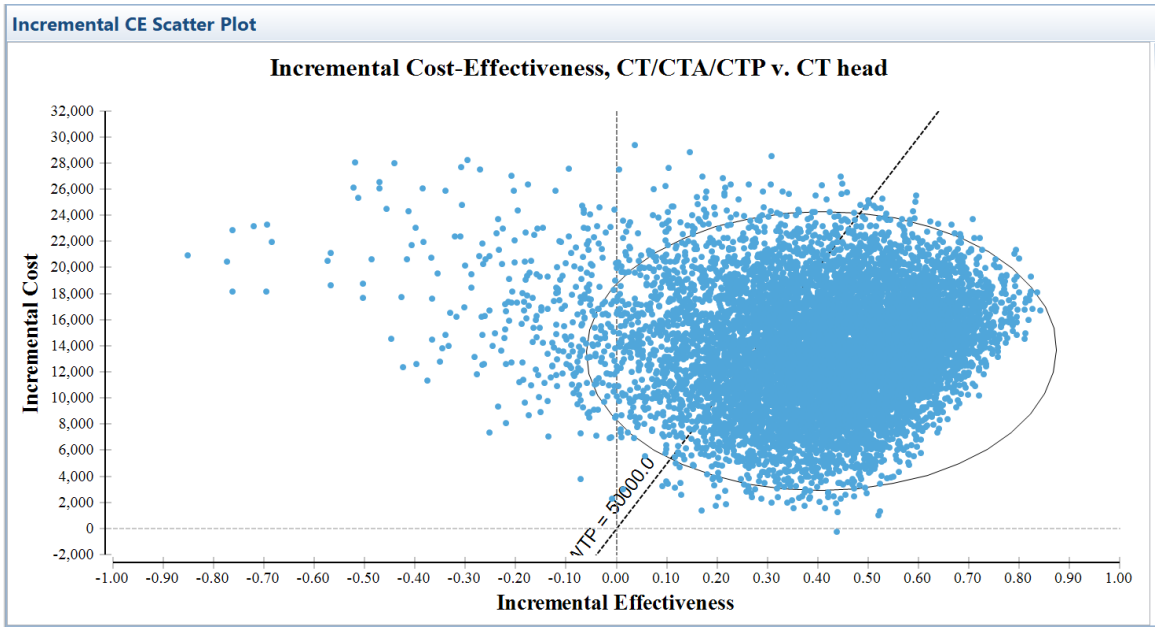


Table 30. Incremental CE Plot Report Beta Distribution.

Incremental CE Plot Report

COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	1	0.0001
C2	I	IE>0	IC>0	ICER<50000.0	7,843	0.7843
C3	III	IE<0	IC<0	ICER>50000.0	0	0
C4	I	IE>0	IC>0	ICER>50000.0	1,838	0.1838
C5	III	IE<0	IC<0	ICER<50000.0	0	0
C6	II	IE<0	IC>0	Inferior	318	0.0318
Indiff	origin	IE=0	IC=0	0/0	0	0

Appendix B

The following is a detailed summary of the major studies associated with stroke treatment.

B.1 National Institute of Neurological Disorders and Stroke (NINDS)

Over the past 20 years, rt-PA has been the standard of practice for treatment of stroke treatment. There have been multiple studies researching the outcomes as well as costs associated with the treatment of stroke thrombolytic agents.[1-3] The initial study that changed stroke treatment, bringing rt-PA into the forefront for treatment of stroke, was the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA study. [4] Prior to this study there were a couple of studies, [5,6] both open-labeled, dose-escalation studies, showing the safety of intravenous rt-PA. The NINDS [7] was an interlinked study of two trials reported together that showed a reduction of disability and a neutral effect on mortality with administration of rt-PA when utilized within 0–3 hours of onset of stroke symptoms, compared to placebo.

The hypothesis study design of Part 1 was, "to test whether t-PA had clinical activity – specifically, whether a greater proportion of patients treated with t-PA, as compared with those given placebos, had early improvement. Early improvement was defined as complete resolution of the neurologic deficit or an improvement from the base line in the score on the National Institute of Health Stroke Scale (NIHSS) by 4 or more points 24 hours after the onset of stroke. Each group was assessed according to the time

from the onset of stroke to the beginning of treatment: 0 to 90 minutes, 91 to 180 minutes, and 0 to 180 minutes after the onset of stoke." [7]. The Part 2 hypothesis was, "..there would be a consistent and persuasive difference between the t-PA and placebo groups in terms of the proportion of patients who recovered with minimal or no deficits three months after treatment." [7].

There were 291 patients in Part 1 of the study, 144 in the t-PA group, and 147 in the placebo group. In Part 2 there were a total of 333 patients, 168 in the t-PA group and 165 in the placebo group. The patients were evaluated with four outcome measures, the NIHSS, Barthel Index, Modified Rankin Scale, and Glasgow Outcome Scale. The results reported in this study showed in Part 1 that there was no statistical difference between the groups. In Part 2, however, there was an improvement in the patients at three months in the t-PA group compared to the placebo group.

> "The number of patients with favorable outcomes for each of the four primary outcome measures three months after stroke was higher in the t-PA group than in the placebo group. As evaluated by the global test statistic, the odds ratio for a favorable outcome in the t-PA group was 1.7 (95 percent confidence interval, 1.2 to 2.6; P=0.008). As compared with the placebo group, there was a 12 percent absolute (32 percent relative) increase in the number of patients with minimal or no disability (a score of 95-100 on the Barthel index) in the t-PA group. There was also an 11 percent absolute (55 percent relative) increase in the number of patients with an NIHSS score of 0 or 1 in this group. A similar magnitude of effect was seen with respect to the absolute and relative improvement in the t-PA group with the use of the modified Rankin scale and the Glasgow outcome scale." [7] (See Table 1 and 2 for outcome scores and hemorrhagic conversion rates.)

In more contemporary studies the modified Rankin score is utilized as an endpoint and is favored over the endpoints utilized in the NINDS study.[4] The trial was criticized and later found refuted in an independent re-analysis, for potentially having an imbalance in the baseline stroke severity favoring the rt-PA population.[8] There have been multiple studies since the NINDS trial, including a meta-analysis study [9] showing favorable benefits

for the treatment of ischemic stroke if utilized within 4.5 hours of the initial onset of stroke symptoms.

Table 1. NINDS Outcome Scores

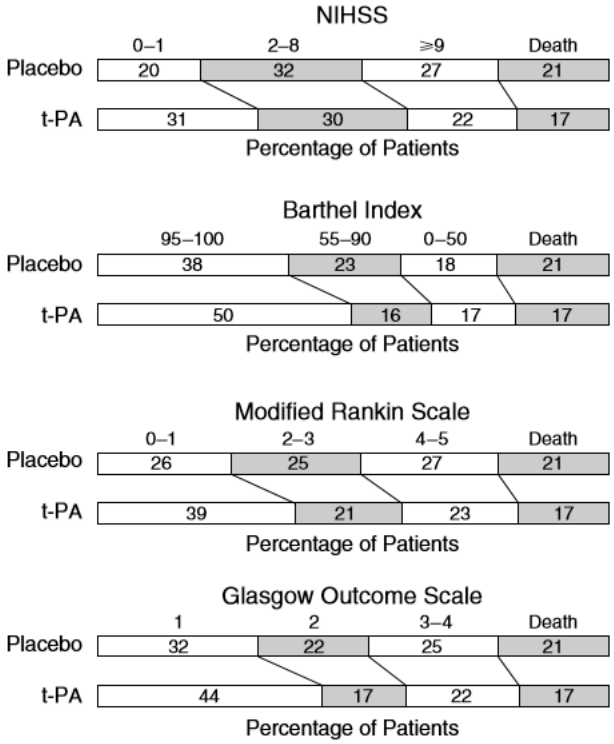


Figure 2. Outcome at Three Months in Part 2 of the Study, According to Treatment.

Scores of ≤1 on the NIHSS, 95 or 100 on the Barthel index, ≤1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome. Values do not total 100 percent because of rounding.

Table 2. NINDS Hemorrhage Rates

Incidence of Intracranial Hemorrhage within 36 Hours of Treatment for Stroke.

Type of Intracranial Hemorrhage	t-PA	Placebo
	no. (%)	
Part 1	144	147
Symptomatic	8 (6)	0
Fatal*	4	0
Nonfatal	4	0
Asymptomatic	5 (3)	3 (2)
Part 2	168	165
Symptomatic	12 (7)	2 (1)
Fatal*	5	1
Nonfatal	7	1
Asymptomatic	9 (5)	6 (4)

*Values include all deaths attributed to hemorrhage.

B.2 Alteplase Thrombolysis for Acute Non-Interventional Therapy in Ischemic Stroke (ATLANTIS)

The initial ATLANTIS study[10] also known as ATLANTIS A, started in 1991. The study was sponsored by Genentech (the makers of rt-PA). The study evaluated the use of Alteplase, also known as rt-PA, in patients with acute ischemic stroke in the time window of 0–6 hours. Because of safety concerns, the Data Monitoring Safety Committee prematurely halted the study in the latter half of 1993, approximately two years after it began. The concern for safety was in the group of patients treated at the 5 to 6-hour time period. The study group eventually changed its focus and the reformatted study became the ATLANTIS B. The ATLANTIS B was further modified in February of 1996 for stroke onset and treatment within the 3 to 5-hour period, based on the results of the NINDS trial.[11] The ATLANTIS A and B trials were reported separately, with the investigators involved

in ATLANTIS A being blinded to the results until 1999, when the results for ATLANTIS B were reported.[10]

There were 142 patients enrolled in ATLANTIS A, and 617 patients in ATLANTIS B. The ATLANTIS designs were the same for part A and part B, with the only change being the endpoints as discussed above. The trial was a phase II, placebo-controlled, double-blind, randomized study. The study design was very similar to the NINDS trial, except for the treatment time, which was 0–3 hours for NINDS vs. 0–6 hours for ATLANTIS. Enrollment in this study was also based on clinical and radiographic evidence pertaining to stroke. The enrollment was scheduled for a total of 300 patients with even division between the treatment groups. The patients were enrolled if they met the inclusion criteria:

> "patient aged 18 to 79 years who presented with a clinical diagnosis of stroke causing a measurable neurological deficit and who could receive the study drug within 6 hours of definite symptoms onset. A CT scan that excluded intracerebral hemorrhage (ICH) was required before randomization. However, there was no exclusion for early infarct signs in the middle cerebral artery territory."[10]

The patients were randomized using a blocked randomized stratification by a clinical center using a central randomization code.

> "The sample-size estimate for the NIHSS primary end point (a 4-point improvement or complete recovery at day 30) was based on a 2-sample test of proportions. The placebo group was assumed to have a 30% improvement rate. Based on this assumption, 300 patients would be required to detect a primary end point rate of 47% in the rt-PA group, with an alfa level of 0.05 and power of 90%. There were 3 planned safety and futility analyses at approximately 75,150, and 225 patients." [10]

There was a total of 142 patients enrolled in the study prior to its premature halting. The intention-to-treat analysis included all the randomized patients. The groups were considered well matched in demographics and co-morbidities. Four hours and 17 minutes

was the mean time to treatment in the placebo group, while four (4) hours and 24 minutes was the mean time to treatment in the rt-PA group. Thirty-four percent (34%) and 31% of the patients were treated between 5–6 hours with placebo and rt-PA, respectively, while 17% and 14% were treated in less than three hours in the placebo and rt-PA groups, respectively.

The findings for this study showed that patients improved in the rt-PA group, with a four-point improvement on the NIH score at 24 hours, 40% for the rt-PA group and 21% for the placebo group. Although promising, there was a reversal of this early finding, with the placebo group having 75% improvement in the four-point scoring of the NIH score and only 60% improvement in the rt-PA group. In the 30-day and 90-day secondary outcome measures, the placebo group actually had lower modified Rankin scores. Radiographically it was also appreciated that the size of the infarcted brain at day 30 was no different in the placebo group compared to the rt-PA group, being 64+/-74 cm^3 versus 45+/-54 cm^3, respectively.

> "In order to provide a direct comparison with the NINDS rt-PA study results several "excellent recovery" (score of 0 and 1) post hoc analyses were conducted. [7] In these tests a higher percentage of rt-PA patients had an excellent outcome on the NIHSS at day 30 (placebo 20%, rt-PA 35%, P=0.04 by uncorrected post hoc test) but not day 90. This, along with the 24-hour 4-point NIHSS findings, suggests that rt-PA treatment produces higher number of cases with early, dramatic neurologic recoveries. In contrast, no benefit was seen on the "excellent recover" post hoc function outcome assessments using the Barthel Index. However, because the trial was not powered to detect differences on these "excellent recovery" variables, these results may reflect a type II error." [10]

Regarding the safety and efficacy of the Intention to Treat, the population showed the occurrence of intracerebral hemorrhage determined by CT scan and defined as any hemorrhage on CT scan, symptomatic, non-symptomatic or fatal intracerebral hemorrhages, at time intervals of the first 24 hours plus or minus 6 hours and a repeat CT

scan within the first 10 days. The determination of symptomatic versus asymptomatic was determined by the local teams who were blinded to the treatment versus placebo group.

> "Treatment with rt-PA increased the rate of both asymptomatic and symptomatic ICH: asymptomatic 4.3% versus 12.7%, symptomatic 0.0% versus 11.3%. The mortality rate of 30 and 90 days was significantly higher in the rt-PA group: 4.2% with placebo, 18.3% with rt-PA (P=0.008); 90 days, 7.0% with placebo, 22.5% with rt-PA (P=0.009)." [10]

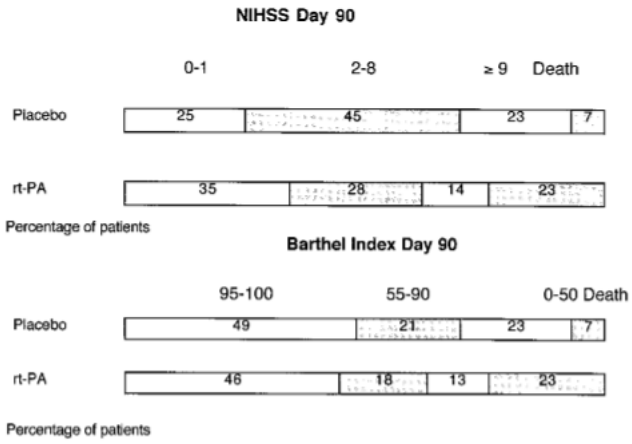
As previously stated, the study was halted early by the Data Safety Monitoring Committee because of the group receiving the rt-PA versus placebo at the 5 to 6-hour time-period. The rate of intracerebral hemorrhage and the 30 and 90-day mortality rates were significantly higher in the rt-PA group than the placebo group. The authors of the study did comment:

> "These increased SAE results in the 5- to 6-hour group may have been confounded by a baseline imbalance in the number of patients with severe strokes. In the 5- to 6-hours group, only 8% (2/24) of the placebo patients had and NIHSS >20 at baseline compared with 23% (5/22) of the rt-PA patients (P<0.05). In the study overall, patients with and NIHSS of >20 had increased ICH rates and very poor outcomes. In the patients with an NIHSS >20, there was a 38% rate of symptomatic ICH and a 100% 90-day mortality rate with rt-PA treatment. If the 5- to 6-hour patients are excluded, the symptomatic ICH rate in the remaining 0- to 5-hour patients is 8.2%." [10]

Overall, the trial did not find any benefit for the rt-PA therapy with ischemic stroke when treatment was initiated within 0-6 hours of symptom onset. The 30-day and 90-day outcomes showed no difference in the rt-PA group versus the placebo group. There was a significant increase in symptomatic intracerebral hemorrhages within the rt-PA group compared to the placebo group and a higher mortality rate in this group. There is possibility of a Type II error because of the early cessation of the study and the decrease of enrollment secondary to the cessation. There were very few patients, less than 15%, that were treated in the time window of within three hours of commencement of symptoms, which is what

is approved by the FDA. There was a percentage of patients at the 30-day mark treated with rt-PA that experienced "..excellent recovery"; however, these results were overshadowed by the significant amount of symptomatic intracerebral hemorrhages and mortalities. When compared to the NINDS trial, patients of this trial had a lower NIHSS score, with a median 11 in ATLANTIS versus 14 in NINDS. Taking this into consideration, it is possible that if more patients had been admitted to the study there would have been more hemorrhages and mortalities than reported. "This study confirms that patients with large strokes (NIHSS >20) have very poor outcomes."[10] (See tables 3 and 5 for outcome scores and tables 4 and 6 for hemorrhagic conversion rates.)

Table 3. ATLANTIS A Outcomes Scores



Outcome at day 90. Scores of 0 to 1 are excellent outcomes on the NIHSS. Scores of 95 to 100 are excellent outcomes on the Barthel Index.

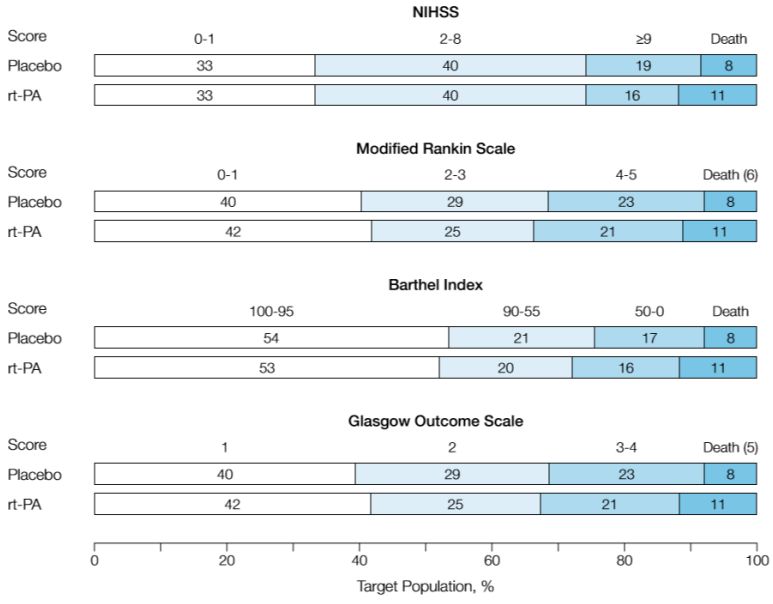
Table 4. ATLANTIS A Hemorrhage Rates

TABLE 6. NIHSS >20 Population

Variable	Placebo (n=7)	rtPA (n=16)	*P*
Asymptomatic ICH, day 10	1 (0)	2 (12.5)	0.32
Symptomatic ICH, day 10	0 (0.0)	6 (37.5)	0.06
Death, 30 days	3 (42.9)	13 (81.3)	0.07
Death, 90 days	5 (71.4)	16 (100)	0.03

Values are given as n (%) unless otherwise indicated.

Table 5. ATLANTIS B Outcomes Scores



The target population is defined as patients aged 18 through 79 years who presented with a clinical diagnosis of ischemic stroke causing a measurable neurologic deficit and who received the study drug between 3 and 5 hours of definite symptom onset. NIHSS indicates National Institutes of Health Stroke Scale (scores range from 0 to 42); rt-PA, recombinant tissue-type plasminogen activator. Not all sums equal 100% due to rounding. Barthel index scores are given in 5-point increments.

Table 6. ATLANTIS B Hemorrhage Rates

	Intent-to-Treat Population			Target Population†		
Serious Adverse Event	Placebo (n = 306)	rt-PA (n = 307)	*P* Value	Placebo (n = 275)	rt-PA (n = 272)	*P* Value
Asymptomatic ICH	4.2	11.3	.001	4.7	11.4	.004
Symptomatic ICH	1.3	6.7	<.001	1.1	7.0	<.001
Fatal ICH	0.3	2.6	<.001	0.3	3.0	<.001
Death within 90 d	6.9	10.9	.08	6.9	11.0	.09
Death within 30 d	4.2	7.6	.08	4.4	7.0	.18

*rt-PA indicates recombinant tissue-type plasminogen activator; ICH, intracerebral hemorrhage. Data are presented as percentages unless otherwise indicated.
†The target population received treatment as assigned between 3 and 5 hours after symptom onset.

B.3 European Cooperative Acute Stroke Study (ECASS)

The first ECASS [12] was a randomized, prospective, multicenter, double-blind, placebo-controlled trial to test the safety and efficacy of rt-PA in patients with ischemic stroke. The study involved 75 hospitals in fourteen European countries between 1992 and early 1994, enrolling 620 patients with ischemic stroke symptoms of stable moderate to severe hemispheric stroke symptoms without major infarct on the initial CT scan. The definition in this study of stable moderate to severe hemispheric stroke symptoms was "..moderate to high-grade hemiparesis, sensory disturbance, dysarthria or non-fluent aphasia, and occasionally hemianopia." [12] Opposed to the NINDS trial, where 0.95 mg per

kilogram of body weight of rt-PA was utilized, this trial used a 1.1 mg/kg of body weight dose of rt-PA. The time from symptom onset to infusion of rt-PA was 0 to 6 hours.

Patients were excluded if, clinically, they presented with severe hemispheric stroke syndrome (hemiplegia, impaired consciousness, or forced head/eye deviation) or mild neurologic deficits with scores of 50–58 on the Scandinavian Stroke Scale, SSS (European version of the American NIH score); patients having neurologic improvement; patients outside the 6-hour time window; patients with pre-existing disease associated with hemorrhage (esophageal varices, gastrointestinal ulcers, colitis, aortic aneurysm) or pre-existing disabling neurologic diseases or recent trauma or surgery (within the last three months); or radiographically, patients were excluded from the trial if they had a CT scan showing intracerebral hemorrhage and signs of infarct.

The patients were randomized with a central randomization code to the treatment arms, rt-PA or placebo. The sample size was 2x240 eligible patients with an 80% power and a global significance level at most of 0.05 utilizing a two-sided Wilcoxon test; however, considering this sample size and adjusting for possible violations the overall sample size was increased to 600. Protocol violations and determination of patients' ineligibility were decided by an external safety committee, the steering committee, and an independent CT reading panel after patient recruitment but prior to the randomization code being broken.

> "The first hypothesis to be tested was that there is a difference between the rt-PA-treated and placebo-treated groups in activities of daily living defined as a difference of 15 points in the Barthel Index (BI)[13] at 90 days after treatment. The results of patients who died were carried forward with the lowest possible score (0) in the BI. The second hypothesis was that there is a difference between the rt-PA-treated and placebo-treated groups in the global clinical impression defined as a difference of one grade in the modified Rankin Scale (RS) at 90 days after treatment. This scale also included mortality, since patients who died were scored

with the worst possible score (6) in this scale. Thus, both primary end points include mortality, although mortality itself was a secondary endpoint.

Secondary outcome events included the difference in the long-term score of the SSS[14,15] at 90 days (patients who died were carried forward with the lowest possible score), the difference in mortality rates at day 30, and the difference in the scores of the combined BI/RS at 90 days in surviving patients. The combined score was introduced to solve a problem inherent in the BI: patients can score the maximum of 100 points because they are independent in daily living activities, but still may have a significant handicap. The score of 100 reflects a broad and heterogenous, although basically positive, outcome. On the other hand, the RS differentiates a little better among patients with good outcome. Grades 0 and 1 on the RS refers to patients with good outcomes without any (0) or only mild nondisabling deficit. The two scales were combined using the following definitions: a patient with 100 points in the BI showing no neurologic symptoms (RS grade 0) scored 110 points on the combined scale. A patient scoring 100 points in the BI but with slight neurologic disability (RS grade 1) scored 105 points on the combined scale. This resulted in a 110-point (22 step) combined BI/RS. [12]

Further parameters of efficacy included the difference in the early neurologic course of patients using the SSS at 120 minutes, 8 hours, 24 hours, 7 days, and 30 days; the difference in the duration of in-hospital stay; National Institute of Health (NIH) stroke scale at day 1 and day 90 after treatment." [12]

Safety parameters were evaluated as well, with multiple entities being evaluated for overall mortality, frequency of hemorrhage, death secondary to hemorrhage, space-occupying infarction, as well as other serious events occurring in either treatment group.

"According to the definitions published elsewhere [16,17], hemorrhagic events were classified as HI types I and II and PH types I and II. HI is defined as small petechiae along the margins of the infarct, while HI II represents more confluent petechiae within the infarcted area, but without space-occupying effect. PH I is defined as blood clot not exceeding 30% of the infarcted area with some mild space-occupying effect, and PH II represents dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect." [12]

The CT scans were performed at intervals of 24 hours and between six and eight days after stroke occurred. The radiographic studies were evaluated by the CT reading panel for early signs of infarct, hemorrhage, infarct size, and space-occupying infarcts. The cause of death was determined by the local investigator for all patients dying and any type of hemorrhage was reviewed by the safety and steering committees. These committees had

the final decision in regard to hemorrhage related deaths before un-blinding the codes. The safety committee performed continuous monitoring for adverse events, and rehabilitation for the study participants was not standardized, nor were they informed of the group the participant was stratified toward.

Analysis was performed on both intention-to-treat and treatment population. The treatment population was prospective, determined by the inclusion and exclusion criteria of the initial CT scan, and represented patients who the investigators believed were the best subjects to treat. A *t* test was used to compare baseline characteristics for continuous variables with a Fisher's exact test used for categorical variables. A multivariate discriminant analysis was used for baseline characteristics and determining the success of the randomized procedure of the explanatory analysis was necessary in evaluating the effects of excluding ineligible patients.

> "Following the protocol, the significance level for each of the primary out-come events was 0.25, and it was understood that trial would be positive if any of the results of the two end points yielded a significant difference. The nominal significance level of 0.25 was initially defined according to the Bonferroni procedure for independent end points during the planning stage, well aware of the crudeness of this procedure the expected high correlation of the two end points.
>
> After completion of the trial, a Spearman rank correlation of r=-0.95 was found between the modified RS and the BI, resulting in an adjusted significance level of alpha=.039 for each of the primary end points. This adjustment is based on the procedure proposed by Pocock et al.[18] The appropriate significance level for correlation of r=-0.95 was calculated using an algorithm given by Gupta.[19] For two of the secondary outcome events, the adjusted significance level was similar (alpha=-.036) given a correlation of r=0.92 between the SSS and the combined BI/RS. Mortality, the third secondary end point, was not included in the correlation because it not only represents an efficacy end point, but also is the most important safety parameter. We did not feel it was justified to apply an alpha adjustment to a safety criterion.
>
> Differences between the further parameters of efficacy were tested with the Wilcoxon test for the duration of in-hospital stay and the NIH stroke scale and Fisher's exact test for the early neurologic course assessed by the SSS at different time points. No alpha adjustment was applied for these further parameters of efficacy. Although not explicitly started in the protocol, the incidence of

> hemorrhagic events and other serious adverse events was compared using Fisher's exact test. Life table methods and the log rank test were performed to calculate the overall mortality, hemorrhage-related mortality, and the Kaplan-Meier survival cures using SAS life test procedures (Cary NC, SAS Institute Inc)." [12]

Six hundred and twenty patients (620) were included in the trial, 313 in the rt-PA group and 307 in the placebo group. All patients that were randomized were included in the intention-to-treat analysis, with five patients who were not treated, three in the rt-PA group and two in the placebo group. One of these patients was followed for 90 days, and of the patients treated 9 were not able to be followed but it was reported that they all survived, 7 in the rt-PA group and 2 in the placebo group. Ten (10) of the patients in the rt-PA group were all considered as the worst possible outcome, while four in the placebo group were considered the best possible outcome. One hundred and nine (109) patients were excluded from the treatment population analysis secondary to early infarct signs, which led to a statistically significant number of protocol violations in the patients in the rt-PA group, 63 patients, versus 43 patients in the placebo group, a P of 0.03. There was a P of 0.12, 31 versus 21, rt-PA versus placebo, among 52 total patients with major early infarct signs. There were other violations of the protocol, including heparin infusion within the first 24 hours, use of other concomitant therapies, lack of follow up, deviations of follow up at the 90-day point that were +/- 14 days, and as previously stated patients were randomized but not treated. The demographics along with the severity of the SSS between the two treatment groups were well matched among the treatment population, with 264 in the placebo group and 247 in the rt-PA group.

In the primary endpoints, there was no statistical difference in the BI between the two groups in either the intention-to-treat group or the treatment population analysis. The modified Rankin score difference of 1 point between the two groups in the intention-to-

treat analysis was not reached, and in the treatment population group there was a significant statistical difference in favor of the rt-PA group with a P value of 0.035.

> "In the ITT analysis 29.3% of patients in the placebo arm and 35.7% of the rt-PA-treated patients had RS scores better than 2 at 90 days. The odds ratio (OR) for being independent was 1.15 (95% confidence interval (CI), 0.98 to 1.35) for the rt-PA group. In the TP the percentages were 29.2% (placebo) and 40.9% (rt-PA), respectively. The OR for being asymptomatic or independent after treatment with rt-PA was 1.29 (95% CI, 1.09 to 1.54) for the rt-PA group. The OR for being asymptomatic (RS 0) was 1.47 (95% CI, 1.05 to 2.05) in the ITT analysis and 1.54 (95% CI 1.28 to 2.85) for the rt-PA group. For both primary outcome measures a stratification for age (<70 years), sex, early initiation of therapy (before 3 hours), and SSS at baseline (>28) was taken into account. These parameters did not affect significantly the results for the primary end points in both study populations. An analysis of variance (ANOVA) based on ranks that took the center of covariate was performed also showing that there was no significant center-treatment interaction."[12]

In the secondary endpoints, in the ITT analysis there was no statistical significance between groups regarding the SSS, but there was a statistical significance in the TP analysis in regard to SSS. There was a statistically significant difference in the combined BI/RS of both the ITT and TP analyses. There was no significant difference in the 30-day mortality of either group in either analysis. (See tables 7 and 8 for outcome scores and hemorrhagic conversion rates)

Table 7. ECASS Outcomes Scores

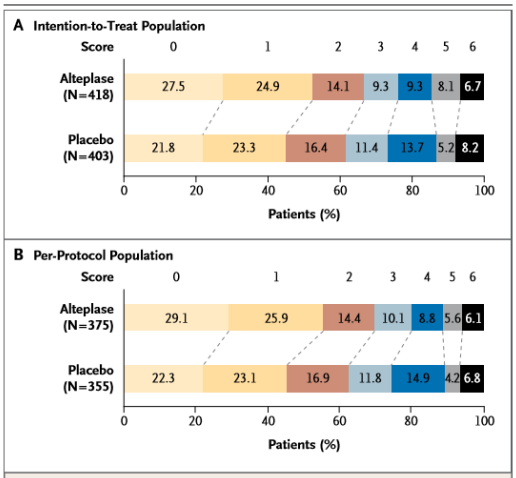


Figure 2. Distribution of Scores on the Modified Rankin Scale.
The distribution of scores is shown for the intention-to-treat population (Panel A) and the per-protocol population (Panel B) at the 3-month visit (90 days plus or minus 14 days). In both the intention-to-treat population and the per-protocol population, stratified analysis of the score distribution showed a significant difference between the study groups (P=0.02 for both comparisons by the Cochran–Mantel–Haenszel test, with adjustment for the baseline score on the National Institutes of Health Stroke Scale and for the interval between the onset of symptoms and the initiation of treatment). In the intention-to-treat population, the number of deaths recorded at the 3-month visit (59) was different from the overall number of deaths (66), since 7 deaths occurred after 90 days. The scores on the modified Rankin scale indicate the following: 0, no symptoms at all; 1, no significant disability despite symptoms (able to carry out all usual duties and activities); 2, slight disability (unable to carry out all previous activities but able to look after own affairs without assistance); 3, moderate disability (requiring some help but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance); 5, severe disability (bedridden, incontinent, and requiring constant nursing care and attention); 6, death.

Table 8. ECASS Hemorrhage Rates

Table 5. Prespecified Safety End Points and Other Serious Adverse Events.*

Adverse Events	Alteplase Group (N=418)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value
	no. (%)			
Prespecified safety end points				
Any ICH	113 (27.0)	71 (17.6)	1.73 (1.24–2.42)	0.001
Symptomatic ICH				
According to ECASS III definition†	10 (2.4)	1 (0.2)	9.85 (1.26–77.32)	0.008
According to ECASS II definition‡	22 (5.3)	9 (2.2)	2.43 (1.11–5.35)	0.02
According to SITS–MOST definition§	8 (1.9)	1 (0.2)	7.84 (0.98–63.00)	0.02
According to NINDS definition¶	33 (7.9)	14 (3.5)	2.38 (1.25–4.52)	0.006
Fatal ICH	3 (0.7)	0	—	—
Symptomatic edema	29 (6.9)	29 (7.2)	0.96 (0.56–1.64)	0.89
Death	32 (7.7)	34 (8.4)	0.90 (0.54–1.49)	0.68
Other serious adverse events				
Total	105 (25.1)	99 (24.6)		
Infectious	16 (3.8)	23 (5.7)		
Neoplastic	4 (1.0)	3 (0.7)		
Blood and lymphatic	0	2 (0.5)		
Endocrine	0	1 (0.2)		
Metabolic and nutritional	2 (0.5)	0		
Psychiatric	3 (0.7)	4 (1.0)		
Neurologic	60 (14.4)	48 (11.9)		
Eye	1 (0.2)	0		
Cardiac	22 (5.3)	16 (4.0)		
Vascular	10 (2.4)	10 (2.5)		
Respiratory	14 (3.3)	24 (6.0)		
Gastrointestinal	5 (1.2)	8 (2.0)		
Hepatobiliary	3 (0.7)	3 (0.7)		
Skin	1 (0.2)	0		
Musculoskeletal	1 (0.2)	3 (0.7)		
Renal	4 (1.0)	2 (0.5)		
Reproductive system	1 (0.2)	0		
Congenital	0	1 (0.2)		
General	1 (0.2)	3 (0.7)		
Associated with injury	4 (1.0)	5 (1.2)		
Surgical	1 (0.2)	0		

* P values were obtained by Pearson chi-square test of proportions. ECASS denotes European Cooperative Acute Stroke Study, ICH intracranial hemorrhage, NIHSS National Institutes of Health Stroke Scale, NINDS National Institute of Neurological Disorders and Stroke, and SITS–MOST Safe Implementation of Thrombolysis in Stroke–Monitoring Study.
† The ECASS III definition of symptomatic intracranial hemorrhage was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.
‡ The ECASS II definition was the same as that for ECASS III, except that establishment of a causal relationship between the hemorrhage and clinical deterioration or death was not a requirement.
§ The SITS–MOST definition was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.
¶ In the NINDS definition, a hemorrhage was considered symptomatic if it had not been seen on a previous CT scan but there was subsequently either a suspicion of hemorrhage or any decline in neurologic status. To detect intracranial hemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical findings suggested hemorrhage.

B.4 European Cooperative Acute Stroke Study (ECASS II)

The ECASS II study was performed following the initial ECASS I study discussed in a prior section. As stated, the ECASS I study was to investigate the use of rt-PA at a dosing of 1.1 mg per kg of body weight versus placebo within 6 hours of stroke symptoms. The results showed no significant difference between the two groups in the median scores

of the primary outcome measures. [12,20] There were, however, favorable outcomes in the Target Population analysis using Alteplase, similar to the results found in the NINDS trial. [12,20] Because of these results the ECASS II was designed to match the NINDS trial with the use of rt-PA at a dosage of 0.9 mg per kg of body weight, but instead of using symptoms starting within 3 hours of onset, as in the NINDS trial, they would extend the infusion start time to 6 hours, similar to the ECASS study. Randomization of the patients was equal for both rt-PA administration versus placebo, with time strata of 0 to 3 hours and 3 to 6 hours, with a hypothesis to see if improved clinical outcome occured in each group treated with rt-PA versus placebo. [20]

The ECASS II study [20] was a non-angiographic trial, so that the precise location of the thrombus was not identified, except for those patients with a hyper-dense MCA sign on initial CT scanning. The study was performed in Europe, Australia, and New Zealand at 108 centers. Eligible patients were 18–80 years of age who could be treated within 6 hours of onset of mild to moderate clinically diagnosed signs and symptoms of stroke that had minimal or no signs of infarct on CT scan and could be followed up to 90 days during the study period. [20] The patients that were excluded were the same as in the ECASS I study, with the exception of those patients with cerebral edema exceeding 33% who were not excluded as against those with cerebral edema of the entire hemisphere in the ECASS I study. [12,20]

ECASS II used a computer-generated randomization in blocks of 4. Each center had at least 1 block of treatment groups at 0–3 hours and 3–6 hours. Each center and all investigators took courses before and during the trial for CT-scanning procedure and assessment. Eligible patients at each center were randomized to a treatment group with

sequential patient numbers. The randomization of the patients was only known to one of the External Safety Committee members and to the Clinical Trial Support Unit at Boehringer Ingelheim. The investigators were blind to the allocation of patients unless there was an emergency (5 instances of emergency occurred), in which case the investigator had access to a sealed opaque envelope revealing the treatment allocation. The investigators could withdraw a participant from the trial if there was a medical issue, administrative issue, or if the patient withdrew consent. Each patient was followed for 90 days if possible and at the 90-day mark the follow up was performed by a local investigator at the local center. The investigator evaluating the patient was blinded to any information that could suggest or lead them to believe which arm of the randomization the patient was allocated to. The patients after randomization and stratification were provided either placebo or Alteplase. The Alteplase or placebo was given as 0.9 mg/kg for body weight with a maximum of 90 mg per patient as a bolus of 10% of the total dose given over 1–2 minutes, with the remainder provided over the next 60 minutes. Each vial was undistinguishable from the others. [20]

> "The primary endpoint was the proportion of patients who had a favorable outcome (score 0 or 1) on the modified Rankin scale (mRS a 7-point scale that assesses overall function; death is rated as 6) 90 (+/-14) days after treatment. A post-hoc analysis of mRS scores dichotomized for dependency (in which scores of 0, 1, and 2 were classified as favorable) was also done. Secondary endpoints were the change from baseline to day 30 on the National Institutes of Health Stroke scale (NIHSS-a 46-point scale that assesses neurological deficit) and the combination of Barthel index (BI-a 100-point scale that assesses activities of daily living) and the mRS at day 90 (as defined in ECASS I).[12] Further endpoints were the BI at day 90, the SSS (a 48-point scale that assesses neurological deficit) at day 90, the duration of hospital stay, and quality of life at day 90 (short-form-36 (SF-36)) rated by the patient. Other endpoints (the infarct volume assessed by CT at days 1 and 7, and the combination of various endpoints) will be the subject for future detailed analysis." [20]

Safety variables of mortality and hemorrhage were the same as the ECASS I study. [12,20]

In the analysis, the sample-size estimation for the primary endpoint was a two-sampled test of proportion with an alpha of 5% and power probability of 80%. The power was devised to detect or disprove an absolute difference of approximately 10% between the treatment groups as to the percentage of patients having a favorable outcome. Eight hundred (800) patients were recruited for the study, firstly to compensate for possible violations, and secondly because it was determined by the sampling analysis that 350 patients in each group would be required to achieve the desired power adjusting for 30% of the placebo groups would have a favorable outcome.

> "The primary analysis as by intention to treat, of all randomized patients. The primary endpoint (mRS) was dichotomized according to the NINDS criteria [7] and analyzed by Fisher's exact test (p=0.05), with scores of 0 or 1 taken to indicate a favorable outcome and scores of 2–6 taken to indicate an unfavorable outcome (death rated as 6). Secondary endpoints were analyzed by the Wilcoxon rank-sum test.
>
> Mortality was analyzed by the log-rank test. Kaplan-Meier estimates were plotted over the observation period of 90 days. The frequency and severity of adverse events, especially of intracranial hemorrhages, were analyzed by Fisher's exact test.
>
> If values were missing, the last observation was carried forward. For the mRS and the BI, a worst-case imputation (mRS=5, BI=0) was made for missing values at day 90.
>
> The Safety Monitoring Committee carried out continuous masked safety monitoring, with an interim analysis for the primary endpoint after 175 evaluable patients in each group had been tested." [20]

There were 409 patients assigned to the rt-PA group and 391 to the placebo group. All patients randomized were included in the intention-to-treat analysis; however, there were 7 that were not treated, 2 in the rt-Pa and 5 in the placebo group (2 withdrew consent, 2 deteriorated, 2 in the rt-Pa group improved prior to administration of rt-PA, and 3 improved prior to the administration of placebo). Both groups were similar in baseline variables and there were 72 protocol violations, most of them violations in the CT criteria 34 and 38, for rt-Pa group and placebo group respectively.

> "At baseline, 341 (42.6%) patients had no signs of infarction on the CT scan. 414 (51.8%) patients had hypodensity of 33% or less of the middle-cerebral-artery territory, and 37 (4.6%) patients had hypodensity of more than 33% of that territory; the CT scan of eight patients was not available or readable because of low quality."[20]

The primary endpoint distribution, mRS scores in all randomized patients, had a favorable outcome (mRS score 0 or 1) in 165 (40.3% (95% CI 35.6-45.4) and 142 (36.6% (31.8-41.6) in the rt-PA group and placebo group respectively. The absolute difference of 3.7% was in favor of the rt-PA group. [20] The post-hoc analysis evaluated the mRS scores with a dichotomization procedure, whereas outcome was classified in terms of independence, mRS scores, or 0–2. Although not a primary endpoint, there were 222 patients (54.3% (49.5-59.1)) in the rt-PA group and 180 in the placebo group (46.0% (51.1-50.9)) who were independent at the 90-day evaluation. There was an absolute difference in favor of the rt-PA group of 8.3% with p=0.024, from the Fisher's exact test. [20] The secondary endpoint showed a median change in the NIHSS score from baseline to 30 days as the only significance between the groups. In the stratifying analysis of the primary and secondary endpoints of patients treated at 0–3 hours and 3–6 hours after the onset of stroke signs and symptoms, there was no significant difference between the rt-PA group and placebo groups, with a note that "The results for the 0-3 h subgroup should be interpreted with caution because the numbers were small." [20]

The adverse events that occurred in the study showed that 85 (10.6%) patients died during the observation period up to 104 days. Two (2) patients, 1 in each group, died after randomization but before administration of the rt-PA or placebo. There was no difference in the 30-day and 90-day mortalities between the two groups, being 43 and 42 for rt-PA and placebo respectively. Forty-five (45) of the deaths occurred within the first 7 days,

being 25 and 20 for rt-PA and placebo respectively. Among the patients that died within the first 7 days, there were more deaths in the rt-PA group specifically due to intracranial hemorrhage (11 rt-PA and 2 placebo). The most common cause of death in the placebo group was from cerebral edema, being 17 compared to 8 in the rt-PA treated group. The combination of intracranial hemorrhage and cerebral edema occurred causing death in 7 of the rt-PA group and 2 in the placebo group. Patients that died after 7 days were similar as to cause and were all non-cerebral (cardiac or pulmonary). Patients in the 0–3 hour subgroup of the rt-PA group had more deaths in the first 102 days compared to the placebo group (11 (14%) versus 6 (8%)). For the same period of 102 days, in the 3–6 hour subgroup the number of deaths in the rt-PA group was 31 (9.5%) and in the placebo group it was 35 (11.3%). [20] Of all adverse events, for up-to-30-day events there were 1804 in the rt-PA group and 1591 in the placebo group, whereas after 30 days only serious events were reported, since most were mild (65.8 and 66.6 for rt-PA and placebo respectively) with less than 20% being non-specific disorders, urinary disorders, cardiovascular disorders, nervous system disorders, and gastrointestinal disorders. Only adverse events associated with platelet, bleeding, and clotting disorders had a clinical or statistical significance between the treatment groups. [20]

Regarding adverse events associated with hemorrhage, there was no significant difference between the two groups as to hemorrhagic conversion of the infarct or hemorrhagic infarction, but there was a considerable difference in parenchymal hemorrhage among the rt-PA group and placebo, being approximately 4 times more common in the former (11.8% versus 3.1%). “Large, confluent, space-occupying intracranial hemorrhage (PH2) was 10 times more common in the Alteplase group. The

difference in the rate of PH2 hemorrhages was apparent in both time-to-treatment subgroups. The frequency of all symptomatic intracranial hemorrhage showed a 2.5-fold excess with Alteplase compared with placebo."[20]

The conclusion of this study showed that, regarding the primary endpoint there was no significant difference between the rt-PA and placebo groups. For the secondary post-hoc endpoint there was a significant effect in favor of the rt-PA group, with 8.3% or 83 per 1000 fewer deaths or dependency in the rt-PA group. Although there is no statistical significance in the outcomes of patients treated with rt-PA, as in the previous studies it does show that in the primary endpoint there was a 3.7% absolute difference or 10% relative difference, which suggests that 37 of every 1000 patients will have a good functional outcome. [20] Comparing the ECASS I, ECASS II, and NINDS, the ECASS II had a lower mortality rate, most likely because of selection bias. The ECASS II had overall less severe neurologic deficits at baseline, with NIHSS scores of 13 and 12 for rt-PA and placebo respectively in the ECASS I study, again 14 and 15 for rt-PA and placebo respectively in the NINDS study, and only 11 in the ECASS II study for both groups. ECASS II also showed less infarct on CT scan than either of the prior studies.

B.5 European Cooperative Acute Stroke Study (ECASS III)

"ECASS III, a randomized, placebo-controlled, phase 3 trial designed to test the hypothesis that the efficacy of Alteplase administered in patients with acute ischemic stroke can be safely extended to a time window of 3 to 4.5 hours after the onset of stroke symptoms." [21] The background for the study was the NINDS study which reported the use of rt-PA given within less than three hours of stroke symptom onset, showing a 30% greater

improvement in functional outcome at three months, and little to no deficits, than those that received placebo, [7,21] the two European trials, ECASS and ECASS II, which failed to show efficacy of thrombolysis up to six hours as defined by the trial, [12,20,21] and a subsequent analysis of the NINDS study, [22] a pooled analysis with data from six randomized trials. [7,10-12,20] The pooled analysis showed favorable outcomes even if treatment was provided between 3 and 4.5 hours with an odds ratio of 1.4 of Alteplase versus placebo. [10,21]

> "International guidelines recommend Alteplase as a first-line treatment for eligible patients when administered within 3 hours after the onset of stroke. [23-25] Despite this recommendation, Alteplase is underused; it is estimated that fewer than 2% of patients receive this treatment in most countries, primarily because of delayed admission to a stroke center. [26]
>
> Thrombolysis with Alteplase has been approved in most countries. In Europe, The European Medicines Agency (EMEA) granted approval of Alteplase in 2002 but included two requests. One request was an observational safety study be initiated; subsequently, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was undertaken. This study confirmed that Alteplase is as safe and effective in routine clinical practice as it is in randomized trials.[27] The second request was that a randomized trial be conducted in which the therapeutic time window was extended beyond 3 hours." [21]

The study was initially devised to treat patients in the age group of 18–80 between 3 to 4 hours after stroke symptoms, with CT or MRI showing no major stroke or intracranial hemorrhage. Because of the pooled analysis study [9] published during ECASS III, the time was extended to 4.5 hours with the approval of the European Medicines Agency. Patients from multiple centers around Europe were randomly assigned in a 1:1 ratio to receive either placebo or Alteplase 0.9 mg/kg with a max limit of 90 mg. Randomization was by voice-randomization system with randomization performed in blocks of four ensuring balanced distribution of groups. The investigators were blinded to the size of the blocks and treatment assignments. A steering committee designed and oversaw the trial, with an independent data and safety monitoring board monitoring safety during the trial. The safety

committee only received information of death and symptomatic hemorrhages with group assignments of A or B and C or D, respectively. The steering committee had access to the trial data only after the database was locked. Concomitant therapies were not able to be utilized in the first 24 hours of the administration of the drug or placebo, except for medications to prevent deep venous thrombosis. Patients were assessed by a blinded examiner. Assessments were performed at the time of enrollment, 1 hour and 2 hours after administration of the drug, at 24 hours after administration, and on days 7, 30, and 90. CT or MRI and physical exam, with the use of the NIHSS score, were used at the initial assessment. The NIHSS score was used on days 1, 7, 30, and 90. The mRS score was used at days 30 and 90 to measure disability along with the Glasgow Outcome Score and Barthel Index as commonly used in other studies to determine disability. CT and MRI were again utilized between 22 and 36 hours after administration of the medication. Blinded evaluators provided the radiographic readings and used the same definition as the ECASS study for hemorrhage evaluation.[12]

> "The primary efficacy end point was disability at day 90 (3-month visit), as assessed by means of the modified Rankin scale, dichotomized as favorable outcome (a score of 0 to 1) or an unfavorable outcome (a score of 2 to 6). The secondary efficacy end point was a global outcome measure that combined the outcomes at day 90 of a score of 0 or 1 on the modified Rankin scale, a score of 95 or higher on the Barthel Index, a score of 0 or 1 on the NIHSS, and a score of 1 on the Glasgow Outcome Scale.[7] Further functional end points were based on predefined cutoff points for the NIHSS score (a score of 0 or 1, or more than and 8-point improvement in the score), the score on the modified Rankin scale (dichotomized as 0 to 2 or 3 to 6), and the Barthel Index (>/= 95 points), assessed on day 90 and also on day 30. Because of recent interest in the scientific community in a stratified analysis of the outcome distribution of the modified Rankin scale at day 90, this type of evaluation was undertaken according to the methods described previously. [28]
>
> Safety end points included overall mortality at day 90, any intracranial hemorrhage, symptomatic intracranial hemorrhage, symptomatic edema (defined as brain edema with mass effect as predominant cause of clinical deterioration), and other serious events." [21]

Symptomatic Intracranial hemorrhage was considered with any patient having extravascular blood in the cranial vault, intra or extra axial or intraventricular, that caused a four-point increase in the NIHSS score or was considered the cause of death.

In the statistical analysis, the efficacy endpoints were used for the intention-to-treat population. All patients were randomized even if they were not treated. If there was any missing outcome data on patients known to be alive, they were given the worst possible score. Chi-square test score or proportions (two-sided alpha level of 5%) were calculated for the primary endpoint between the two groups. Confidence intervals of 95% were uses for odds ratios and relative risk. The study protocol was utilized and all predefined analysis without adjustment for other confounding factors was utilized. A logistic regression post-hoc analysis of the primary endpoints was used in the intention-to-treat population. The analysis performed included all baseline variables with retention of those that were significant at the level of $P<0.10$ in the models. Secondary endpoint probability of favorable outcome with rt-PA compared to placebo was performed with a global odds-ratio test with a linear regression model; this is a Wald-type test which is used to perform generalized estimation equations. The pre-protocol population used the same statistical tests. Regarding the modified Rankin scale, it was adjusted in the post-hoc analysis with the two most strongly prognostic base line variables, the NIHSS score and the start of treatment time. Sample size was provided by an analysis of the pooled data from the cohorts that received rt-PA or placebo during the 3 to 4.5-hour period after the symptom onset. The ECASS I data was excluded because higher doses of rt-PA were utilized. It was calculated that 400 patients per group were needed to obtain 90% power to detect an odds ratio of 1.4 for the primary endpoint.

The results of this study showed a total of 821 patients from 130 sites in 19 countries in Europe who were randomized and assigned to study groups. Four hundred and eighteen (418) were assigned and received rt-PA, while 403 were assigned and received the placebo. The groups were assigned based on intervals of 0.5 hours with 10% of the patients treated in the 3 to 3.5-hour group, 46.8% in the 3.5 to 4-hour group, and 39.2% in the 4 to 4.5-hour group. The discrepancy in the total not adding up to 100% is because multiple patients being treated did not have an exact time of treatment, 12 and 15, and treatment started after 4.5 hours, for 1 and 5, in the rt-PA group and placebo groups respectively. The patients in both groups from a demographic standpoint were similar, except for initial severity of stroke and presence of absence of previous stroke. Regarding efficacy, the primary endpoint:

> "...219 of the 418 patients in the Alteplase group (52.4%) had a favorable outcome (defined as a score of 0 or 1 on the modified Rankin scale), as compared with 182 of the 403 patients in the placebo group (45.2%), representing an absolute improvement of 7.2 percentage points (odds ratio, 1.34; 95% confidence interval (CI), 1.02 to 1.76; relative risk, 1.16; 95% CI, 1.01 to 1.34; P=0.04). In the post hoc intention-to-treat analysis, adjusted for confounding baseline variables (logistic regression), study-group assignment, baseline NIHSS score, smoking status, time form the onset of stroke to treatment and presence or absence of prior hypertension were identified as significant at P<0.10. In the adjusted analysis, treatment with Alteplase remained significantly associated with a favorable outcome (odds ratio, 1.42; 95% CI, 1.02 to 1.98; P=0.04)." [21]

Regarding secondary endpoints, the rt-PA treatment group showed better outcomes than the placebo group in regard to the global odds ratio. It was noted that the global odds-ratio test was a linear regression model, with a Wald-type test that used general estimation equations resulting in probabilities and not absolute numbers. "The global odds ratio for a favorable outcome was 1.28 (95% CI, 1.00 to 1.65; P<0.05), indicating that the odds for a

favorable outcome (the ability to return to an independent lifestyle) after stroke were 28% higher with Alteplase than with placebo." [21].

Evaluation of the modified Rankin scale at the 90-day evaluation showed favorable outcomes with Alteplase as compared with placebo, showing a P=0.02.

> "In the intention-to-treat analysis, the odds ratios for a score of 0 or 1 on the modified Rankin scale, an NIHSS score of 0 or 1, and more than an 8-point improvement in the NIHSS score at day 30 showed a significant advantage of Alteplase treatment whereas there were no significant differences between the groups with respect to the other functional end points. Neurologic status up to day 30 did not differ significantly between the two groups." [21]

The safety profile in this study showed a total of 66 deaths, 32 in the rt-PA group and 34 in the placebo group, being 7.7% and 8.4% respectively; 2.9% and 3.2% respectively within the first 7 days; 2.4% and 2.0% respectively between 8 and 30 days; 1.4% and 2.5% respectively between days 31 and 90; and 1.0% and 0.7% respectively after day 90. Intracranial hemorrhage occurred more often in the rt-PA group than in the placebo group, 27% versus 17.6% with P=0.001. However, the incidence of symptomatic hemorrhage was greater in the placebo group than in the rt-PA group, which was similar to other studies. The rt-PA group had an incidence of 3 cases per 100 patients, 2.4%, and the placebo group 0.3%, with odds ratio of 9.85, CI of 95%, 1.26 to 77.32; P=0.008. All the symptomatic intracranial hemorrhages occurred during the first 22 to 36 hours after treatment was started. In regard to other adverse events like symptomatic edema or adverse events of other organ systems, there was no significant difference. [21] (See tables 9 and 10 for outcome scores and hemorrhagic conversion rates.)

Table 9. ECASS III Outcomes Scores

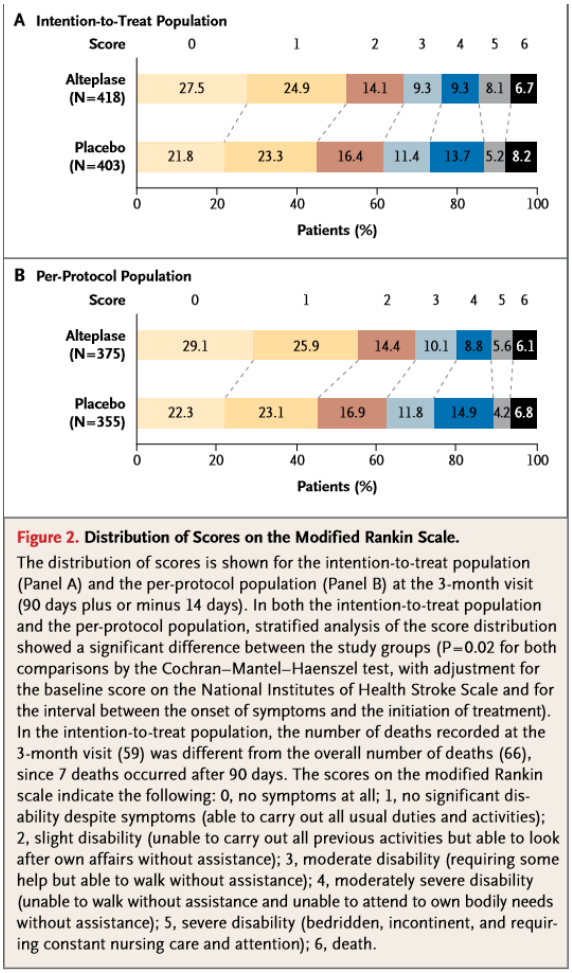


Figure 2. Distribution of Scores on the Modified Rankin Scale.

The distribution of scores is shown for the intention-to-treat population (Panel A) and the per-protocol population (Panel B) at the 3-month visit (90 days plus or minus 14 days). In both the intention-to-treat population and the per-protocol population, stratified analysis of the score distribution showed a significant difference between the study groups (P=0.02 for both comparisons by the Cochran–Mantel–Haenszel test, with adjustment for the baseline score on the National Institutes of Health Stroke Scale and for the interval between the onset of symptoms and the initiation of treatment). In the intention-to-treat population, the number of deaths recorded at the 3-month visit (59) was different from the overall number of deaths (66), since 7 deaths occurred after 90 days. The scores on the modified Rankin scale indicate the following: 0, no symptoms at all; 1, no significant disability despite symptoms (able to carry out all usual duties and activities); 2, slight disability (unable to carry out all previous activities but able to look after own affairs without assistance); 3, moderate disability (requiring some help but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance); 5, severe disability (bedridden, incontinent, and requiring constant nursing care and attention); 6, death.

Table 10. ECASS III Hemorrhage Rates

Adverse Events	Alteplase Group (N=418)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value
	no. (%)			
Prespecified safety end points				
Any ICH	113 (27.0)	71 (17.6)	1.73 (1.24–2.42)	0.001
Symptomatic ICH				
According to ECASS III definition†	10 (2.4)	1 (0.2)	9.85 (1.26–77.32)	0.008
According to ECASS II definition‡	22 (5.3)	9 (2.2)	2.43 (1.11–5.35)	0.02
According to SITS–MOST definition§	8 (1.9)	1 (0.2)	7.84 (0.98–63.00)	0.02
According to NINDS definition¶	33 (7.9)	14 (3.5)	2.38 (1.25–4.52)	0.006
Fatal ICH	3 (0.7)	0	—	—

† The ECASS III definition of symptomatic intracranial hemorrhage was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.
‡ The ECASS II definition was the same as that for ECASS III, except that establishment of a causal relationship between the hemorrhage and clinical deterioration or death was not a requirement.
§ The SITS–MOST definition was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.
¶ In the NINDS definition, a hemorrhage was considered symptomatic if it had not been seen on a previous CT scan but there was subsequently either a suspicion of hemorrhage or any decline in neurologic status. To detect intracranial hemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical findings suggested hemorrhage.

B.6 Effects of Alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomized trial.

Based on the literature prior to this trial which suggested that providing Alteplase was effective if provided within three hours, the authors aimed to evaluate if:

> "The aims of thrombolytic therapy are arterial recanalization and salvage of the ischaemic penumbra, a region of critically hypoperfused but viable brain tissue around the irreversibly damaged infarct core. [29] The ischemic penumbra is present in at least 80% of patients within 3 h of stroke onset but this proportion diminishes with time. [30,31] The potential clinical gains from Alteplase related to tissue reperfusion and attenuation of infarct growth, [32,33] which depends on the degree of irreversible damage and the presence and extent of ischaemic penumbra. The penumbra can be evaluated with echoplanar MRI, diffusion-weighted MRI (DWI), and perfusion-weighted MRI (PWI). DWI lesions are regions of cytotoxic oedema, which usually proceed to infarction, and the mismatch between a large PWI lesion and smaller DWI lesion is thought to be a signature of the ischaemic penumbra. [34,35] The probability of infarction depends on the severity and duration of

> hypoperfusion in the ischaemic penumbra. [36] Therefore, imaging of the penumbra might allow selection of patients for thrombolysis beyond 3 h. No previous randomized trials of Alteplase have used MRI scans before and after therapy to assess the effects on reperfusion, infarct evolution, and clinical outcome. Our primary hypothesis was that Alteplase would attenuate infarct growth in patients who have a mismatch between DWI and PWI lesions. However, we did not plan to use mismatch in the selection of patients, because rapid online detection of mismatch was not feasible, and we were keen to include a proportion of patients without mismatch for an exploratory analysis. Our aim was to establish the effect of intravenous Alteplase on lesion growth, reperfusion, and clinical outcome in penumbral patients 3-6 h after stroke onset." [37]

EPITHET is a phase II prospective, randomized, double-blinded, placebo-controlled, multinational trial. The trial was performed at 15 centers in Australia, New Zealand, the UK, and Belgium. The patients were evaluated with serial echoplanar MRIs after treatment with placebo or rt-PA 3–6 hours after stroke onset. [37-39] Patients that were included in the study had stroke symptoms for longer than 3 hours and less than 6 hours, were older than 18 years of age, had an NIHSS score of 4 or more, modified Rankin score of 2 or less, and a CT scan showing no significant ischemic stroke or hemorrhage as described by the ECASS study. [12,37] Patients excluded from the trial were those not eligible for rt-PA, [23] contraindicated or unable to have an MRI, or patients with life threating illnesses or confounding neurologic disease like dementia. [37] Monitoring of the screening logs was performed by the steering committee, and it was noted that one center with 12 patients utilized MRI as the screening tool for hemorrhage instead of CT and the decision to exclude patients at this center for the trial was decided by the managing physician. [37]

The patients enrolled in the study were randomized and then had a baseline MRI scan prior to the start of treatment with either rt-PA or placebo. In the institution that performed the MRI as the screening tool, the MRI was first completed before the patient was randomized and the MRI was post processed for PWI images, so the MRI was not

used to determine the eligibility or select the therapy. [37] Block randomization design of four treatment packs per block was used within each center with treatment allocation provided by the Clinical Trials Pharmacy at the Royal Melbourne Hospital, Australia. The treatment pack numbers were computer generated for random allocation. Treatment was performed with the next sequential numbered treatment pack containing either placebo or rt-PA in a double-blinded design. An independent biostatistician unblended the treatment allocation after the database was cleaned and locked and performed prespecified statistical analyses which were presented to the steering committee. [37]

The study procedures were detailed and technical, and are beyond the scope of this paper. In summary, the patients had an MRI prior to treatment and then repeated at days 3–5 post treatment. The sequences utilized were DWI, PWI, and MRA. Isotropic diffusion trace images were created from DWI images and Perfusion images were performed. At day 90, MRA as well as T2-weighted images were obtained for final infarct volumes. For patients that expired prior to the 90-day point, the last results of the 3 to 5-day MRI were utilized as a measure of imaging outcome. All the studies were read at the coordinating center by investigators blinded to the treatment assignment and clinical outcomes but not to the time interval, in an attempt to keep imaging analysis standardized. The DWI at baseline and 3–5 days and the T2-weighted images were assessed by 2 independent raters using a standard planimetric software.

> "The region of interest included haemorrhagic transformation if it was within the infarct. The mean DWI and T2-weighted lesion volumes from the two raters were used for subsequent analysis. Postprocessing of perfusion data was done centrally with deconvolution algorithms [40] to create maps of $T_{max,}$ defined as the time to peak of the impulse response. The arterial input function was selected from the contralateral middle cerebral artery, with no correction for associated stenosis of the internal carotid artery. Hypoperfusion volumes were defined using a T_{max} delay of 2 s or more, which we previously showed to be the most accurate estimate of

> critical hypoperfusion in a blinded analysis of the first 40 patients enrolled in EPITHET. [39].” [37]

Further description of the definitions of the variables utilized in the trial included perfusion mismatch, reperfusion, [39,41] recanalization, [42] and outcomes associated with neurologic and functional outcomes.

> “MRA images were analyzed by a neurologist and neuroradiologist and rated by consensus. At baseline and day 3-5, we assessed the presence and degree of arterial obstruction in major intracerebral arteries (internal carotid, middle cerebral, and anterior cerebral arteries) with an adapted Thrombolysis In Myocardial Infarction (TIMI) grading. [42].” [37]

Certified NIHSS investigators evaluated the patients prior to therapy, at days 3–5 and at day 90. The modified Rankin score was estimated at the initial exam and was performed at the 90-day exam with or without imaging studies. The physical exams were blinded to the MRI findings and treatment groups. Serious adverse events including ICH were sent to the data safety monitoring committee and human research and ethics committee for each institution. If a patient had neurologic deterioration, an immediate CT was performed to assess for ICH transformation. The definition of ICH was from the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) [27].

> “We tested the primary hypothesis that there would be greater attenuation of infarct growth in patients with an imaging mismatch who received Alteplase than in those who received placebo. Four measures of infarct growth were predefined efficacy endpoints. Of these, geometric mean relative growth (exponential of mean log relative growth) was the primary endpoint because this parametric measurement allowed for potential statistical adjustment for baseline covariates, which might have been necessary in light of the non-normal data from the EPITHET pilot study. [33] The secondary hypotheses were that reperfusion, good neurological outcome, and good functional outcome would be more likely in mismatch patients who received Alteplase than in those who received placebo, and that the incidence of symptomatic ICH would be associated with larger baseline DWI volumes in patients who received Alteplase. After publications of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study, [43] we added a further prespecified hypothesis that infarct growth would be greater and good clinical outcomes less likely in patients who had very large baseline lesions

> (which we referred to as a malignant profile; than in those who had smaller lesions. We did a post-hoc analysis of the effects of Alteplase versus placebo in target mismatch patients (patients who had mismatch but no malignant profile)." [37]

Statistical analysis was performed by an independent biostatistician prior to the investigators being made aware of the treatment allocations. The primary hypothesis had multiple tests. The first test was a Student's *t* test of means of log relative growth. Because the relative growth is determined by the division of lesion volume at the 90-day point by the baseline test of DWI lesion volume, there was adjustment made for the differences. Relative and absolute growth were analyzed by using Wicoxon's non-parametric test. A Student's *t* test was utilized to find the difference of cube-root transformed volume changes. There were potentially confounding variables of:

> "..age, baseline NIHSS, time to treatment, baseline DWI volume and baseline mismatch volume. We planned to adjust baseline variables that differed between treatment groups with $p<0.1$. Fisher's exact test was used for comparison of categorical variables. In the post-hoc analysis, we used binary logistic regression to assess the influence of baseline variables and treatment allocation on mortality.
>
> The non-randomized pilot study [33] suggested a mean log expansion of about 0.5 in the Alteplase group and 1.2 in the control group, each with SD 1.0. We estimated that 76% of patients would have mismatch. Based on an estimated difference of 0.65 (ratio of geometric means = 1.9) between the Alteplase and placebo groups, 81% power at the 5% level would be achieved with 38 patients in the Alteplase group and 38 controls, supporting a sample size of 100 patients. Modelling and simulation suggested greater power for Wilcoxon's test, but the Student's *t* test was preferred for the ability to adjust for baseline imbalance." [37]

When MRI was immediately available, 3908 patients screened from April 2001 to January 2007. Eight percent (8%) of the 1224 patients enrolled were screened within 6 hours, i.e., 101 patients out of 1224. "Principal reasons for exclusion among the 1123 patients who presented within 6 h were haemorrhage detected by screening CT (29%), Alteplase treatment indicated within 3 h (20%), NIHSS of 4 or less (16%), symptoms that resolved rapidly (9%), declined consent (7%), comorbid illnesses (7%), inability to

perform MRI before 6 h (3%), an major early ischaemic change (2%)."[37] Mean time was 3 days for the median time between baseline and the 3–5 day MRI scan.

The DWI lesion volume at the 3 to 5-day MRI was measured in 91 of the patients; 9 did not have the MRI, 7 died, one had a poor quality study, and one did not have DWI imaging. PWI lesion volumes were measured in 87 patients, whereas 7, 4, and 2 patients respectively died, had poor DWI quality, or there was no DWI performed.

Twenty patients died before the 90-day point. The 90-day MRI was not performed in 19 patients of the Alteplase group, with 13 dying and 6 lost to follow up, whereas in the placebo group 7 died and 1 was lost to follow up. Seventy-two (72) and 79 of the patients that survived who had T2-weighted lesion volumes had baseline DWI and PWI. DWI lesion volume at 3–5 days as a surrogate for the 90-day lesion was used for 19 patients who did not have the 90-day MRI scan, being 12 and 7 for Alteplase and placebo respectively. Barring the 91 patients having baseline PWI and DWI imaging around the ninetieth day or from the last observation carried forward, the results between the baseline DWI and the 90-day T2-weighted MRI lesion correlated. "There was complete agreement between raters in the classification of patients into the mismatch and non-mismatch groups (k=1)." [37] There was no statistical correction needed for baseline variables of patient with mismatch of PWI and DWI for either groups. "The prevalence of mismatch was 86% (85/99). Of the 42 patients who had mismatch and received Alteplase, all had assessment of clinical outcome and 37 had a valid imaging outcome; all 43 of the patients who had mismatch and received placebo had clinical and valid imaging outcomes."[37]

In 87 patients with good MRIs at baseline, 54 had arterial obstruction with TIMI grading; 38 had grade 0, 11 had grade 1, and 4 had grade 2.

> "According to the primary analytical method, the geometric mean growth in the Alteplase group was about two-thirds of that in the placebo group, although this difference was not significant. The ratio of the geometric means between the Alteplase and placebo groups was 0.69 (95% CI 0.38-1.28; p-0.239). In the secondary analytical method, median relative infarct growth in the Alteplase group was two-thirds (0.00, 95% CI 0.36-0.92; p=0.054) that in the placebo group." [37]

The proportion of patients with growth of the mismatch was significantly lower in patients who received Alteplase than in those who did not. However, lesions that were 5mL or less, 6 and 5 patients in the Alteplase group and placebo group respectively, were excluded because small lesions had been described to be prone to measurement issues relative to growth in multiple studies. [44,45]

> "In all patients with imaging at day 90 or a last observation carried forward, median relative growth was significantly higher in patients who did not achieve good neurologic outcome than in those who did (2.2, IQR 1.4-5.7 vs 0.9, 0.3-1.5; p<0.0001), and higher in patients who did not achieve a good functional outcome than in those who did (2.1, 1.3-4.5 vs 0.3-1.8; p<0.0001).
>
> Both the incidence of reperfusion and the median percentage reperfusion were significantly higher in patients with mismatch who received Alteplase than in those who did not. Reperfusion was significantly associated with lower geometric mean infarct growth, good neurologic outcome, and good functional outcome, for all patients and for mismatch patients." [37]

Forty-eight (48) of the 54 patients with baseline MRA showing arterial occlusion were recanalized in 30 of the patients at the 3 to 5-day MR study.

> "...47 patients for whom recanalization could be assessed and who had mismatch, recanalization was greater with Alteplase than with placebo but this difference was not significant. Recanalization was associated with lower infarct growth (geometric mean growth 1.45 vs 3.49, ratio 0.42, 95% CI; o.17-0.99; p=0.048), good neurological outcome (15/30 (50%) vs 3/17 (18%), 95% CI 7%-58%; p=0.034), and good functional outcome (16/30 (53%) vs 2/17 (12%), 95% CI 18%-65%; p=0.0006) in patients with mismatch.
>
> Among all patients and mismatch patients, the incidence of good neurological outcome and good functional outcome did not differ between treatment groups. For the mismatch patients, functional outcome was excellent (mRS 0-1) in 15% more patients in the Alteplase group compared with the placebo group for all patients (13/51, (25%) vs 749 (49%); 95% CI -4% to 27%; p=0.161) or for mismatch patients (11/42 (26%) vs 5/43 (12%), 95% CI -2% to 31%; p=0.102). Mulitvariate analysis of all patients with treatment group, age, baseline

NIHSS, hypertension, and diabetes as variables showed that baseline NIHSS (odds ratio 1.10, 95%CI 1.00-1.21; p=0.053) and diabetes (3.30, 0.97-11.17; p=0.055) were non-significant predicators of increased mortality, but treatment with Alteplase (2.14, 0.72-6.41; p=0.170), age (1.03, 0.98-1.07; p=0.268), and hypertension (0.55, 0.16-1.94; p=0.353) were not.

The incidence of symptomatic ICH was 7.7% (4/52, 95% CI 2.1-18.5) with Alteplase and 0% with placebo. Of the patients with symptomatic ICH, three had mismatch. Median baseline DWI volumes did not differ between patients with symptomatic ICH (median 32.2 mL, IQR 21.3-47.4) and those without (19.6, 8.2-44.7).

Eleven (11) patients in whom primary outcome could be assessed had no mismatch. Growth, major reperfusion, and clinical outcomes did not differ significantly between mismatch and non-mismatch patients. In non-mismatch patients, infarct growth did not differ significantly between the Alteplase and placebo groups (geometric mean growth 1.06 vs 1.22, ratio 0.87, 95% CI 0.43-1.74; p=0.649)

Of the 88 patients with mismatch for whom imaging outcomes were valid and clinical outcomes were assessed, 53 had target mismatch and 35 had a malignant profile. Patients with a malignant profile had a larger lesions and worse baseline clinical impairment than did those with target mismatch. None of the patients with malignant profile developed symptomatic ICH. In patients treated with Alteplase, the malignant profile was associated with less reperfusion, greater infarct growth, and poorer clinical outcomes than was target mismatch. In patients with target mismatch, the Alteplase and placebo groups did not differ with respect to geometric mean growth (0.91 vs 1.41, ratio 0.65, 95% CI 0.29-1.43; p=0.274), good neurological outcome (17/26 (65%) vs 11/27 (41%), 95% CI -1% to 51%; p=0.072), or good functional outcome (6/26 (62%) vs 13/27 (48%), -13% to 40%; p=0.328)." [37]

B.7 **EXTEND International**

This is a recent study and expected to be published in 2019; however, the results were presented at the World Stroke Conference. The trial was the first to extend the time window of treatment for stroke with rt-PA. The WAKE-UP trial published in 2018 [46] (see details in the previous section) showed that patients with unknown timing of symptom onset using MRI can be treated effectively with rt-PA with no significant increase in risk. However, based on the MRI results it is likely the stroke occurred within 4.5 hours. The EXTEND International trial utilized CTP to determine if a patient can be treated with rt-

PA up to 9 hours after stroke symptoms started. The trial was stopped early with the publication of the WAKE-UP trial.

This trial enrolled 225 patients that had stroke symptoms longer than 4.5 hours up to 9 hours or experienced a wake-up stroke with uncertain onset of stroke symptoms. Either MRI or CTP with RAPID software image processing was used to identify patients with perfusion lesion of at least 10 ml and ischemic core greater than 70 ml. The results have not been presented yet, as to how many received MRI vs CTP, but it has been rumored that more patients had CTA. All patients were randomized to either placebo or to receive standard dosing of rt-PA (0.9 mg/kg), with none of the patients going on to have mechanical thrombectomy. The primary endpoint of patients having a modified Rankin score of 0–1 at 90 days was obtained in at least 44% more of the patients receiving rt-PA than placebo, with symptomatic hemorrhage rates of 6% in the rt-PA patients and 1% in the placebo patients, similar to patients treated with rt-PA within the 4.5 hours current standard of care. There was no significant difference in mortality rate between the two groups, being 12% in the rt-PA patients and 9% in the placebo patients.

B.8 Summary of Tissue Plasminogen Activator for Acute Ischemic Stroke

As detailed above in the NINDS, ATLANTIS A and B, ECASS I, II, and III, and EPITHET trials, utilization of Alteplase, rt-PA, improves clinical outcomes if utilized within 3 to 4.5 hours of stroke symptom onset.[7,10-12,20,21,37] In the NINDS trial the results in part 1 of the study showed that "no statistical significant difference were detected between groups in the primary outcome…..However, post hoc comparisons of median NIHSS scores showed improvement in the condition of the patient treated with t-PA as compared

to those given placebo in most time strata in parts 1 and 2 and in the combined analysis." [7]

Overall, in this study:

> "As compared with the placebo group, there was a 12 percent absolute (32 percent relative) increase in the number of patients with minimal to no disability (a score of 95 or 100 on the Barthel index) in the t-PA group. There was also an 11 percent absolute (55 percent relative) increase in the number of patients with an NIHSS score of 0 to 1 in this group. A similar magnitude of effect was seen with respect to the absolute and relative improvement in the t-PA group with the use of the modified Rankin scale and the Glasgow outcome scale." [7]

Of the patients in the NINDS study that had symptomatic intracranial hemorrhage within 36 hours of treatment, in Part 1 of the study 8 were in the t-PA group and 0 in the placebo group, whereas in Part 2 of the study 12 were in the t-PA group and 2 in the placebo group, i.e., approximately 6%.

The Atlantis A trial proved that providing rt-PA in the 0 to 6–hour range did more harm than good, with a significant increase in the intracranial hemorrhage rate of 11% compared to 0% with the use of placebo, whereas for patients receiving rt-PA in less than 3 hours (15%) and those receiving rt-PA between 5–6 hours (32%), there was no benefit at the 30-day point.

> "The groups were well matched on baseline characteristics, including NIHSS (mean of 13 for both). For the primary end points, a higher percentage of rt-PA patients had a 4-point improvement at 24 hours (placebo 21%, rt-PA 40%; P=0.02); however, this early effect was reversed by 30 days, with more placebo patients having a 4-point improvement (75%) than patients treated with rt-PA (60%, P=0.05). Treatment with rt-PA significantly increased the rate of symptomatic intracerebral hemorrhage within 10 days (11% versus 0%, P<0.01) and mortality at 90 days (23% versus 7%, P<0.01)." [10]

The Atlantis B trial re-evaluated the data from the Atlantis A trial and sought to determine if administering rt-PA to patients with acute ischemic stroke within 3 to 5 hours of symptom onset was safe. The authors concluded:

> "This study found no significant rt-PA benefit on the 90-day efficacy end points in patients treated between 3 and 5 hours. The risk of symptomatic ICH increased with rt-PA treatment. The results do not support the use of intravenous rt-PA for stroke treatment beyond 3 hours." [11]

The ECASS study treated patients with acute ischemic stroke, who had moderate to severe neurologic deficits and no major signs of early infarct on the initial CT scan, with 1.1 mg per kilogram of body weight and not 0.9 mg per kilogram of body weight as previously studied.

The study results showed:

> "There was no difference in the primary endpoints in the ITT analysis, while the TP analysis revealed a significant difference in the RS in favor of rt-PA-treated patients (P=.035). Of the secondary end points, the combined BI and RS showed a difference in favor of the rt-PA-treated patients in both analysis (P<.001). Neurologic recovery at 90 days was significantly better for the rt-PA-treated patients in the TP (=.03). The speed of neurologic recovery assessed by the SSS was significantly better up to 7 days in the ITT analysis and up to 30 days for the TP in the rt-PA treatment arm in both analyses." [12]

The study results in regard to hemorrhage were:

> "The overall incidence of intracranial hemorrhagic events was not significantly different between the treatment groups. In the ITT analysis, 247 patients (39.8%) had intracranial hemorrhage of any degree, 134 patients in the rt-PA group and 113 patients in the placebo group. In the TP analysis, 205 patients (40.1%) had hemorrhagic events of any degree, 108 patients in the rt-PA group and 97 patients in the placebo group. In both analyses, HI was more frequent in the placebo-treated groups, while PH was more frequent in the rt-PA-treated groups. Fisher's exact test showed a significant difference in the subtypes of intracranial bleed events in both analyses (P<.001)." [12]

The study concluded:

> "Intravenous thrombolysis in acute ischemic stroke is effective in improving some functional measures and neurologic outcome in a defined subgroup of stroke patients with moderate to severe neurologic deficit and without extended infarct signs on the initial CT scan. However, the identification of this subgroup is difficult and depends on recognition of early major CT signs of early infarction. Therefore, since treating ineligible patients is associated with an unacceptable increase of hemorrhagic complications and death, intravenous thrombolysis cannot currently

be recommended for use in an unselected population of acute ischemic stroke patients." [12]

The ECASS II study was developed to evaluate if rt-PA administered in the dose of 0.9 mg/kg bodyweight within 6 hours was efficacious and safe. The study concluded:

> "The results do not confirm a statistical benefit for Alteplase. However, we believe the trend towards efficacy should be interpreted in the light of evidence from previous trials. Despite the increase risk of intracranial hemorrhage, thrombolysis with Alteplase at a dose of 0.9 mg/kg in selected patients may lead to a clinically relevant improvement in outcome." [20]

The ECASS III study evaluated if providing Alteplase within 3–4.5 hours was safe and efficacious, considering the fact no studies have concluded that providing Alteplase after 3 hours was safe or efficacious. The study concluded, "As compared with placebo, intravenous Alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; Alteplase was more frequently associated with symptomatic intracranial hemorrhage." [21]

The EPITHET trial was to evaluate if Alteplase is effective within 3 to 6 hours after stroke symptoms and if it effects reperfusion along with attenuation of infarct growth in patients who had an MRI, with a perfusion mismatch on a perfusion weighted and diffusion weighted MRI. They concluded, "Alteplase was non-significantly associated with lower infarct growth and significantly associated with increased reperfusion in patients who had mismatch. Because repercussion was associated with improved clinical outcomes, phase III trials beyond 3 hours after treatment are warranted." [37]

B.9 MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

This is a multicentered trial wherein patients were randomly assigned to receive Alteplase or placebo. For a patient to be eligible, they had to have ischemic lesion on diffuse weighted imaging MRI but not on FLAIR MRI sequence to indicate stroke in the

last 4.5 hours. Patients were excluded if they were candidates for thrombectomy. The endpoint was for a favorable outcome with a modified Rankin score of 0–1 (scale of 0–6) at 90 days, and secondary outcome that Alteplase would lead to lower scores on the modified Rankin score compared to placebo.

The results showed match groups with 254 patients in the Alteplase group and 249 in the placebo group. There were favorable outcomes in 131 (53%) versus 102 (41.8%) in the treatment group and placebo group respectively. Median score for the Alteplase group was 1 and for the placebo group it was 2 on modified Rankin scores at 90 days, with intracranial hemorrhage and mortalities in the Alteplase group of 2.0% and 4.1% respectively, and 0.4% and 1.2% respectively in the placebo group. [47]

B.10 A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke (MR CLEAN)

Intravenous rt-PA, Alteplase, is the only medication proven to have efficacy in patients with symptoms of stroke within 4.5 hours. [48,49] Although this therapy is beneficial, it has its limitations. To quote, "well-recognized limitations of this therapy include the narrow therapeutic time window and contraindications such as recent surgery, coagulation abnormalities, and a history of intracranial hemorrhage." [50]. Moreover, intravenous Alteplase appears to be much less effective at opening proximal occlusions of the major intracranial arteries, which account for more than one third of cases of acute anterior-circulation stroke. [51,52] Early recanalization after intravenous Alteplase is seen in only about one third of patients with an occlusion of the internal-carotid-artery terminus, [53] and the prognosis without revascularization is generally poor for such patients. [54] For these reasons, intraarterial treatment is regarded as a potentially important component of the therapeutic armamentarium." [49]

The MR CLEAN trial was performed secondary to the neutral results of randomized control studies associated with intraarterial treatment and the efficacy of the catheter-based approach. [49,55-57] The results of these studies prompted many questions with regard to the study designs, conduct of the trials, protocol of the trial and interval of treatment, lack of vascular diagnostic testing prior to treatment confirming large/proximal

vessel disease, and that earlier generation devices were utilized and not the more recent third generation devices.[49]

The MR CLEAN assessed if intraarterial treatment plus standard care was more effective than standard care alone in patients with proximal arterial occlusion in the anterior circulation within 6 hours of symptom onset. Standard care as previously explained is the use of chemical thrombolytic agents, such as prourokinase, urokinase, and Alteplase. The study was a

> "..pragmatic, phase 3, multicenter clinical trial with randomized treatment-group assignments, open-label treatment, and blinded end-point evaluation. Intraarterial treatment (intraarterial thrombolysis, mechanical treatment, or both) plus usual care (which could include intravenous administration of Alteplase) was compared with usual care alone (control group) in patients with acute ischemic stroke and proximal intracranial arterial occlusion of the anterior circulation that was confirmed on vessel imaging." [49]

The study was performed only in the Netherlands, with patients 18 years or older with no upper age limit who had sustained an acute ischemic stroke caused by intracranial arterial occlusion in the anterior circulation which includes the distal internal carotid artery, first and second branches of the middle cerebral artery, and the first and second branches of the anterior cerebral artery. Patients with extracranial anterior arterial circulation thrombosis could be included at the discretion of the treating physician. Treatment had to occur within 6 hours of stroke symptom onset. Diagnosis of the arterial distribution was provided by CTA, MRA, or digital subtracted angiography. Patients clinically had to have an NIH score of greater than 2.[49]

Randomization of the patients was performed by a Web-based procedure with permuted blocks. Randomization was stratified per medical center with use of rt-PA,

planned treatment method of mechanical thrombolysis or other means of thrombolysis, and the severity of the stroke based on the NIH score of less than or greater than 14. [49] Interventional treatment was at the discretion of the treating physician and could include mechanical thrombectomy, chemical lysis with urokinase or Alteplase or both, with the microcatheter at the level of the occlusion. Dose of urokinase or Alteplase was dependent on the administration of rt-PA. If rt-PA was provided, the dose of Alteplase was decreased from maximum dose of 90 mg to 30 mg and urokinase was decreased from 1,200,000 IU to 400,000 IU. The mechanical devices were all approved by the Food and Drug Administration (FDA) and the Conformité Européenne (CE), with approval of the steering committee as well. Five (5) complete procedures with the device to be utilized had to be completed by all interventionalists.[49,58]

The primary outcome was a modified Rankin scale at the 90-day mark. "Secondary outcomes included the NIHSS score at 24 hours and at 5 to 7 days or discharge if earlier, activities of daily living measured with the Barthel index, and the health-related quality of life measured with the EuroQol Group 5-Dimension Self-Report Questionnaire at 90 days." (citation 17,18)[49,59]" [49] "Imaging outcomes included arterial recanalization measured with CTA or MRA at 24 hours and the final infarct volume on non-contrast CT at 5 to 7 days."[49] Hemorrhagic complications, new ischemic stroke in a different vascular territory, progression of ischemic stroke, and death were all included in the safety variables. In the event the patient had neurologic deterioration the patient was sent for additional imaging. If hemorrhage was present on the follow up studies, [13] it was only considered symptomatic if the patient had a neurologic deterioration on their NIHSS score of 4 or more.

> "All patients underwent clinical assessment (including determination of the NIHSS score) at baseline, after 24 hours, and at 5 to 7 days or at discharge if earlier. A

> single experienced trial investigator, who was unaware of the treatment group assignments, conducted the follow-up interviews at 90 days by telephone with the patient, proxy, or health care provider. This interview provided reports for the assessment of the modified Rankin score by reviewers who remained unaware of the treatment-group assignments. [13,59,60]
>
> The imaging committee evaluated the findings on baseline non-contrast CT for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range 0-10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan), [61] baseline vessel imaging (CTA, MRA or DSA) for the location of the occlusion , and follow-up CRA or MRA at 24 hours for vessel recanalization. Recanalization was classified as complete or not complete and was further evaluated with the use of modified Arterial Occlusive Lesion score. [62,63] Follow up CT scans obtained at 5 days were assessed for the presence of intracranial hemorrhage. [64] All neuroimaging studies were evaluated by two neuro-radiologists who were unaware of the treatment-group assignments. The final infarct volume on the follow-up CT, scan was assessed with the use of an automated, validated algorithm. [65] An independent core laboratory assessed angio-graphic outcomes on DSA imaging, using the Modified Thrombolysis in Cerebral Infarction (TICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion).[65]." [49]

Statistical analysis was based on an intention-to-treat principle, with the primary effect variable being the adjusted common odds ratio shifting in the better-outcomes direction on the modified Rankin scale, with the use of a multivariable ordinal logistic regression for estimation. [66] The adjusted common odds ratio and all secondary effect variables were adjusted for possible imbalances in major prognostic variables between the intervention group and the control group. The prognostic variables included age, stroke severity on the NIHSS score at baseline, onset of stroke time to randomization, previous stroke status, diabetes mellitus, a-fib, and was the internal carotid artery terminus occluded or not. [67]

> "We imputed missing values of baseline variables that were used to adjust the regression models or treatment effect on primary and secondary outcomes with mean or mode, as applicable. No outcomes were imputed, except for single missing values of items on the NIHSS at 24 hours and at 5 to 7 days or discharge. Patients who died were not assigned NIHSS scored and were not included in analyses of such scores.

> The adjusted and unadjusted common odds ratios are reported with 95% confidence intervals to indicate statistical precision. Binary outcomes were analyzed with logistic regression and are reported as adjusted and unadjusted odds ratios with 95% confidence intervals. All P values are two-sided.
>
> Treatment-effect modification was explored in prespecified subgroups of patients, defined by NIHSS score (2 to 15, 16 to 19, or greater than or equal 20), age (>80 years or <80 years), occlusion of the internal carotid-artery terminus (yes or no), additional extracranial internal-carotid-artery occlusion (yes or no), time from stroke onset to randomization (less than or equal to 120 minutes or >120 minutes), and ASPECTS (0 to 4, 5 to 7, or 8 to 10). The statistical significance of possible differences between subgroups in the treatment effect was tested with interaction terms. No adjustments for multiple tests were made. All analyses were performed with the use of the Stata/SE statistical package, version 13.1 (StataCorp.). Assuming a 10% crossover rate, [68] we calculated that a sample of 500 patients (250 patients in each group) would yield a power of 82%, at a significance level of 0.05, to detect a treatment effect that resulted in an absolute increase 10 percentage points in the proportion of patients with a modified Rankin score of 0 to 3 in the intervention group as compared with the proportion in the control group." [49]

The results were depicted in titles or randomization and baseline characteristics, treatment assignments and crossovers, intervention details, primary outcome, secondary outcome, safety, and subgroup analysis. In the randomization and baseline characteristics, there were 502 patients enrolled and randomized in 16 Dutch centers between 2010 and 2014. There were two patients that withdrew after randomization and were not included in the intention-to-treat analysis. The mean age of the patients was 65 years old, with 58.4% males. There was otherwise even distribution between the two groups with respect to risk factors for poor outcome, aspects or pre-randomization treatment, and clinical risk factors for stroke. Two hundred and thirty-three (233) patients were in the intervention group and 267 in the control group, 46.6% and 53.4% respectively. Seventeen (17) of the patients that were assigned to the treatment group did not have the intraarterial treatment and one patient assigned to the control group received intraarterial treatment. The interventional details report reads:

> "Actual intraarterial therapy (with or without mechanical thrombectomy) was performed in 196 of the 233 patients in the intervention group (84.1%). In 88 patients (37.8%), general anesthesia was used. A simultaneous second revascularization procedure (acute cervical carotid stenting) was performed in 30 patients (12.9%).
>
> Mechanical treatment was performed in 195 of the 233 patients (83.7%). Retrievable stents were used in 190 patients (81.5%), and other devices were used in 5 (2.1%). Additional intraarterial thrombolytic agents were given to 24 patients (10.3%). Intraarterial thrombolytic agents were used as monotherapy in 1 of the 233 patients (0.4%). No intervention was given in 37 patients (15.9%)." [49]

The primary outcomes showed that the 90-day modified Rankin score had a shift in favor of intervention with a 1.67 (95% CI, 1.21 to 2.30) adjusted common odds ratio. There were better outcomes in the intervention group that were consistent across all areas of the modified Rankin score except death. "The absolute between-group difference in the proportion of patients who were functionally independent (modified Rankin score, 0 to 2) was 13.5 percentage points (95% CI, 5.9 to 21.2) in favor of the intervention (32.6% vs 19.1%), with an adjusted odds ratio of 2.16 (95% CI, 1.39 to 3.38)." [49]

The secondary outcomes revealed that all clinical imaging favored the intervention group, with NIHSS scores after the 5 to 7 days on average being 2.9 points lower than the control group with a 95% CI of 1.5 to 4.3. The recanalization after 24 hours with a CTA was performed on 394 patients, with resolution of the occlusion at the target site being more common in the intervention group compared to the control group, at 141 of 187 patients (75.4%) vs 68 of 201 patients (32.9%), respectively. The intervention group also had favorable outcomes compared to the control group regarding the infarct volume. There were 298 of the 500 patients evaluated with a between-group difference in volume of 19 ml; 95% CI 3 to 34, and a good reperfusion, TICI score of 2b or 3, achieved in 115 of the 196 (58.7%) patients in the intervention group.

Safety showed no significant between-group difference in serious adverse events during the 90-day period. Thirteen of the 233 (5.6%) patients in the intervention group did have new symptomatic strokes in a different vascular territory, apposed to 1 of the 267 (0.4%) of the control group. There was no significant difference in mortality between the groups at any of the evaluation points (7, 30, or 90-day follow-up). There were procedure related complications in the intervention group of new, different vessel embolization in 20 (8.6%) of the 233 patients, with 4 patients (1.7%) and 2 patients (0.9%) incurring dissection and vessel perforations, respectively.

The subgroup analysis was:

> "There were no significant interactions between subgroups and treatment effect. The treatment effect remained consistent in all predefined subgroups, including those based on age (<80 years or greater than or equal to 80 years), NIHSS score (2 to 15, 16 to 19, or greater than or equal to 20), and ASPECTS (0 to 4, 5 to 7, or 8 to 10). The point estimate for treatment effect in the subgroup with ASPECTS of 0-4 was close to unity but with wide confidence interval (adjusted common odds ratio, 1.09; 95% CI, 0.14 to 8.46)." [49]

Tables 11 and 12 show the outcome scores and hemorrhagic conversion rates.

Table 11. MR CLEAN Outcome Scores

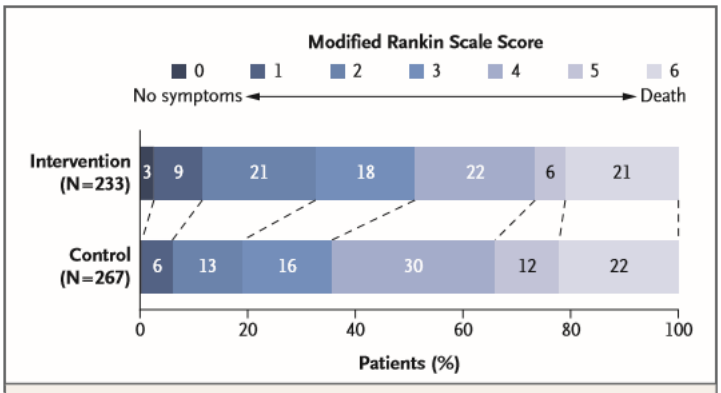


Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.

Shown is the distribution of scores on the modified Rankin scale. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (patient is able to look after own affairs without assistance but is unable to carry out all previous activities), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (patient requires constant nursing care and attention), and 6 death. There was a significant difference between the intervention group and the control group in the overall distribution of scores in an analysis with univariable ordinal regression (common odds ratio, 1.66; 95% CI, 1.21 to 2.28), as well as after adjustment of the treatment effect for age; National Institutes of Health Stroke Scale score at baseline; time from stroke onset to randomization; status with respect to previous stroke, atrial fibrillation, and diabetes mellitus; and occlusion of the internal-carotid-artery terminus (yes vs. no) in an analysis with multivariable regression (adjusted common odds ratio, 1.67; 95% CI, 1.21 to 2.30). In the control group, only 1 patient (0.4%) had a modified Rankin score of 0.

Table 12. MR CLEAN Hemorrhage Rates

Table 3. Safety Variables and Serious Adverse Events within 90 Days after Randomization.

Variable	Intervention (N=233)	Control (N=267)
	no. of patients (%)	
Safety variables		
Death		
Within 7 days	27 (11.6)	33 (12.4)
Within 30 days	44 (18.9)	49 (18.4)
Hemicraniectomy	14 (6.0)	13 (4.9)
Serious adverse events*		
Any serious adverse event	110 (47.2)	113 (42.3)
Symptomatic intracerebral hemorrhage		
Any type	18 (7.7)	17 (6.4)
Parenchymal hematoma†		
Type 1	0	2 (0.7)
Type 2	14 (6.0)	14 (5.2)
Hemorrhagic infarction‡		
Type 1	1 (0.4)	0
Type 2	1 (0.4)	1 (0.4)
Subarachnoid hemorrhage	2 (0.9)	0
New ischemic stroke in a different vascular territory§	13 (5.6)	1 (0.4)
Progressive ischemic stroke	46 (19.7)	47 (17.6)
Pneumonia	25 (10.7)	41 (15.4)
Other infection	16 (6.9)	9 (3.4)
Cardiac ischemia	1 (0.4)	4 (1.5)
Extracranial hemorrhage	0	2 (0.7)
Allergic reaction	1 (0.4)	0
Other complication	22 (9.4)	33 (12.4)

* Only first events of a type are listed. Patients having multiple events of one type were counted once.
† For parenchymal hematoma, type 1 was defined by one or more blood clots in 30% or less of the infarcted area with a mild space-occupying effect, and type 2 was defined by blood clots in more than 30% of the infarcted area with a clinically significant space-occupying effect.
‡ For hemorrhagic infarction, type 1 was defined by small petechiae along the margins of the infarction, and type 2 was defined by more confluent petechiae within the infarction area.
§ P<0.001.

B.11 Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke (ESCAPE)

Large vessel occlusion in the anterior circulation has a very high morbidity and mortality, with approximately 60–80% of the patients dying within the first 90 days or being unable to regain functional independence even with Alteplase treatment. [49,55] It is believed that the modest rate of early reperfusion of patients with large-vessel occlusion with the utilization of Alteplase is why the patients have poor outcomes. [69,70] To quote:

> "Local treatment of large-vessel occlusion began with intraarterial delivery of thrombolytic drugs. [71] The Prolyse in Acute Cerebral Thromboembolism (PROACT) II study was the first positive trial of endovascular treatment involving patients with angiographically visualized occlusion of the middle cerebral artery. [72] Unfortunately, subsequent trials did not confirm the clinical benefit even with the addition of first generation thrombectomy devices. [55-57] Key lessons learned from these previous trials are the need for proof of proximal vessel occlusion, [73] rapid and effective imaging methods to exclude patients with a large infarct core, [74-76] and efficient workflow to achieve fast recanalization, [77,78] and high reperfusion rates [79-81]." [82]

With the advent of newer technologies and the MR CLEAN trial showing the clinical benefit of these new, improved technologies, the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) was designed to test if patients with acute ischemic stroke evaluated with CT and CTA would benefit from rapid endovascular treatment with the new, improved technologies and techniques. [82]

The trial was designed as a "multicenter, prospective, randomized, open-label controlled trial with blinded outcome evaluation (PROBE design). [83] Participants were assigned, in a 1:1 ratio, to receive endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone (control group)." [82] The major question the investigator set out to determine was, "Should this patient undergo endovascular

thrombectomy?" [82] This was a study funded by Covidien, but they were not involved in the design or conduct of the study including the collection or analysis of any data, nor were they involved in the publication of the data or results and conclusion. The sites involved in the study were invited to participate after the principal investigator carried out a site visit and determined that the site was able to document fast treatment times and efficient workflow and with the invitee accepting the responsibility of attempting to enroll patients, who were eligible, in a consecutive manner. [84]

> "Randomization was performed with the use of a real-time, dynamic, Internet-based, randomized minimization procedure (minimal sufficient balance method) [84] to achieve distribution balance with regards to age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating greater stroke severity), site of arterial occlusion, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), and status with respect to intravenous Alteplase treatment." [82]

Patients' eligibility to participate was not based on age but on their ability to perform activities of daily living prior to the stroke symptoms. Their ability to perform activities of daily living and functionality in the community were determined by utilizing the Barthel Index scoring (0-100 with greater scores suggesting high activity ability). A patient had to have a Barthel Index score of 90 or greater to be eligible for enrollment. Patients were eligible to be enrolled if the symptoms of stroke occurred within 12 hours, and a CT and a multiphase CTA showed a small infarct core and an anterior circulation, proximal artery occlusion, and moderate-to-good collateral circulation. [76,85-88] Small infarct core was described as an ASPECTS score of 6–10, anterior circulation, proximal artery occlusion was described as an "…occlusion of the middle-cerebral-artery trunk and its immediate branches, with or without intracranial occlusion of the internal carotid artery," [82] and moderate-to-good collateral circulation was described as 50% or more filling of the

pial middle-cerebral-artery circulation on CTA. For any patient transferred from an outside institution all radiographic studies were repeated and all patients eligible to be treated with rt-PA as dictated by the current standard of care at that time were provided rt-PA. [82]

All patients treated in the interventional group had rapid interventional procedure. The interventionalist was encouraged to use any available thrombectomy devices available, but recommended to use retrievable stents technology along with suction via the balloon guided catheter in the relevant internal carotid artery. The control group all received current to the time standard of care treatment with rt-PA within 4.5 hours after onset of stroke symptoms. Current standard of care was based on the Canadian or local guidelines. [50,89] Weekly monitoring and mentoring was performed with each site after review of the imaging and treatment speed. The sites were provided feedback to ensure there was adherence to patient selection and workflow of treatment. The target time to treatment once the CT was performed was groin puncture within 60 minutes and reperfusion of the middle-cerebral-artery within 90 minutes. The timing of treatment was consciously decided to emphasize speed and efficiency of workflow, given the concerns about rapid acquisition and interpretation of base radiographic studies, transfer to the angiographic suite, and preparation of the angiogram suite to perform a rapid reperfusion. Patient enrollment was also determined on the tortuosity and possible degree of difficulty in placement of the microcatheter in the occluded vessel, as well as the feasibility associated with workflow, such as availability of the angiogram suite and the interventional team. If there was potential for delay in rapid treatment, the patient was not recommended to be enrolled in the study. [82]

Patient clinical assessments were all performed as previously published, [83] and the study protocol included standard assessments of demographics, past medical history, laboratory values, and NIHSS scores showing stroke severity. The modified Rankin score, the primary outcome, at the 90-day mark was performed by a blinded trained practitioner.

> "Secondary and safety outcomes included early recanalization and reperfusion, intracranial hemorrhage, angiographic complications, neurologic disability at 90 days, and death. Interpretation of the imaging was performed at an external core laboratory by personnel who were unaware of the treatment-group assignments (when they interpreted the CT images), clinical data, and outcomes. External, independent clinical monitors validated the clinical data. [82]
>
> The trial was powered to detect a shift in the distribution of scores on the modified Rankin scale at 90 days between the intervention and control groups, with scores of 5 (bedbound, with severe disability) and 6 (death) combined, with the assumption that the different effect would lead to a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 1.8. A total required sample of 500 participants was anticipated. On formal interim analysis after the enrollment of 300 participants was planned. The stopping rule for efficacy was defined with the use of O'Brien-Fleming boundaries on the binary outcome of a modified Rankin score at 90 days of 0 to 2 versus 3 to 6. [83] The primary analysis was unadjusted and was performed in the intention-to-treat population. P values of less than 0.05 were considered to indicate statistical significance, and all tests of hypotheses were two sided. No adjustments were made for multiple comparisons. Adjusted estimates of effect were calculated, with adjustment for age, sex, baseline NIHSS score, baseline ASPECTS, location of occlusion (internal carotid artery plus middle cerebral artery only), and status with respect to intravenous Alteplase treatment (yes vs. no). The assessment of effect modification (heterogeneity of treatment effect) was performed with the inclusion of multiplicative interaction terms. All analyses were performed with the use of STATA software, version 12.1 (StataCorp). Figures were drawn with the use of both Stata software, version 12.1, and R software (R Development Core Team 2014, www.r-project.org). Further details are provided in the statistical analysis plan (available at NEJM.org)" [82]

Because of the MR CLEAN trial results, this study was stopped early, because "the prespecified boundary for efficacy had been crossed." [82] Prior to cessation of the trial, 316 participants were randomized in 22 centers. Most of the centers were in Canada, followed by the United States, South Korea, Ireland, and the United Kingdom, with 11, 6, 3, 1, and 1, respectively. The majority, 165 participants, were randomized to the intervention group,

while 150 participants were randomized to the control group between February 2013 and October 2014. Approximately 10%, 14 participants, in the intervention group did not receive endovascular treatment, 1 participant in the control group crossed over to the intervention group, and 1.3% (4 participants) were lost to follow up and the missing data on these participants were not imputed.[82]

Of the participants that were included in the results, the baseline characteristics were similar in the 2 groups. There were imaging protocol violations identified in 8.3%, 26 participants, by the core laboratory personnel.

> "Eleven (11) of the 308 participants in whom the ASPECTS could be evaluated (3.6%) had a score of less than 6 on the ASPECTS scale, 20 or 315 participants (6.3%) had poor collateral circulation, and 14 of 315 participants (4.4%) had inappropriate target-vessel occlusion (some participants had >1 protocol violation). Collateral circulation was assessed with the use of multiphase CTA in a majority of participants." [82]

More than 80% of the participants consented to the procedure, and monitoring of appropriate documentation including informed consent, demographics, inclusion and exclusion criteria, randomization information, baseline assessment of NIHSS score, Barthel Index score and 90-day NIHSS score, modified Rankin scale, and Barthel Index score was completed for all randomized patients. The primary outcomes were:

> "Analysis of the primary endpoint showed a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 2.6 (95% confidence interval (CI), 1.7 to 3.8) favoring the intervention (P<0.001). The median 90-day modified Rankin score was 2 in the intervention group and 4 in the control group (P<0.001). The proportion of patients with a modified Rankin score of 0 to 2 at 90 days was 53.0% in the intervention group and 29.3% in the control group (rate ratio, 1.8; 95% CI, 1.4 to 2.4; P<0.001). Mortality at 90 days was 10.4% in the intervention group and 19.0% in the control group (rate ratio, 0.5; 95% CI, 0.3 to 1.0; P=0.04). The rate of symptomatic intracerebral hemorrhage was 3.6% in the intervention group and 2.7% in the control group (rate ratio, 1.4; CI, 0.4 to 4.7; P=0.75). Device related, or procedural complications was observed in 18 patients: 4 had a serious adverse event and 14 had a non-serious adverse event." [82]

The secondary outcomes were:

> "Secondary clinical and imaging end points favored the intervention group. The rate of patients with a score on the Barthel Index of 95 to 100 at 90 days was 57.7% in the intervention group versus 33.6% in the control group, the rate of patients with a 90-day NIHSS score of 0 to 2 was 51.6% versus 23.1%, and the median 90-day score on the EuroQol Group 5-demention Self-Report Questionnaire (EQ-5D) visual-analogue scale (range 0 to 100, with higher scores indicating better quality of life) was 80 versus 65." [82]

The subgroups were homogeneous regarding age, sex, baseline NIHSS and ASPECTS scores, occlusion location, utilization of rt-PA, and if there was extracranial arterial occlusion. There was predilection toward the intervention group with regard to the subgroups, but the absolute proportion of good outcomes varied substantially per subgroup. To cite examples of this varied outcome, "A total of 49 patients underwent randomization 6 or more hours after stroke onset; in the analysis of a modified Rankin score of 0 to 2 at 90 days, the direction of effect favored the intervention in these patients (rate ratio, 1.7; 95% CI, 0.7 to 4.0), but the between-group difference was not significant." [82] Of the 165 participants, 151 (91.5%) had endovascular treatment, with 72.7% (120 participants) receiving rt-PA and 9.1% (15 participants) general anesthesia. Retrievable stents were used in 85.1% (130 of the 151 participants), with 77.0% (100 of the 130 participants) receiving a Solitaire stent (Covidien). In the intervention group the CT to groin puncture time was 30 minutes, CT to first perfusion time was 84 minutes, with a median time from symptom onset to first perfusion time of 241 minutes. Of the 156 participants in the intervention group, 113 (72.4%) had a TICI score of 2b or 3 in the intervention group, with 70.5% (79 of the 112 participants) receiving rt-PA while 77 % (34 of the 44 participants) did not receive rt-PA. [82]

For the control group, secondary outcome in regard to timing and successful recanalization of the occluded artery showed that CTA was performed in 138 participants with a median time to CTA from start of symptoms of 425 minutes with successful recanalization, for a TICI score of 2b or 3 on the CTA in 31.2% (43 of the 138 participants), with 37.3% (41 of the 110 participants) receiving rt-PA and 7% (2 of 18 participants) not receiving rt-PA. [82]

Tables 13 and 14 show the outcome scores and hemorrhagic conversion rates.

Table 13. ESCAPE Outcome Scores

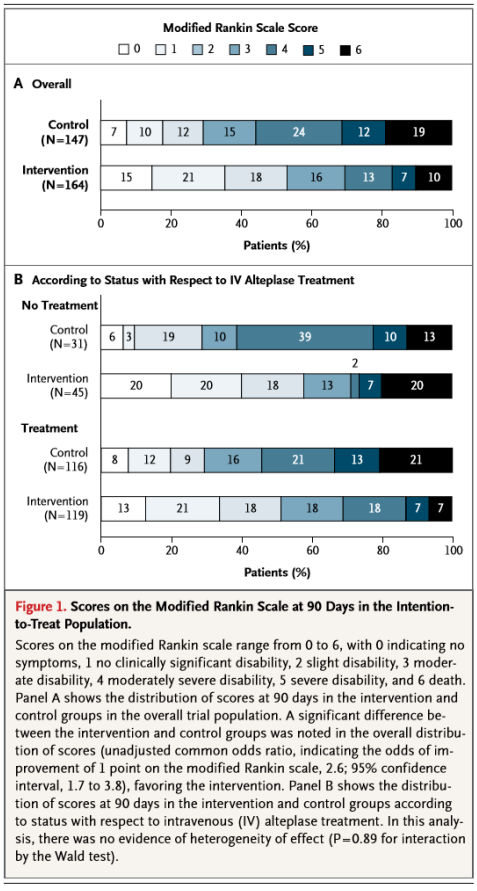


Figure 1. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Panel A shows the distribution of scores at 90 days in the intervention and control groups in the overall trial population. A significant difference between the intervention and control groups was noted in the overall distribution of scores (unadjusted common odds ratio, indicating the odds of improvement of 1 point on the modified Rankin scale, 2.6; 95% confidence interval, 1.7 to 3.8), favoring the intervention. Panel B shows the distribution of scores at 90 days in the intervention and control groups according to status with respect to intravenous (IV) alteplase treatment. In this analysis, there was no evidence of heterogeneity of effect (P=0.89 for interaction by the Wald test).

Table 14. ESCAPE Hemorrhage Rates

Table 3. Reported Serious Adverse Events.

Event	Intervention (N=165)	Control (N=150)	Difference (95% CI)*	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
Death — no./total no. (%)	17/164 (10.4)	28/147 (19.0)	8.6 (0.8 to 16.6)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)
Large or malignant middle-cerebral-artery stroke — no. (%)‡	8 (4.8)	16 (10.7)	5.8 (0.1 to 11.7)	0.5 (0.2 to 1.0)	0.3 (0.1 to 0.7)
Symptomatic intracerebral hemorrhage — no. (%)‡§	6 (3.6)	4 (2.7)	1.0 (–2.9 to 4.8)	1.4 (0.4 to 4.7)	1.2 (0.3 to 4.6)
Hematoma at access site — no. (%)¶	3 (1.8)	0			
Perforation of the middle cerebral artery — no. (%)	1 (0.6)	0			

* Differences (intervention group – control group) are shown as percentage points.
† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.
‡ Two hemicraniectomy procedures were performed. The indications for hemicraniectomy were malignant middle-cerebral-artery ischemic stroke (one patient in the control group) and symptomatic intracerebral hemorrhage (one patient in the intervention group).
§ Symptomatic intracerebral hemorrhage was clinically determined at the study site.
¶ Hematoma occurred in two participants at the site of groin puncture. Neck hematoma occurred in the single participant in whom direct carotid access was used, after femoral access was unsuccessful.

B.12 Stent-Retrieve Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke (SWIFT-PRIME)

Utilization of t-PA within 4.5 hours of symptoms of ischemic stroke has been shown to have improved outcomes. [7,21,48,90] Although the use of t-PA has improved outcomes, it is not without its issues. The issues include narrow time window of utilization, poor response to large thrombus, short duration, and cerebral and systemic hemorrhage. Regarding poor response to large thrombus, it has been shown that only 13 to 50% of the occlusions in the internal carotid artery and/or the first segment of the middle cerebral artery benefit from t-PA. [90-94] Endovascular treatments of large, proximal clots in a timely fashion have shown to have improved rates of outcomes compared to intravenous t-PA.

Initially, there were a few trials that did not show improved outcomes of endovascular treatment compared to intravenous t-PA, and it was postulated that these studies did not show improvement because the researchers utilized intraarterial delivery of t-PA or they used early-generation devices along with the use of vessel imaging to evaluate the occluded target artery and were very slow to initiate endovascular treatments. [55-57,90] This trial utilized the Solitaire revascularization device (Covidien). Before this trial, the Solitaire revascularization device was compared to early generation devices and shown to have faster reperfusion rates, increase in reperfusion rates, decrease in hemorrhage, and improved outcome scores. [80,81,90,95-97]

> "We performed the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial to establish the efficacy and safety of rapid neurovascular thrombectomy with the stent retriever in conjunction with intravenous t-PA versus intravenous t-PA alone in patients with acute ischemic stroke. The trial was among several contemporaneous trials launched worldwide to test new-generation strategies for mechanical thrombectomy. [49,82] Our trial was conducted in multiple countries and health systems as a registration trial capable of supporting expansion of regulatory labeling. We used uniform device procedures in intervention group and tested intracranial neurovascular thrombectomy alone rather than in combination with cervical stenting." [90]

Covidien funded the trial as well as was part of the team that designed the trial; academic investigators along with the representatives of the sponsor made up the steering committee. Covidien maintained the database, but the investigators gathered the data and wrote the manuscripts with unrestricted access to the data and performed the data analysis with primary and independent statisticians to attest to the accuracy and trial completeness of the reported data.

Thirty-nine (39) centers in Europe and the United States participated in the study. To be eligible to be a study center, the interventionalists had to have performed at least 40 mechanical thrombectomies, at least 20 of them with the Solitaire stent retriever system,

annually. Patients had to have sustained an ischemic stroke with moderate to severe neurologic symptoms with imaging showing occlusion of the first segment of the middle cerebral artery and/or the intracranial internal carotid artery, be able to have the required imaging, have received intravenous t-PA, and be able to undergo endovascular treatment within 6 hours of stroke symptom onset.

> "To identify patients with salvageable tissue, at trial launch the entry criteria regarding imaging selection required patients to have a target-mismatch penumbral profile, with a small core of tissue that was likely to be irreversibly injured and a large region of hypo-perfused tissue that was likely to be salvageable. Penumbral imaging analysis was performed with the use of RAPID (iSchemaView), an operator-independent image-postprocessing system. [98] After the enrollment of the first 71 patients, these criteria were revised to use a small-to-moderate core-infarct strategy to accommodate study sites with limited perfusion imaging capability and to ensure accelerated treatment delivery. Study sites with advanced imaging capability were still encouraged to obtain penumbral imaging and to exclude patients who did not meet the target-mismatch profile." [90]

In the intervention group, the patients were treated with the Solitaire FR or the Solitaire 2 device. Carotid stenting was not allowed, but carotid angioplasty to allow the Solitaire device to be utilized at the target site was permitted. The patients that underwent the interventional procedure were expected to have expedient, quality workflow and transfer to the neuro-interventional suite with qualifying imaging to groin puncture of 70 minutes.

The primary outcome measure was disability evaluated with the modified Rankin score at 90 days. Secondary clinical efficacy outcomes were death at 90 days, modified Rankin score at 90 days, change from the initial NIHSS score at 27 hours after randomization. Regarding the technical efficacy with revascularization with TICI score of 2b or 3 and reperfusion at 27 hours in the two study groups. The definition of reperfusion was taken as being equal to or greater than 90% compared to the initial perfusion-lesion

volume, evaluated by CT perfusion or MRI at 27 hours after randomization. Safety outcomes were evaluated throughout the study and for symptomatic intracranial hemorrhage 27 hours after randomization.

Clinical assessments on each patient randomized were performed at baseline, 27 hours after randomization, 7 to 10 days or at discharge if prior to 7 to 10 days, 30 days, and 90 days after randomization. Clinical scores utilized were the modified Rankin score and the NIHSS score. Radiographic imaging, entry and outcome neurovascular imaging were evaluated by a blinded staff member at the core imaging laboratories (iSchemaView) for penumbral and volumetric imaging along with (Synare) for parenchymal and angiographic imaging.

Statistically, for the study to be declared positive both the modified Rankin scale at 90 days showing the proportion of patients functionally independent and the overall distribution of the score were necessary. The authors needed to show not only that there was a general improvement, but an improvement over the entire range of scores compared to the control group, with analyses utilizing the Cochran-Mantel-Haenszel test.

> "A simultaneous requirement for success was that the difference in the proportion of patients with a score of 0 to 2 nominally meet a prespecified minimum, which varied according to the final sample size at trial discontinuation or completion, with a larger benefit required with a smaller sample size. Missing final scores on the modified Rankin scale were handled with the use of the last-observation-carried-forward approach when a score was available from the 30-day visit or visit at 7 to 10 days. Power and sample size were determined with the use of the dual success criteria, incorporating a group sequential-analysis plan with five interim analyses for efficacy, futility, and safety." [90]

Secondary to the MR CLEAN and ESCAPE trials, the safety and data monitoring board recommended the cessation of enrollment. The study was halted in February 2015, when an efficacy analysis was conducted and showed that the stopping criteria for efficacy

had been crossed. All *P* values are two-sided, with pooled study results shown because there was no evidence of heterogeneity of the treatment effect with a P=0.73 by the Breslow-Day test.

During the period of December 2012 through November 2014, there were 198 patients that underwent randomization, half in the intervention group and half in the non-intervention/control group. The patients randomized to each group were well matched from a demographic and clinical perspective. The intervention group was treated within 224 minutes from time of symptoms to the time of groin puncture, 77 minutes from the time of intravenous t-PA to groin puncture, and the time from study-qualifying imaging to the time to groin puncture was 57 minutes. In the patients randomized to the intervention group, 87 of the 98 patients (89%) had stent retriever deployment with the median time of groin puncture to deployment of the stent being 24 minutes, with general anesthesia utilized in 36 patients (37%).

> "Treatment with thrombectomy with the use of the stent retriever met both of the simultaneous success criteria. Thrombectomy treatment was associated with a favorable shift in the distribution of global disability scores on the modified Rankin scale at 90 days (P<0.001) by the Cochran Mantel-Haenszel test, which was lower than the P value of 0.01 that was specified for early stopping; number needed to treat for one additional patient to have a less-disabled outcome, 2.6. The shift toward better outcomes was consistent in direction across all the score levels of the modified Rankin scale. The proportion of patients who were functionally independent (modified Rankin scale score, less than or equal 2) at 90 days was higher in the intervention group than in the control group, with an absolute difference of 25 percentage points, which exceeded the 12-percentage-point boundary that was prespecified for early stopping. Results remained significant in sensitivity analyses that used multiple imputation and worst-case and best-case scenarios to account for missing data and in analyses that were adjusted for imbalances in baseline prognostic features." [90]

> With regard to secondary outcomes:

> "The proportion of outcomes indicating functional independence at 90 days was significantly higher in the intervention group than in the control group, with an

absolute difference of 25 percentage points (95% confidence interval (CI), 11 to 38) and a risk ratio of 1.70 (95% CI, 1.23 to 2.33, P<0.001; number needed to treat for one additional patients to be functionally independent, 4.0) Mortality at 90 days did not differ significantly between the intervention group and the control group (9% and 12%, respectively; P=0.50).

In the Intervention group, substantial reperfusion (50 to 99%) of complete reperfusion (100%) at the end of the procedure occurred in 73 of the 83 patients (88%) who underwent placement of the stent retriever. A total of 4 additional patients who underwent the intervention did not have a final angiogram that could be assessed. Successful reperfusion (greater than or equal to 90%) at 27 hours, assessed by means of perfusion CT or MRI, was more frequent in the intervention group than in the control group (53 or 64 patients (83%) vs. 21 or 52 (40%)." [90]

Serious adverse events occurred in the interventional group at 36% and in the control group at 31% with a P=0.54. Symptomatic hemorrhage occurred in 0% of the interventional group and 3% of the control group with a P=0.12, and was not significant between the two groups. The intervention group did have a higher rate of radiologically assessed subarachnoid hemorrhage than the control group, 4 and 1 respectively, with a P=0.37. There were also seven non-serious adverse events associated with the use of the device.

In the subgroup analysis:

"Within the constraints of the study sample size, no evidence of heterogeneity of treatment effect was detected in any of the eight prespecified subgroups. The benefit of thrombectomy with stent retriever plus intravenous t-PA over intravenous t-PA alone was also observed in the prespecified subgroup of patients who received intravenous t-PA within 3 hours after symptom onset." [90]

Tables 15 and 16 show outcome scores and hemorrhagic conversion rates.

Table 15. SWIFT-PRIME Outcome Scores

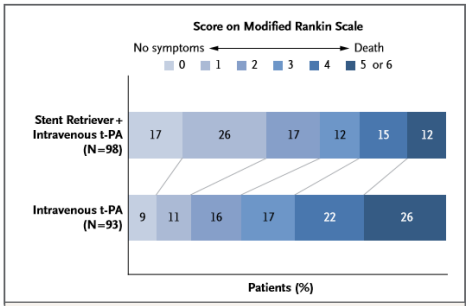


Figure 1. Functional Outcomes at 90 Days, According to the Score on the Modified Rankin Scale.

Shown are the 90-day scores on the modified Rankin scale for the patients in the two treatment groups. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), and 6 death. Persons with a score of 0, 1, or 2 are considered to be independent in daily function. Neurovascular thrombectomy with the use of a stent retriever was associated with a significant shift in the distribution of scores toward lesser disability (P<0.001 by the Cochran–Mantel–Haenszel test), including an absolute increase of 25 percentage points in the proportion of patients who were functionally independent at 90 days (P<0.001). The term t-PA denotes tissue plasminogen activator.

Table 16. SWIFT PRIME Hemorrhage Rates

Table 3. Safety Outcomes.*

Outcome	Intravenous t-PA Alone (N=97)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	P Value
	no. of patients (%)			
Primary safety outcomes				
Any serious adverse event at 90 days†	30 (31)	35 (36)	1.15 (0.78–1.72)	0.54
Symptomatic intracranial hemorrhage at 27 hr	3 (3)	0	0.00 (NA)	0.12
Additional safety outcomes at 27 hr				
Parenchymal hematoma	7 (7)	5 (5)	0.71 (0.23–2.15)	0.57
Type 1	3 (3)	4 (4)	1.32 (0.30–5.74)	1.00
Type 2	4 (4)	1 (1)	0.25 (0.03–2.17)	0.21
Subarachnoid hemorrhage	1 (1)	4 (4)	3.96 (0.45–34.79)	0.37

* NA denotes not applicable.

† A serious adverse event was an adverse event that led to death, a life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function, or fetal distress, fetal death or a congenital anomaly or birth defect. Serious adverse events that are classified according to organ system are shown in Table S11 in the Supplementary Appendix. None of the serious adverse events were adjudicated by the clinical-events committee to be device-related. Nonserious adverse events that were deemed to be device-related are shown in Table S12 in the Supplementary Appendix.

B.13 Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection (EXTEND-IA)

Prior to this study, the MR CLEAN study established disability reduction with the use of endovascular thrombectomy along with general standard of care for ischemic strokes, [49] making it a study that advanced stroke care. Prior to the MR CLEAN study, there were a few studies that showed thrombectomy as having a neutral effect in regard to improved outcome. The interventional management of stroke 3 (IMS-3) was the largest of the trials and had been stopped early secondary to futility. [55-57] The neutral results of these previous studies are potentially associated with low rates of angiographic reperfusion, poor patient selection regarding advanced imaging ensuring large vessel occlusion and penumbral stroke mismatch, and timing of reperfusion, along with the studies having safety concerns with symptomatic hemorrhage of 6% in both the interventional group and the control group. With the advent of improved technology devices, the rate and efficacy of reperfusion and recanalization improved. [79-81] In regard to poor patient selection associated with advanced imaging, Campbell and Straka demonstrated that CT perfusion can show the penumbra versus core infarct differentiation, indicating potentially salvageable brain.[98,99]

> "In the Extending the Time for Thrombolysis in Emergency Neurologic Deficits-Intra-Arterial (EXTEND-IA) trail, we sought to test the hypothesis that patients with anterior circulation ischemic stroke who are selected with a dual target vessel occlusion and evidence of salvageable tissue on perfusion imaging within 4.5 hours after the onset of stroke will have improved reperfusion and early neurologic improvement when treated with early endovascular thrombectomy with the use of the Solitaire FT (Flow Restoration) stent retriever after intravenous administration of Alteplase, as compared with the use of Alteplase alone. The release of the MR CLEAN trial results prompted the data and safety monitoring board for our study to review the data, and the trial was stopped early because efficacy was clearly shown." [100]

Quoting further:

> "The EXTEND-IA trial was an investigator-initiated, multicenter, prospective, randomized, open label, blinded-end-point study involving patients with ischemic stroke who were receiving intravenous Alteplase within 4.5 hours after stroke onset." [100]

Covidien, the manufacturer of the Solitaire FT did provide financial support with an unrestricted grant, but was not involved in the design, conduct, or writing of the manuscript. They did however review the protocol to ensure that the Solitaire FT directions for use were followed and the device was used as specified.

The study design was to have 100 patients at the 14 centers in New Zealand and Australia. For patients to be eligible they had to be qualified to have Alteplase provided within 4.5 hours of stroke symptom onset with anterior circulation including intracranial carotid arterial occlusion or occlusion of the first order or second order segments of the middle cerebral artery diagnosed on CT angiography. After the above criteria were met the patient had a CT perfusion, and further:

> "automated software (RAPID, noncommercial research version, Stanford University)[98,99] was used to identify potentially salvageable brain tissue. Brain tissue at risk for infarction ("ischemic penumbra") was distinguished from minimally hypo-perfused tissue if the time to maximum (Tmax) delay was more than 6 seconds. [101] Irreversibly injured brain ("ischemic core") was diagnosed if the relative cerebral blood flow was less than 30% of that in normal tissue. [102]." [100]

If the patient met the above criteria and the patient had a pre-stroke-symptom modified Rankin score of less than 2, regardless of age and NIHSS score, they were recruited for the study and had to have groin puncture within 6 hours of symptom of stroke onset and the procedure had to be complete by 8 hours after onset of stroke symptoms.

All patients admitted to the study were either entered in the control group, Alteplase only, or in the treatment group, Alteplase and endovascular intervention with Solitaire FR,

on a 1:1 ratio via centralized website and then stratified based on which vessel was occluded, internal carotid artery or first or second order portions of the middle cerebral artery. Sedation or anesthesia of patients was at the option of the operator. The occluded vessel was confirmed with a diagnostic cerebral angiogram, and if there was no occlusion of a vessel amendable to thrombectomy the procedure was aborted. If the patient had an occlusion amendable to thrombectomy, the Solitaire FR was deployed to the site of occlusion and the thrombectomy performed with the use of negative-pressure aspiration. Post thrombectomy, a concluding angiogram was performed and a TICI score was recorded.

> "The coprimary outcomes were reperfusion (which was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and imaging at 24 hours, which can be negative if hypoperfusion worsens) and early neurologic improvements (which was defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 at 3 days). Secondary outcomes were the score on the modified Rankin scale at 90 days, death due to any cause, and symptomatic intracranial hemorrhage associated with clinical symptoms and symptomatic intracerebral hemorrhage, which was defined as parenchymal hematoma type 2 within 36 hours after treatment combined with an increase on the NIHSS of at least 4 points from baseline. [27]". [100]

Secondary to the MR CLEAN results, the trial was suspended in October 2014 with 70 patients enrolled.

> "A prespecified Haybittle-Peto stopping boundary was applied to the coprimary outcome in the intention-to-treat population with the use of Holm's step-down procedure, [103] so that one coprimary outcome was tested at a z value of more than 3.29 and the other at a z value of more than 3. The data and safety monitoring board stopped the trial for efficacy after this analysis.
>
> For the intention-to-treat analysis of the coprimary outcome, we compared the median percentage reperfusion between the endovascular-therapy group and the Alteplase-only group after the adjustment for baseline arterial occlusion strata using the van Elteren test, a stratified version of the Wilcoxon rank-sum test. We used logistic regression to compare the between-group difference in the proportion of patients with early neurologic recovery, as indicated by a reduction of 8 or more points on the NIHSS or a score of 0 or 1 at 3 days, after adjustment for age and baseline NIHSS score.

> Although results are reported with and without adjustment for baseline covariates, the analysis with adjustment was prespecified as the primary analysis. The results are also reported for the target group who underwent endovascular thrombectomy according to the protocol, as compared with the Alteplase-only group, to adjust for effects such as recanalization before cerebral angiography was performed and any off-protocol interventions.
>
> As prespecified in the protocol, the initial analysis of the secondary outcome for the score on the modified Rankin scale was designed to be an assumption-free ordinal analysis [104,105] that uses the Wilcoxon-Mann-Whitney generalized odds ratio across the full range of the modified Rankin scale (from 0 to 6). Then, we used a logistic-regression model to compare the proportions of patients with scores or 0 or 1 (defined as an excellent outcome) and those with scores of 0 to 2 (defined as a functionally independent outcome) in the two study groups after adjustment for age and baseline NIHSS score." [100]

During the study period from August 2012 through October 2014, 70 patients were admitted to the study, 35 in each group in one center in New Zealand and at 9 centers in Australia.

> "Approximately 25% of clinically eligible patients with vessel occlusion were excluded on the basis of perfusion-imaging criteria. The majority of the thrombus had been lysed before angiography in 4 of 35 patients (11%) in the endovascular therapy group. Four other patients in the endovascular-therapy group did not undergo thrombectomy because they had either major clinical deterioration or major clinical improvement, stenting of the extracranial internal carotid artery to obtain access achieved a flow with a rating of 2b on the modified Treatment in Cerebral Ischemia classification without requiring thrombectomy, or the procedure was terminated before deployment of the Solitaire FR stent retriever owing to vessel perforation caused by microcatheter manipulation." [100]

Endovascular patients did have better outcomes in both coprimary endpoints compared to the Alteplase control group.

> "Endovascular therapy resulted in increased reperfusion at 24 hours (P<0.001) and a probability of reperfusion of more than 90% without symptomatic intracerebral hemorrhage, as compared with Alteplase-only group (89% vs. 34%, P<0.001). The improvement in reperfusion remained highly significant in a sensitivity analysis in which 100% reperfusion was imputed for the three patients in the Alteplase-only group who had missing data owing to poor clinical status." [100]

In the endovascular group there was a higher early neurologic recovery at 3 days with a P=0.002 and functional outcome scores with modified Rankin scale at 90 days with

a P=0.006 and generalized odds ratio of 2.0 and 95% CI (1.2 to 3.8). It was determined that for patients to have at least a 1-point improvement of their functional score, 2.8 patients would need to be treated with endovascular treatment compared to Alteplase alone.

> "Patients in the endovascular therapy group were also more likely to be independent (functional score 0 to 2) at day 90 (71% vs 40%, p=0.01); we determined that 3.2 patients would need to be treated to achieve an independent outcome, as compared with Alteplase alone. The median number of days spent at home (as compared with the hospital or other impatient facility) in the first 90 days after stroke [106] was 64 days greater in the endovascular-therapy group than in the Alteplase-only group (P=0.001)." [100]

It was found that patients with 90% or more of the vascular territory perfused compared to those with less than 90% reperfusion had significant improvement in outcomes associated with the modified Rankin scale at 90 days and increased independence as well as excellent outcomes, "generalized odds ratio, 4.5; 95% CI, 2.2 to 9.0; P<0.001; score 0 to 2; 72% vs. 30%; P<0.001; and score 0 to 1, 58% vs. 11%; P<0.001." [100]

There were 2 patients in the Alteplase group that had symptomatic intracerebral hemorrhage, and both died, as opposed to none in the endovascular group. There were multiple (2) patients in the endovascular group that had intracerebral hemorrhage but were not symptomatic, resulting in the patients having modified Rankin scores of 3 and 4. One of the patients had intracerebral hemorrhage associated with perforation by a wire during the angiogram but prior to insertion of the Solitaire FR stent retriever. Six percent (2 of the 35) patients ended up with embolization in a different vascular territory but the patients were asymptomatic. Regarding mortality there was no significant difference between the two groups, but it was noted that the patients in the endovascular group had deterioration after Alteplase infusion but before endovascular intervention secondary to a new cerebral embolism.

Tables 17 and 18 show the outcome scores and hemorrhagic conversion rates.

Table 17. EXTEND IA Outcome Scores

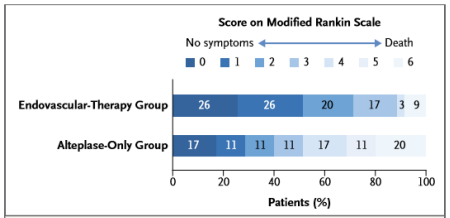


Figure 2. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Shown are the percentages of patients in the endovascular-therapy group and the alteplase-only group with scores from 0 to 6 on the modified Rankin scale as follows: 0, no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (requiring constant nursing care and attention); and 6, death. In the endovascular group, no patients had a score of 5.

Table 18. EXTEND IA Hemorrhage Rates

Table 3. Study Outcomes.*

Outcome	Alteplase-Only Group (N=35)	Endovascular-Therapy Group (N=35)	Effect Size (95% CI)†			
			Adjusted	P Value	Unadjusted	P Value
Primary outcomes						
Median reperfusion at 24 hr (IQR) — (%)‡	37 (−0.5 to 96)	100 (100 to 100)	4.7 (2.5 to 9.0)	<0.001	4.9 (2.5 to 9.5)	<0.001
Early neurologic improvement — no. (%)§	13 (37)	28 (80)	6.0 (2.0 to 18.0)	0.002	6.8 (2.3 to 20)	<0.001
Secondary outcomes						
Score on the modified Rankin scale at 90 days¶						
Median score (IQR) on ordinal analysis	3 (1 to 5)	1 (0 to 3)	2.0	0.02	2.1 (1.2 to 3.8)	0.006
Independent outcome — no. (%)	14 (40)	25 (71)	4.2 (1.4 to 12)	0.01	3.8 (1.4 to 10.0)	0.009
Excellent outcome — no. (%)	10 (29)	18 (51)	2.4 (0.87 to 6.6)	0.09	2.6 (1.0 to 7.1)	0.05
Safety — no. (%)						
Death	7 (20)	3 (9)	0.45 (0.1 to 2.1)	0.31	0.38 (0.1 to 1.6)	0.18
Symptomatic intracerebral hemorrhage‖	2 (6)	0	NA	NA	−6 (−13 to 2)**	0.49
Parenchymal hematoma	3 (9)	4 (11)	NA	NA	3 (−11 to 17)**	0.99
Tertiary outcomes††						
Reperfusion of >90% at 24 hr without symptomatic intracerebral hemorrhage — no. (%)	12 (34)	31 (89)	27.0 (5.5 to 135.0)	<0.001	15.0 (4.0 to 52.0)	<0.001
Recanalization at 24 hr — no. (%)‡‡	15 (43)	33 (94)	29.0 (5.4 to 155.0)	<0.001	22.0 (4.5 to 106.0)	<0.001
Median infarct growth at 24 hr (IQR) — ml§§	35.3 (6.3 to 73.4)	10.9 (0 to 23.6)	−0.44 (−0.76 to −0.13)‖‖	0.007	NA	NA
Median home time (IQR) — days¶¶	15 (0 to 69)	73 (47 to 86)	64 (28 to 90)‖‖	0.001	58 (17 to 90)‖‖	0.006

* NA denotes not applicable.
† Values are odds ratios unless otherwise indicated. Odds ratios or median differences are for the endovascular-therapy group as compared with the alteplase-only group.
‡ Reperfusion was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and 24-hour imaging. This value can be negative if hypoperfusion becomes more severe over time. This analysis was adjusted for the site of vessel occlusion at baseline. The effect size in this category is the Wilcoxon–Mann–Whitney generalized odds ratio.
§ Early neurologic improvement was defined as a reduction of 8 points or more on the National Institutes of Health Stroke Scale (NIHSS) or a score of 0 or 1 at 3 days. This analysis was adjusted for the NIHSS score and age at baseline.
¶ The initial analysis of the modified Rankin scale was an ordinal analysis that used the full range of the scale from 0 (normal function) to 6 (death) and is expressed as a Wilcoxon–Mann–Whitney generalized odds ratio. The analysis was adjusted for the baseline NIHSS score (≤15 vs. >15) and age (≤70 years vs. >70 years) with the use of a permutation method to accommodate small stratum size. This method does not produce confidence intervals. In addition, scores on the modified Rankin scale were analyzed for an ordinal independence (score of 0 to 2) or an excellent outcome (score of 0 or 1), adjusted for the full range of ages and baseline score on the NIHSS.
‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score.
** The effect size in this category is a risk difference, as measured in percentage points for symptomatic intracerebral hemorrhage and parenchymal hematoma.
†† A more detailed list of tertiary outcomes is provided in Table S3 in the Supplementary Appendix.
‡‡ Recanalization was defined as a Thrombolysis in Myocardial Infarction score of 2 or 3 (partial or complete restoration of flow at the site of arterial occlusion).[21] This analysis was adjusted for the site of vessel occlusion at baseline.
§§ Infarct growth was defined as the increase in the ischemic core volume from baseline to 24 hours and was adjusted for the ischemic core volume at baseline.
¶¶ Home time (the number of days spent at home during the first 90 days after the diagnosis of stroke) was adjusted for the NIHSS score and age at baseline.
‖‖ The effect size in this category is the median difference in infarct growth (as measured in milliliters and transformed by an exponent of 0.2 owing to a non-normal distribution) and the median difference in days for home time, as calculated by median regression.

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B.14 Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke (REVASCAT)

Prior to this study, multiple prospective, randomized studies showed the benefit of mechanical thrombectomy.[49,82,90]

> "Our study, called the Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT), shares the following four features with the previously cited trials: enrollment limited to patients with imaging-based evidence of proximal occlusion of the M1 segment (main trunk) of the middle cerebral artery with or without concomitant occlusion of the internal carotid artery, imaging-based exclusion of patients with a large core (indicating large cerebral infarct), use of a stent retriever, and ongoing quality-improvement efforts to reduce the time to reperfusion to the minimum." [107]

One of the criticisms of the previous studies was the poor consecutive enrollment. [108] This study took this fact into account:

> "The study was conducted within Sistema Online d'Informacio de l'Icuts Agut de Catalunya (SONIIA), a concomitant, population based registry of acute stroke reperfusion procedures.[109] that captured patients within the same catchment area as that of the participating hospitals in our study, including patients who were treated in the thrombectomy group." [107]

This study was unique compared to the previous studies, on account of treating patients within 8 hours after the onset of stroke symptoms.

"REVASCAT was a multicenter, prospective, randomized, sequential, open-label phase 3 study with blinded evaluation." [107] In this study a patient, if eligible, received Alteplase within 4.5 hours of stroke symptoms. Thirty minutes after the infusion of Alteplase, or if the patient was not eligible for Alteplase, patients had a thrombectomy procedure. They compared the patients that had thrombectomy to patients with medical therapy alone. Covidien provided an unrestricted grant for the study; however, they were not involved in the study design, conduct, or writing of the protocol or manuscript. The study design, conduct, writing of protocol and manuscript were all performed by the steering committee who had unrestricted access to the data and reviewed the analysis with study statisticians along with the co-authors of the manuscript.

Patients were screened at 4 study centers in Catalonia, Spain, between November 2012 and December 2014. Eligible patients were between the ages of 18 and 80 (after 160 patients were enrolled the age ceiling was raised from 80 to 85 years old, but patients had to have an ASPECTS score of greater than 8), prior to stroke symptoms had a modified Ranking score of 1 or less, had an NIHSS score of at least 6, an ASPECTS score of 7 or less on CT without contrast or less than 6 on MRI, were able to be treated within 8 hours

of their stroke symptoms, and had a proximal anterior circulation occlusion. Patients were excluded if they had a large core infarct on imaging indicated by a score of less than 7 or 6 with ASPECTS on CT or MRI, respectively.

The study sites and interventionalists were all part of large comprehensive stroke centers that treated at least 500 stroke patients per year with more than 60 mechanical thrombectomies, at least 20 of them with the Solitaire device.

> "We randomly assigned 206 patients in a 1:1 ratio to receive either medical therapy (including intravenous Alteplase when eligible) and endovascular treatment with the Solitaire stent retriever (thrombectomy group) or medical therapy alone (control group). We used a real-time computerized randomized procedure that was stratified according to age (less than or equal to 70 or greater than 70 years), baseline NIHSS score (6 to 16 or greater than or equal to 17), therapeutic window (less than or equal to 4.5 or greater than 4.5 hours), occlusion site (intracranial internal carotid artery or M1 segment (main trunk of the middle cerebral artery)), and participating center." [107]

The primary outcome of the study was with use of the modified Rankin scale. The patients were evaluated with a structured interview by a blinded, certified assessor. [110]

> "The primary evaluation by means of video recording (in 106 evaluations). In case in which the video recording was unavailable, outcomes as determined in person by local investigators in a blinded manner were used as default (in 65 evaluations). Sensitivity analyses were performed with outcome determinations in a blinded manner by local investigators and central readers. Decisions regarding the adjudication method for the primary outcome were made by the steering committee in a blinded manner before the first interim analysis." [107]

Secondary outcomes were CT or MRI 24 hours after treatment to evaluate for infarct volumes, evaluation at 24 hours with NIHSS score to evaluate for early dramatic improvement, defined as an initial NIHSS score of greater than or equal to 8 improved to an NIHSS score of 2 or less, and for the interventional/ thrombectomy group the TICI score. At the 90-day evaluation, the patient was evaluated with NIHSS score, Barthel Index score, and the health status determined by the EuroQol Group 5-dimension Self-Report

Questionnaire. The safety outcomes of death and symptomatic intracranial hemorrhage were confirmed with radiographic studies, CT or MRI, as described by the SITS-MOST [27] criteria and the ECASS II, [20] which included radiographic evidence of hemorrhage and a decrease in NIHSS of at least 4 points, at 90 days, as well as an independent clinical events committee that evaluated procedure related complications such as arterial perforation or dissection.

> "The first interim analysis was performed as planned after 25% patients (174 of the maximum sample size) had completed 90 days of follow-up. The steering committee accepted the recommendation of the data and safety monitoring board to stop recruitment because of the loss of equipoise. Although the interim results did not reach the prespecified stopping boundaries, study recruitment was terminated because of emerging results from three other studies [RW.ERROR - Unable to find reference:387] that showed the efficacy of thrombectomy, which raised ethical concerns about further assignment of patients to the control group. Since the trial was stopped because the primary hypothesis was no longer an open question, we changed our goal from hypothesis testing to estimation. Since just one analysis was performed, adjustment for multiple comparisons was no longer required, and 95% confidence intervals reported. All reported 95% confidence intervals and P values are nominal and based on the recorded data." [107]

The analyses were performed in the intention-to-treat population. Measurement of the effect of size was a cumulative odds ratio calculated by shift analysis. The primary analysis was adjusted for minimization factors and use of intravenous Alteplase administration. The enrollment of 690 patients was determined to provide a power of 90% in detecting the difference in the distribution of scores associated with the modified Rankin scale with a one-sided significance at a level of 0.025 in the primary outcome analysis with an expected results odds ratio of 1.615. This was a sequential study because of the inability to determine the size of the treatment effect in association with the primary outcome. To determine the stopping boundaries using a Whitehead triangular test, the study planned to

have four equally spaced review periods (25%, 50%, 75%, and 100%) of the sample size, decreasing the individual limits of significance to a one-sided alpha level of 0.025.

There were 205 patients included in the analysis. Of the 206 enrolled, one withdrew after randomization. All patients were evaluated at the 90-day mark for the primary outcome. Of these patients only 5 were evaluated by telephone instead of by video interview because of the clinical status with a modified Rankin score of 4 or 5. There were 103 patients in each group, thrombectomy and control, of the intention-to-treat analyses. In Spain, during this period there were 2576 ischemic stroke patients in the SONIIA registry. Of these, 15.6% were in Catalonia, with an aggregate reperfusion-therapy rate of 17/100,000 per year. Alteplase as the primary therapy occurred in 2036 (79%) patients, with the remaining 540 (21%) patients having endovascular therapy, including 260 of them having both Alteplase and endovascular therapy. Of the 540 patients, 464 (86%) were treated at the hospitals in the study. The data was reviewed periodically to confirm eligibility and 111 of the 464 patients undergoing endovascular therapy met the study criteria, with 103 treated in the study.

> "Baseline characteristics were similar in the two study groups. The median NIHSS score was 17, the median ASPECTS score was 7 in the thrombectomy group and 8 in the control group, and intravenous Alteplase was administered to 68% of patients in the thrombectomy group and 77.7% of those in the control group. The median time from stroke onset to randomization was 225 minutes." [107]

In the thrombectomy group, 98 of the 103 patients underwent the procedure; 9 of the 98 had ipsilateral carotid stenting, with 7 of the 98 procedures being performed under general anesthesia, and there was 1 patient treated with intracranial angioplasty secondary to failed stent retriever results and 1 was given intra-arterial Alteplase, both considered as being outside the protocol.

> "The primary outcome analysis showed a common odds ratio of improvement in the distribution of the modified Rankin scale score of 1.7 (95% confidence interval (CI), 1.05 to 2.8) favoring thrombectomy. The absolute between-group difference in the proportion of patients who were functionally independent (score of 0 to 2 on the modified Rankin scale) was 15.5 percentage points, favoring thrombectomy (43% vs 28.2%; adjusted odds ratio 2.1; 95% CI, 1.1 to 4.0)." [107]

"The primary outcome analysis that was based only on the local evaluator's adjudication in a blinded manner showed higher treatment effects for thrombectomy (odds ratio, 1.9, 95% CI, 1.1 to 3.2) than the above-mentioned odds ratio." [107]

"Secondary outcomes also favored the thrombectomy group. Successful revascularization was achieved in 66% of patients in the thrombectomy group according to core laboratory assessment and in 80% of the patients according to the assessment of local interventionalists." [107]

Tables 19 and 20 show outcome scores and hemorrhagic conversion rates.

Table 19. REVASC Outcome Scores

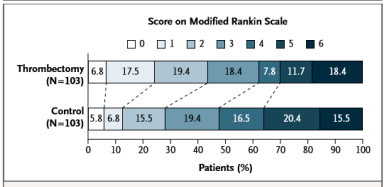

Figure 1. Distribution of Functional Scores at 90 Days (Intention-to-Treat Population).

Shown are scores on the modified Rankin scale for patients in the thrombectomy group and the control group who were evaluated by means of video recording (in 106 patients) and by local investigators (in 65 patients). Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help, but able to walk unassisted; 4, moderately severe disability (unable to attend body needs and unable to walk); 5, severe disability (requiring constant nursing care and attention); and 6, death. Scores of 5 and 6 were combined for the analysis. A significant difference between the thrombectomy group and the control group was noted in the overall distribution of scores (adjusted common odds ratio for improvement of 1 point on the modified Rankin scale, 1.7; 95% confidence interval, 1.05 to 2.8).

Table 20. REVASC Hemorrhage Rates

Table 4. Serious Adverse Events within 90 Days.*

Variable	Thrombectomy (N=103)	Control (N=103)	Between-Group Difference (95% CI)	Risk Ratio (95% CI)
	no. (%)			
Safety variable				
Death				
At 90 days	19 (18.4)	16 (15.5)	−2.9 (−13.2 to 7.3)	1.2 (0.6 to 2.2)†
At ≤7 days	10 (9.7)	5 (4.9)	−4.8 (−11.9 to 2.2)	2.0 (0.7 to 5.6)
Intracranial hemorrhage				
Symptomatic‡				
SITS-MOST criteria	2 (1.9)	2 (1.9)	0.0 (−3.8 to 3.8)	1.0 (0.1 to 7.0)
ECASS II criteria	5 (4.9)	2 (1.9)	−2.9 (−7.8 to 2.0)	2.5 (0.5 to 12.6)
Asymptomatic§	17 (16.5)	11 (10.7)	−5.8 (−15.2 to 3.5)	1.5 (0.7 to 3.1)
Subarachnoid hemorrhage	5 (4.9)	2 (1.9)	−2.9 (−7.8 to 2.0)	2.5 (0.5 to 12.6)
Parenchymal hematoma¶				
Any	6 (5.8)	6 (5.8)		
Type 1	3 (2.9)	4 (3.9)		
Type 2	3 (2.9)	2 (1.9)		
Other adjudicated serious adverse event				
Neurologic worsening‖	16 (15.5)	13 (12.6)	−2.9 (−12.4 to 6.6)	1.2 (0.6 to 2.4)
Malignant cerebral edema**	11 (10.7)	10 (9.7)	−1.0 (−9.2 to 7.3)	1.1 (0.5 to 2.5)
Recurrent stroke	4 (3.9)	3 (2.9)	−1.0 (−5.9 to 4.0)	1.3 (0.3 to 5.8)
Procedure-related complication††		NA	NA	NA
Distal embolization in a different territory	5 (4.9)			
Arterial dissection	4 (3.9)			
Arterial perforation	5 (4.9)			
Groin hematoma	11 (10.7)			
Groin pseudoaneurysm	1 (1.0)			
Vasospasm requiring treatment‡‡	4 (3.9)			

* Negative values for the between-group difference favor the control group. The risk ratio is for the thrombectomy group as compared with the control group. A complete list of adverse events is provided in Tables S6 and S7 in the Supplementary Appendix.
† The adjusted risk ratio for death at 90 days was 1.1 (95% CI, 0.8 to 1.4).
‡ Symptomatic intracranial hemorrhage was defined as parenchymal hemorrhage type 2 on follow-up imaging and neurologic deterioration of at least 4 points on the NIHSS, according to the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) criteria, or any symptomatic intracranial hemorrhage and neurologic worsening of at least 4 points on the NIHSS, according to the second European–Australasian Acute Stroke Study (ECASS II) criteria.
§ Asymptomatic intracranial hemorrhage was defined as any parenchymal hematoma with no neurologic worsening, as adjudicated by local investigators.
¶ Parenchymal hematomas were graded according to the neuroimaging core laboratory classification.
‖ Neurologic worsening was defined as an increase of at least 4 points on the NIHSS within 5 days after stroke onset that was not attributed to intracranial hemorrhage or malignant cerebral edema.
** Malignant cerebral edema was treated with decompressive hemicraniectomy in 3 patients in the thrombectomy group and in 6 patients in the control group.
†† All procedure-related complications were reported by the clinical events committee.
‡‡ Vasospasm events were reported by local investigators and the angiography core laboratory.

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B.15 THERAPY Trial

To quote the authors:

"The THERAPY trial assessed the effectiveness of the Penumbra aspiration system (Penumbra, Inc.) in patients with acute ischemic stroke from large vessel occlusions. [111] Although the results of the study are yet to be published, data were presented at the European Stroke Organization Conference in April 2015 in Glasgow, Scotland. The trial was stopped early after 108 of the planned 692 patients had been enrolled because of favorable data on endovascular treatment from other recently reported trials. Thirty-eight percent of mechanical thrombectomy patients achieved good outcomes (mRs, 1-2 at 90 days), whereas only 30% of medically treated patients had good outcomes. [111]." [112]

B.16 Thrombectomy 6-24 Hours after Stroke with Mismatch between Deficit and Infarct (DAWN Trial)

It is a well-published fact that thrombectomy within 6 hours of the symptom onset of stroke is beneficial. RW.ERROR - Unable to find reference:387 All the cited studies utilized time as the key determinant for performing the procedure. Performing the procedure after the 6-hour mark showed diminishing benefits, since time to thrombectomy increased. (8) Limited information is available on the benefit of performing thrombectomy after 6 hours of symptom onset, but recent research suggested that a mismatch of ischemia and infarct with perfusion studies may benefit from treatment. (10,11) The DAWN Trial attempted to compare thrombectomy in addition to standard medical care with standard medical care alone in patients with ischemic stroke that was last known well between 6–24 hours. Moreover, a mismatch of clinical deficits was compared to infarct.[113]

"The DAWN trial was a multicenter, prospective, randomized, open-label trial with a Bayesian adaptive-enrichment design and with blinded assessment of end points."[113]

The eligible patients fulfilled the following criteria:

> "...evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both on computed tomographic (CT) angiography or magnetic resonance angiography. In addition, patients had to have a mismatch between the severity of the clinical deficit and the infarct volume, which defined according to the following criteria: those in Group A were 80 years of age or older, had a score of 10 or higher on the National Institute of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating a more severe deficit), and had an infarct volume of less than 21 ml; those in Group B were younger than 80 years of age, had a score of 20 or higher on the NIHSS, and had an infarct volume of 31 to less than 51 ml. Infarct volume was assessed with the use of diffusion-weighed magnetic resonance imaging (MRI) or perfusion CT and was measured with the use of automated software (RAPID, iSchemaView).
>
> Other inclusion criteria were age of 18 years or older, an interval between the time that the patient was last known to be well and randomization of 6 to 24

> hours, a prestrike score of 0 to 1 on the modified Rankin scale (which ranges from 0 to 6, with a score of 0 indicating no disability and higher scores indicating more severe disability), no evidence of intracranial hemorrhage on CT or MRI, an no evidence of an infarct involving more than one third of the territory of the middle cerebral artery on CT or MRI at baseline. Patients either did not meet the usual criteria for treatment with intravenous Alteplase because of a late presentation or received treatment with intravenous Alteplase and had a persistent occlusion of the vessel at the time that they were eligible for enrollment in the trial)." [113]

The treatment randomization comprised of a 1:1 ratio of thrombectomy with standard medical care and standard medical care alone. A central web-based procedure with block minimization process was used to balance the two treatment groups, which were stratified into three subgroups based on the mismatch criteria for time periods of 6–12 hours, greater than 12–24 hours, or last known well along with the occlusion site of intracranial, anterior circulation, first order vessel of the internal carotid artery and middle cerebral artery only. Patient were admitted to a stroke unit or intensive care unit. They received either rt-PA or anti-platelet agents 24 hours after randomization. The patients who received thrombectomy underwent the procedure at centers that performed at least 40 mechanical thrombectomy procedures annually. The Trevo device (Stryker Neurovascular), a self-expanding stent retriever, was the thrombectomy device utilized. Patients with occlusions or stenosis of the extracranial carotid artery were not permitted to undergo angioplasty in order to allow intracranial access.

The primary endpoint was the mean score of disability using the utility-weighted modified Rankin score at 90 days, and the secondary endpoint was the rate of functional independence using the modified Rankin score at 90 days that, at the request of the FDA, became a coprimary endpoint 30 months after the commencement of the trial. The prespecified secondary endpoints were death at 90 days for any reason, infarct volume, central reviewing with a change from the baseline infarct volume at 24 hours, radiographic

evidence of blood vessel recanalization on the CTA or MRA at 24 hours, and therapeutic response with a decrease in the improvement of an NIHSS score of greater than 10 from the baseline or in the range 0–1 within either a week of hospitalization or at discharge between 1–7 days, whichever occurs first. The secondary endpoint for the thrombectomy group included a TICI score of 2b or 3 in each randomized subgroup as well as an occlusion site, sex, age, admitting NIHSS score, time last known well, time to randomization, and type of stroke onset (wake-up, unwitnessed, witnessed). The safety endpoints were stroke-related death at 90 days, symptomatic hemorrhage within 24 hours, neurologic deterioration or a change in an NIHSS score of greater than 4 points within 5 days of the stroke, and procedure-related complications, all of which were reviewed by an independent clinical events committee.

The statistical analysis involved 150–500 patients with the interim analysis, and the study was stopped early based on the data that showed the probability of thrombectomy combined with standard medical care being superior to standard medical care alone in terms of the primary endpoint of disability at 90 days. The Bayesian statistical modeling, with a one-sided posterior probability of superiority of at least 0.986 with adjustments for infarct volume at baseline, was used for the primary endpoint of disability on the utility-weighted modified Rankin score. The initial second primary endpoint—the rate of functional independence at 90 days using a modified Rankin score—was evaluated using the posterior probability of thrombectomy combined with standard medical care being superior to medical standard of care. It was conducted using the same statistical model in a nested hierarchical fashion as the first primary endpoint.

> "The trial had 86% power to detect an adjusted difference between the two treatment groups in the mean score on the utility-weighted modified Rankin scale of 1.0. No additional adjustments for multiplicity were made for analysis of the secondary end points. Bayesian multiple imputations were used for patients who had missing values for the primary analysis. Descriptive statistics were calculated with the use of the last-observation-carried forward method for patients who had missing values for the subgroup analysis." [113]

See Tables 21-22 below for tabulated results of the outcomes and safety.

Table 21. DAWN Outcome Scores.

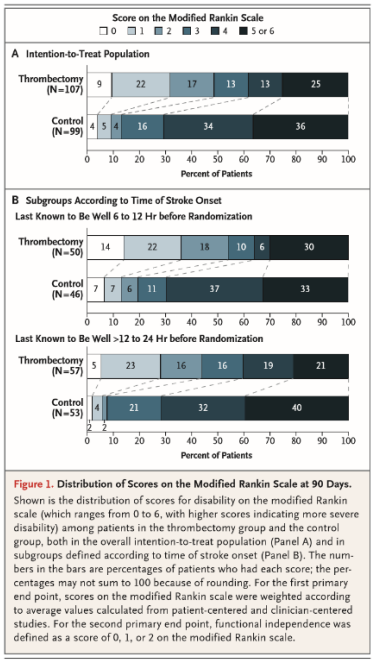

Figure 1. Distribution of Scores on the Modified Rankin Scale at 90 Days.
Shown is the distribution of scores for disability on the modified Rankin scale (which ranges from 0 to 6, with higher scores indicating more severe disability) among patients in the thrombectomy group and the control group, both in the overall intention-to-treat population (Panel A) and in subgroups defined according to time of stroke onset (Panel B). The numbers in the bars are percentages of patients who had each score; the percentages may not sum to 100 because of rounding. For the first primary end point, scores on the modified Rankin scale were weighted according to average values calculated from patient-centered and clinician-centered studies. For the second primary end point, functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale.

Table 22. DAWN Hemorrhage Rates.

Table 3. Safety Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)	Risk Ratio (95% CI)
	no. (%)		*percentage points*	
Stroke-related death at 90 days	17 (16)	18 (18)	−2 (−13 to 8)	1 (1 to 2)
Death from any cause at 90 days	20 (19)	18 (18)	1 (−10 to 11)	1 (1 to 2)
Symptomatic intracranial hemorrhage at 24 hr†	6 (6)	3 (3)	3 (−3 to 8)	2 (1 to 7)
Neurologic deterioration at 24 hr‡	15 (14)	26 (26)	−12 (−23 to −1)	1 (0 to 1)
Procedure-related complications	7 (7)	NA		
Distal embolization in a different territory	4 (4)	NA		
Intramural arterial dissection	2 (2)	NA		
Arterial perforation	0	NA		
Access-site complications leading to intervention	1 (1)	NA		

* There were no significant differences between the two treatment groups with respect to safety outcomes, except for neurologic deterioration (P=0.04). All safety outcomes were adjudicated by an independent clinical-events committee.
† Symptomatic intracranial hemorrhage was defined according to European Cooperative Acute Stroke Study III criteria as the presence of extravascular blood in the cranium that was associated with an increase in the NIHSS score of 4 points or more or death and was judged to be the predominant cause of neurologic deterioration.
‡ Neurologic deterioration was defined as an increase in the NIHSS score of 4 or more points within 5 days after stroke that was not attributed to intracranial hemorrhage or malignant cerebral edema.

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B.17 Thrombectomy for Stroke at 6 to 16 hours with Selection by Perfusion Imaging (DEFUSE III)

The results of the DAWN trial demonstrated that the time window for treating ischemic strokes may be treated up to 24 hours following the onset of symptoms or last known well if patients are carefully selected based on clinical deficits disproportionate to the size of the stroke on advanced radiographic images. [113] The Endovascular Therapy Imaging Evaluation for Ischemic Stroke (DEFUSE III) trial was developed along with other studies, [114,115] suggesting that CT perfusion studies and/or MR diffusion and perfusion studies can estimate the volume of infarct versus ischemia to indicate which patients may experience favorable outcomes with thrombectomy DEFUSE III. The design

of the trial aimed to test the hypothesis, "Patients who were likely to have salvageable ischemic brain tissue as identified by perfusion imaging and who underwent endovascular therapy 6 to 16 hours after they were last known well would have better functional outcomes than patients treated with standard medical therapy." [116]

The trial was funded by the NIH (National Institute of Health) through StrokeNet, a network of over 300 hospitals in the United States, of which 38 centers that were preapproved, since they had neuro-interventionalists with appropriate training and experience, participated in the study, all centers being in the United States. Patients were enrolled if they met the clinical and radiographic criteria and were able to undergo the treatment within the 6–16-hour time window of being last known well, regardless of whether they experienced a witnessed or wake-up type of stroke. RAPID software (iSchemaView) was utilized to determine "if they had an initial infarct volume (ischemic core) of less than 70 ml, a ratio of volume of ischemic tissue to initial infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischemia (penumbra) of 15 ml or more." [116] Furthermore, patients had to have either an occlusion of the extracranial or intracranial internal carotid artery or the first order MCA on CTA or MRA.

The trial was a "randomized, open-label trial with blinded outcome assessment that compared endovascular therapy plus standard medical therapy with standard medical therapy alone in patients with acute ischemic stroke." [116] Patients were randomized by a web-based dynamic system in a 1:1 ratio to the endovascular with medical therapy group or to the only medical therapy group. They were then stratified based on age, time of last known well, NIHSS score on initial exam, age, trial site, and infarct volume. The thrombectomy devices were FDA-approved devices, and the neuro-interventionalists

decided which device was to be used. Patients were able to undergo extracranial internal carotid artery treatment with or without stent, and all the patients had to have the groin punctured within 90 minutes of the completion of the advanced imaging. Standard medical therapy was based on the current American Heart Association (AHA) guidelines at the time, and intra-arterial t-PA was not permitted in the thrombectomy group.

> "The primary efficacy outcome was the ordinal score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at day 90; the score was assessed in person, or by telephone if an in-person visit was not feasible by a certified rater who was not aware of the trial-group assignments. The secondary efficacy outcome was functional independence (defined as a score on the modified Rankin scale of 0 to 2) at day 90. The primary safety outcomes were death within 90 days and the occurrence of symptomatic intracranial hemorrhage within 36 hours, defined as an increase of at least 4 points in the NIHSS score associated with brain hemorrhage on imaging within 36 hours after symptom onset.
>
> Imaging outcomes were infarct volume measured at 24 hours (with a window of +/-6 hours) after randomization; lesion growth (increase in volume of the infarct) between baseline imaging and 24 hours; reperfusion, defined as a greater than 90% reduction in the region of perfusion delay (Tmax of >6 seconds) between baseline and 24 hours; and complete recanalization of the primary arterial occlusive lesion at 24 hours on CTA or MRA." [116]

The radiographic assessments were at baseline, 30 days, and 90 days with CT and MRI. All the studies were evaluated independently by assessors at Stanford University's core imaging laboratory, who were blinded to the assigned group. Clinical assessments of the patients were done at baseline, randomization, hospital discharge, 30 days, and at 90 days. The subjects were evaluated with NIHSS scores while the modified Rankin scale were assessed by blinded certified assessors.

A statistical analysis of the trial was planned for an adaptive enrichment design with a maximum sample of 476, with interim analyses for 200 and 350 patients at the 90-day point. Due to the DAWN trial results being published and the two studies having a similar patient population and treatments, the DEFUSE III trial was placed on hold to

perform the interim analysis, which included a subgroup analysis of patients who would have been eligible for the DAWN trial. The DEFUSE III trial was halted after the interim analysis, as explained below:

> "…the trial was halted because the prespecified efficacy boundary (P<0.0025) had been exceeded. The statistical analysis plan specified one-sided hypothesis testing for the Wilcoxon rank-sum test and a P value of less than 0.025 as a measure of statistical significance, but we reported two-sided results and use a P values for the primary efficacy outcomes were calculated with the use of ordinal regression on the full modified Rankin scale and stratified Cochran-Mantel-Haenszel tests, with randomization stratification variables split at their medians as the covariates. For patients lost to follow-up at 90 days, the missing 90-day score on the modified Rankin scale was imputed from the 30-day score by the last-observation-carried-forward method. "[116]

Tables 23-24 depict the tabulated results of outcomes and safety.

Table 23. DEFUSE III outcome scores.

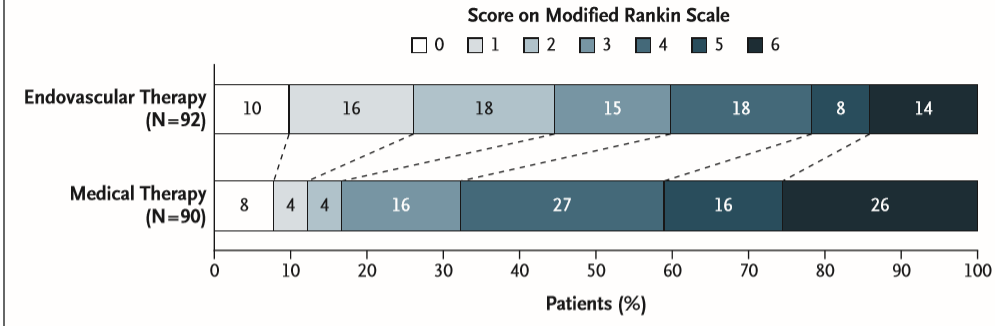

Figure 2. Scores on the Modified Rankin Scale at 90 Days.

Patients in the endovascular-therapy group received endovascular therapy plus standard medical therapy. Patients in the medical-therapy group received standard medical therapy alone. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. There was a significant difference favoring the endovascular-therapy group over the medical-therapy group in the overall distribution of scores (unadjusted common odds ratio, 2.77; 95% CI, 1.63 to 4.70; P<0.001).

Table 24. DEFUSE III Hemorrhage Rates

Table 2. Clinical and Imaging Outcomes.

Outcome	Endovascular Therapy (N = 92)*	Medical Therapy (N = 90)	Odds Ratio or Risk Ratio (95% CI)†	P Value
Primary efficacy outcome: median score on modified Rankin scale at 90 days (IQR)‡	3 (1–4)	4 (3–6)	2.77 (1.63–4.70)§	<0.001
Secondary efficacy outcome: functional independence at 90 days — no. (%)¶	41 (45)	15 (17)	2.67 (1.60–4.48)	<0.001
Safety outcomes — no. (%)				
Death at 90 days	13 (14)	23 (26)	0.55 (0.30–1.02)	0.05
Symptomatic intracranial hemorrhage‖	6 (7)	4 (4)	1.47 (0.40–6.55)	0.75
Early neurologic deterioration	8 (9)	11 (12)	0.71 (0.30–1.69)	0.44
Parenchymal hematoma type 2	8 (9)	3 (3)	2.61 (0.73–14.69)	0.21
Imaging outcomes**				
Median infarct volume at 24 hr (IQR) — ml	35 (18–82)	41 (25–106)	—	0.19
Median infarct growth at 24 hr (IQR) — ml	23 (10–75)	33 (18–75)	—	0.08
Reperfusion >90% at 24 hr — no./total no. (%)	59/75 (79)	12/67 (18)	4.39 (2.60–7.43)	<0.001
Complete recanalization at 24 hr — no./total no. (%)	65/83 (78)	14/77 (18)	4.31 (2.65–7.01)	<0.001
TICI score of 2b or 3 — no./total no. (%)	69/91 (76)	—	—	

* An intervention was attempted in 90 patients (98%), of whom 88 had an attempted mechanical thrombectomy and 2 had carotid stenting alone. In one of these two cases, the interventionalist elected not to perform a thrombectomy. The other patient did not have an occlusion on the baseline angiogram but was treated with carotid stenting for presumed dissection. The 2 patients with no intervention had carotid-artery occlusions, one in the common carotid and the other in the internal carotid, and the interventionalist decided that treatment was not feasible. Revascularization of the carotid artery with angioplasty, stenting, or both was performed in 13 patients (14%).

† The odds ratio is shown for the primary efficacy outcome, and risk ratio is shown for the other outcomes.

‡ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability. The protocol required the score to be assessed by a person who was not aware of the trial-group assignments. However, three patients in the endovascular-therapy group and one patient in the medical-therapy group had an assessor who was aware of the trial-group assignments.

§ Shown is the unadjusted common odds ratio. The odds ratio with adjustment for stratification factors is 3.36 (95% CI, 1.96 to 5.77; P<0.001). The proportional-odds assumption was not met when core volume was included in the fully adjusted model; without core volume included, the adjusted odds ratio is 3.24 (95% CI, 1.89 to 5.55).

¶ Functional independence was defined as a score on the modified Rankin scale of 0 to 2.

‖ Among the patients with symptomatic intracranial hemorrhage, the hemorrhage was rated as parenchymal hematoma type 2 (dense blood clot exceeding 30% of the infarct volume with substantial space-occupying effect; in two patients in the endovascular-therapy group and three patients in the medical-therapy group), parenchymal hematoma type 1 (blood clot not exceeding 30% of the infarcted area with some mild space-occupying effect; in one patient in the endovascular-therapy group), hemorrhagic infarction type 2 (confluent petechiae within the infarcted area, but without space-occupying effect; in three patients in the endovascular-therapy group), or hemorrhagic infarction type 1 (small petechiae along the margins of the infarct; in one patient in the medical-therapy group).

** Infarct volume at 24 hours was assessed on diffusion-weighted MRI (or CT if MRI was not feasible). Infarct volume and infarct growth at 24 hours were assessed in 90 patients in the endovascular-therapy group and 89 patients in the medical-therapy group (2 patients in the endovascular-therapy group and 1 patient in the medical-therapy group died before imaging).

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B.18 MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (WAKE-UP)

The use of rt-PA is a standard of care for the treatment of ischemic stroke, and Alteplase, rt-PA, must be administered within 4.5 hours as part of the standard of care. [7,21,117,118] However, as many as 27% of the patients with ischemic stroke cannot be treated with rt-PA because they exceed the 4.5-hour window due to their last known well or waking up from sleep with the symptoms. [119,120] Wake-up strokes are thought to be strokes that occur during the last few hours of sleep, and these patients could possibly be candidates for treatment with rt-PA. [121] It has been proved that MRI diffusion weighted and FLAIR imaging in patients with stroke can predict patients with stroke of less than 4.5 hours. [122-125] The purpose of the study is detailed below:

> "We conducted the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial to determine whether treatment with Alteplase would improve functional outcomes in patients with an unknown time of stroke onset and a mismatch between diffusion-weighted imaging and FLAIR findings on MRI." [47]

The trial design is "an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial involving patients with an unknown time of onset of stroke." [47] The trial was conducted in 70 centers in European countries selected on the basis of their experience of stroke at their centers, routine use of rt-PA, and ability to perform an emergency MRI. The MRI consisted of DWI showing acute ischemic lesion and no parenchymal hyperintensity on FLAIR imaging, with all researchers certified by web-based training on the image interpretation. The trial was overseen by an independent data and safety monitoring board as well as a steering committee. The patients were eligible if they fulfilled the criteria given below:

> "…they presented with clinical signs of acute stroke, were 18-80 years of age, and had been able to carry out usual activities in their daily life without support before the stroke. The patient either recognized stroke symptoms on awakening or could not report the timing of the onset of symptoms (e.g., as a result of aphasia or confusion). The time that had elapsed since the patient was last known to be well had to be more than 4.5 hours (with no upper limit) in order to exclude patients who otherwise would have fulfilled the standard eligibility criteria for the use of Alteplase. Patients underwent MRI examination that included diffusion-weighted imaging, FLAIR, a sequence sensitive to hemorrhage, and time-of-flight magnetic resonance angiography of the circle of Willis. Patients underwent randomization if they had a mismatch between the presence of an abnormal signal on MRI diffusion-weighted imaging and no visible signal change on FLAIR in the region of the acute stroke." [47]

Patients were excluded if they had an NIHSS score greater than 25, a hemorrhage, or a large stroke, defined as greater than one-third of the MCA territory. They were randomized with the help of a web-based procedure using a permuted-block design. They were assigned in a 1:1 ratio to receive standard dosing of either Alteplase or placebo. The

stratification of patients was done based on age greater or less than 60 and an NIHSS score of greater or less than 10.

Patients were assessed clinically and radiographically at baseline, at 22 and 36 hours after randomization, between 5 and 9 days (or at discharge if earlier), and at 90 days. Patients were evaluated based on their NIHSS scores as well as the modified Rankin scale. An MRI was performed at baseline and 22–36 hours after the randomization to assess the final infarct volume and determine if a hemorrhage had occurred.

The outcome measures are detailed below:

> "The primary efficacy endpoint was a favorable clinical outcome, which was defined as a score of 0 to 1 on the modified Rankin scale 90 days after randomization. Secondary efficacy endpoints were the ordinal score on the modified Rankin scale at 90 days; the proportion of patients with a treatment response at 90 days (defined as a score on the modified Rankin scale of 0 for patients with an NIHSS score </= 7, a score of 0 or 1 for the patients with an NIHSS score of 8 to 14, and a score of 0 to 2 for patients with an NIHSS score >14)." [47]

Death, or a composite outcome of death, and dependence were the primary safety endpoints, with scores of 4–6 on the modified Rankin scale at 90 days. The secondary endpoint was symptomatic hemorrhage.

The statistical analysis was based on an intention-to-treat population of primary and secondary outcomes. An unconditional logistic-regression model was used for primary outcomes, with the model fitted for an odds ratio and 95% confidence interval. Proportional-odds logistic-regression models were used for the secondary efficacy outcomes and fitted for the common odds ratio to determine if rt-PA led to a lower modified Rankin scale than placebo.

Tables 25-26 below depicts the tabulated results of outcomes and safety.

Table 25. WAKE-UP trial outcome scores.

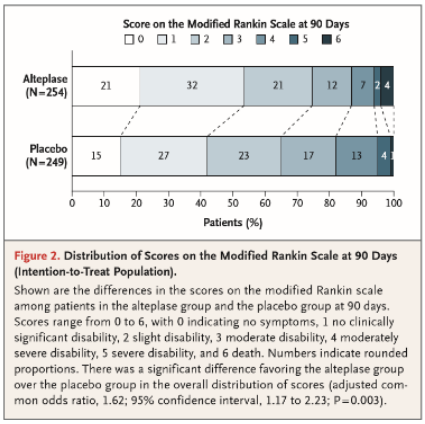

Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

Shown are the differences in the scores on the modified Rankin scale among patients in the alteplase group and the placebo group at 90 days. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Numbers indicate rounded proportions. There was a significant difference favoring the alteplase group over the placebo group in the overall distribution of scores (adjusted common odds ratio, 1.62; 95% confidence interval, 1.17 to 2.23; P=0.003).

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Table 26. WAKE-UP trial hemorrhage rates

Table 3. Safety Outcomes.

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Adjusted Odds Ratio (95% CI)*	P Value
	no. (%)			
Primary†				
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39–1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.2)	3.38 (0.92–12.52)	0.07
Secondary				
Symptomatic intracranial hemorrhage				
As defined in SITS-MOST‡	5 (2.0)	1 (0.4)	4.95 (0.57–42.87)	0.15
As defined in ECASS II§	7 (2.8)	3 (1.2)	2.40 (0.60–9.53)	0.21
As defined in ECASS III¶	6 (2.4)	1 (0.4)	6.04 (0.72–50.87)	0.10
As defined in NINDS‖	20 (8.0)	12 (4.9)	1.78 (0.84–3.71)	0.13
Parenchymal hemorrhage type 2**	10 (4.0)	1 (0.4)	10.46 (1.32–82.77)	0.03
Other††				
Space-occupying brain infarction or edema with clinical deterioration	6 (2.4)	2 (0.8)		
Recurrent ischemic stroke				
Asymptomatic‡‡	58 (23.1)	55 (22.5)		
Symptomatic	17 (6.8)	8 (3.3)		
Major extracranial bleeding	3 (1.2)	0		
Severe anaphylactic reaction	0	1 (0.4)		

* Odds ratios were adjusted for the stratification factors (i.e., age and symptom severity) at randomization.
† The primary safety outcome was analyzed in 244 patients in the alteplase group and in 241 in the placebo group because of loss to follow-up.
‡ The definition of symptomatic intracranial hemorrhage according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS–MOST) was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.
§ The definition according to the European Cooperative Acute Stroke Study (ECASS) II was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death.
¶ The definition according to ECASS III was the same as that in ECASS II, plus the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.
‖ The definition according to the National Institute of Neurological Disorders and Stroke (NINDS) was any new hemorrhage associated with any neurologic deterioration.
** Parenchymal hemorrhage type 2 was defined as an intracerebral hemorrhage that involved more than 30% of the infarcted area with a substantial space-occupying effect or that was remote from the original infarcted area.
†† Other safety outcomes were determined by the safety adjudication committee on the basis of the evaluation of clinical and imaging information. Odds ratios and P values were not calculated for these comparisons.
‡‡ Asymptomatic recurrent stroke was defined as any new lesion on follow-up MRI that was not considered to be a growth of the original stroke lesion.

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B.19 Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (Extend-IA TNK)

The use of Alteplase for acute ischemic stroke with thrombectomy procedures to improve outcomes has been documented in multiple publications. [118,127] Alteplase has been shown to be less effective when used in isolation in large vessel occlusion compared to Alteplase and thrombectomy. [82,90,100] However, Tenecteplase Alteplasehad better clinical and functional outcomes when compared to Alteplase. [128] Tenecteplase Alteplaseis beneficial not only in terms of administration, a one-time bolus with no further infusion, but also because it is a genetically modified variant of Alteplase and, as a result, it has a longer half-life. “In one trial involving patients with ST-segment elevation myocardial infarction, Tenecteplase resulted in 30-day mortality, similar to Alteplase, and led to a lower incidence of symptomatic hemorrhage.” [129] “We conducted the tTenecteplase versus aAlteplase before endovascular therapy for Ischemic Stroke (EXTEND-IA TNK) trial to compare Tenecteplase with Alteplase in establishing reperfusion in patients before endovascular thrombectomy when it was administered within 4.5 hours after the onset of symptoms.”

The trial design was “an investigator-initiated, multicenter, prospective, randomized, open-label, blinded-outcome trial [130] involving patients with ischemic stroke within 4.5 hours after onset who had large-vessel occlusion of the internal carotid, middle cerebral, or basilar artery and who were eligible to undergo intravenous thrombolysis and endovascular thrombectomy.” [131] The enrollment of patients was done in Australia and New Zealand, and they were eligible if they fulfilled the following criteria:

> "…they could undergo intravenous thrombolysis within 4.5 hours after the onset of ischemic stroke and had cerebral vascular occlusion on CT angiography of the internal carotid artery, the second segment of the middle cerebral artery, or the basilar artery and if treatment to retrieve the intraarterial clot could commence (arterial puncture) within 6 hours after stroke onset…patients with severe preexisting disability, defined as a modified Rankin scale score of more than 3 (scores range from 0 [no neurologic deficit] to 6 [death], were excluded…The entry criteria originally required CT-perfusion mismatch for anterior circulation strokes." [131]

The CT-perfusion hypoperfusion was defined "according to a delayed arrival of an injected tracer agent (time to maximum of the residue function exceeding 6 seconds), and an irreversibly injured ischemic core was estimated with the use of relative cerebral blood flow less than 30% of that in normal brain," while a mismatch was defined as "a ratio of greater than 1.2 between the volume of less than 70 ml." [131]

For treatment, patients were randomized in a 1:1 ratio to receive Tenecteplase or Alteplase per protocol. "Randomization was performed with the use of a centralized Web server, with stratification according to the site of the involved vessel (internal carotid artery, basilar artery, first segment of the middle cerebral artery). All other treatments were guided by the standard of care for thrombolysis and thrombectomy for ischemic stroke."[131]

The primary outcome was defined as a substantial reperfusion:

> "Substantial reperfusion was defined as the restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment. Perfusion was assessed with the use of the modified Treatment in Cerebral Ischemia classification (scores range from 0 [no flow] to 3 [normal flow]). [132] If no lesion was suitable for thrombectomy, the endovascular procedure was terminated. If intracranial angiography could not be performed, the primary outcome was assessed as reperfusion of at least 50% of the involved territory on CT perfusion imaging 1 to 2 hours after thrombolysis." [131]

Secondary outcomes were based on a modified Rankin scale score at 90 days via telephone with at least an 8-point improvement in the NIHSS score or an NIHSS score of

0 to 1 at 72 hours. The safety outcomes were death or symptomatic intracranial hemorrhage, including intracerebral or subarachnoid hemorrhage.

The statistical analysis was based on 202 patients to determine noninferiority. Superiority had been initially planned to be evaluated, but since no patients were excluded from the pre-protocol analysis of the primary outcome, only one analysis could be performed and presented. The noninferiority boundary was based on a meta-analysis of multiple Alteplase with endovascular treatment studies [82,90,100]:

> "Noninferiority would be established if the lower boundary of the two-sided 95% confidence interval of the difference in the percentages of patients with substantial reperfusion at the initial angiographic assessment in the Tenecteplase versus the Alteplase group was greater than -2.3 percentage points. The two-sided 95% confidence interval of the incidence difference was estimated by generating incidence differences with corresponding 95% confidence intervals for each of the four strata of patients (those with occlusion of the internal carotid artery, basilar artery, first segment of the middle cerebral artery, or the second segment of the middle cerebral artery) with subsequent pooling across strata with the use of the Mantel-Haenszel method. If noninferiority was established, superiority of Tenecteplase was tested with the use of binary logistic regression, with adjustment for the site of vessel occlusion. Incidence ratios were established with the use of modified Poisson regression with robust error estimation, [133] with adjustment for the site of vessel occlusion." [131]

The secondary outcome analysis of the modified Rankin scale was an ordinal logistic regression comparing the Tenecteplase and Alteplase groups, along with a logistic regression model of the NIHSS score. A Wilcoxon-Mann-Whitney generalized odds ratio was used for the differences in the distributions of the NIHSS scores between the Tenecteplase and Alteplase groups at the 24- and 72-hour evaluations of the patients who showed early improvement.

See Tables 27-28 for tabulated results of outcomes and safety.

Table 27. EXTEND-IA TNK trial outcome scores.

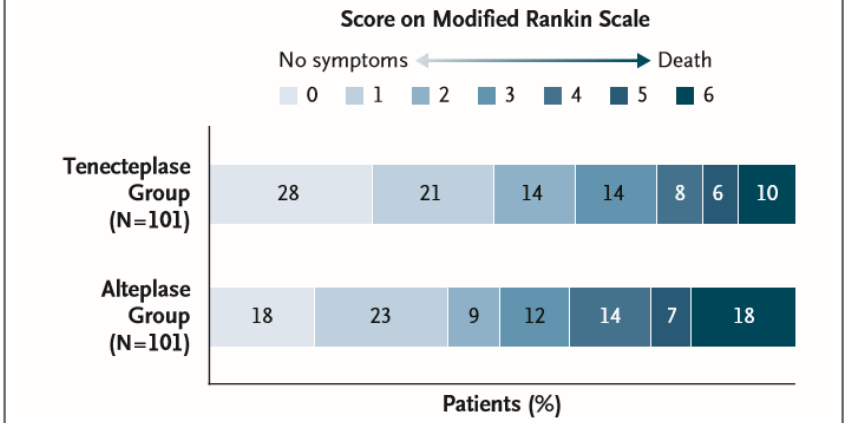

Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.

Shown are the results of the ordinal analysis of the modified Rankin scale scores at 90 days. Scores range from 0 to 6, with 0 indicating no neurologic deficit, 1 no clinically significant disability, 2 slight disability (able to handle own affairs without assistance but unable to carry out all previous activities), 3 moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requiring constant nursing care and attention), and 6 death. Patients in the tenecteplase group had a median score of 2, as compared with a median score of 3 among patients in the alteplase group (common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). Percentages may not total 100 because of rounding.

Table 28. EXTEND-IA TNK trial safety scores.

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				
Median score (IQR) on ordinal analysis‡	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Functionally independent outcome — no. (%)§	65 (64)	52 (51)		
Adjusted incidence ratio			1.2 (1.0–1.5)	0.06
Adjusted odds ratio			1.8 (1.0–3.4)	0.06
Excellent outcome — no. (%)§	52 (51)	43 (43)		
Adjusted incidence ratio			1.2 (0.9–1.6)	0.20
Adjusted odds ratio			1.4 (0.8–2.6)	0.23
Early neurologic improvement — no. (%)§¶	72 (71)	69 (68)		
Adjusted incidence ratio			1.0 (0.9–1.2)	0.70
Adjusted odds ratio			1.1 (0.6–2.1)	0.70
Safety outcomes				
Death — no. (%)§	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3–1.0)	0.049
Adjusted odds ratio			0.4 (0.2–1.1)	0.08
Symptomatic intracerebral hemorrhage — no. (%)§‖	1 (1)	1 (1)		
Risk ratio			1.0 (0.1–15.9)	0.99
Odds ratio			1.0 (0.1–16.2)	0.99
Parenchymal hematoma — no. (%)§**	6 (6)	5 (5)		
Risk ratio			1.2 (0.4–3.8)	0.76
Odds ratio			1.2 (0.4–4.1)	0.76

* Substantial reperfusion was defined as the restoration of blood flow to greater than 50% of the involved territory or no retrievable thrombus at the time of the initial angiographic assessment. The analysis was adjusted for the site-of-vessel-occlusion strata. The P value for the difference is for noninferiority, and the P values for the incidence ratio and odds ratio are for superiority.

† Scores on the modified Rankin scale range from 0 (no neurologic deficit) to 6 (death). A functionally independent outcome was defined as a modified Rankin scale score of 0 to 2 or no change from baseline. An excellent outcome was defined as a modified Rankin scale score of 0 or 1 or no change from baseline.

‡ The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed with a common odds ratio from ordinal logistic regression.

§ The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed as an incidence or risk ratio from Poisson regression and as an odds ratio from logistic regression.

¶ Early neurologic improvement was defined as a reduction of 8 points in the NIHSS score between baseline and 72 hours or as a score of 0 or 1 at 72 hours. An 8-point reduction is considered to be highly clinically significant.

‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of the infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score.

** Parenchymal hematoma was defined as intraparenchymal blood clot with mass effect.

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