# Modern Cranial Surgery: Innovative Treatments for Tumors and Vascular Diseases

Virginia Mason Franciscan Health™

Center for Neurosciences & Spine

# Let’s Get LITT!

Minimally Invasive MR-guided Robotic Thermotherapy in Neuro-oncology

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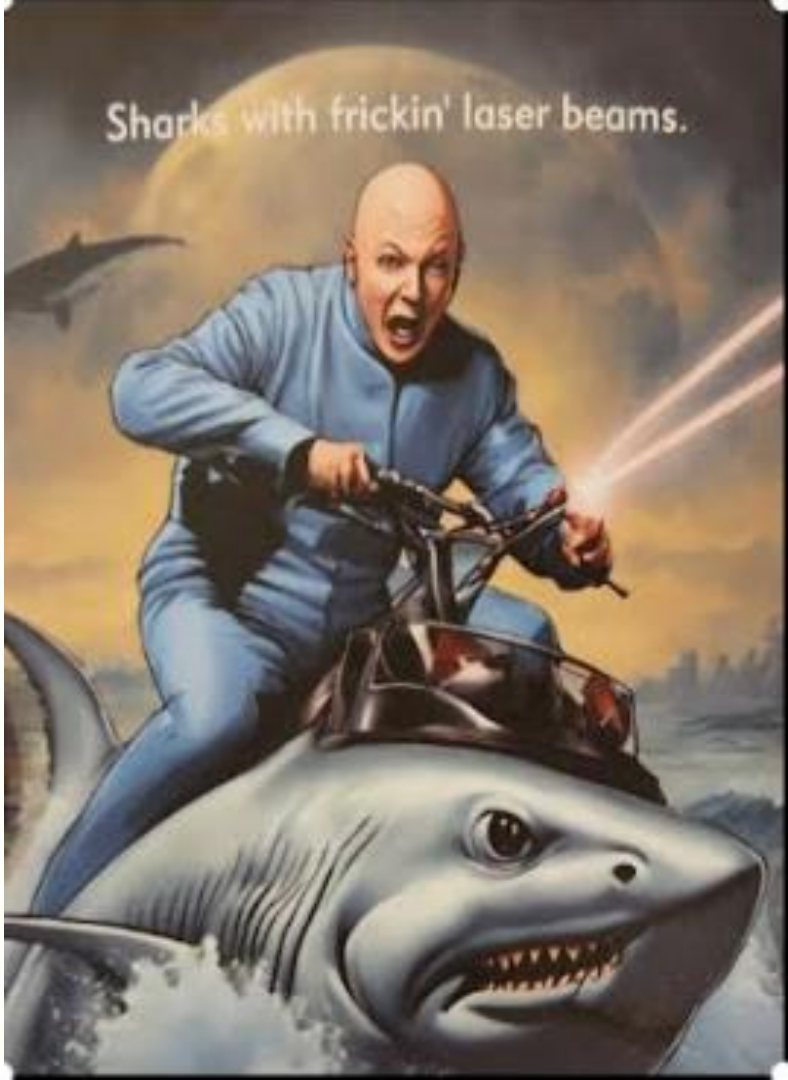

# A Childhood Dream Come True!

Brain Surgery

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# LITT System Overview

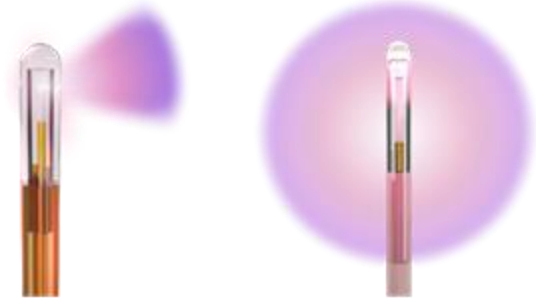
A minimally invasive surgical option for cytoreduction in the brain.

- The only minimally invasive, robotically-controlled, MR-guided laser ablation tool designed specifically for use in the brain.
- Offers an alternative to traditional, open surgery for patients diagnosed with brain tumors or who have epileptic seizures not controlled by medications.
- The procedure is performed through a small hole in the skull.
- Because LITT is MR-guided, the neurosurgeon is able to visualize the specific area of the brain to be ablated.
- The precise nature of the procedure helps to lessen the likelihood of harm to nearby healthy brain tissue.

# Simple Parts

**Directional Laser Probe**

**Diffusing Tip Laser Probe**



Laser Probes

Robotic Probe Driver

Cranial Fixation Device

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# System Hardware & Software

LITT utilizes MR-guidance to protect healthy brain tissue during the ablation.

Robotic laser interface allows for precise, remote manipulation of the laser probe position and orientation at the workstation.

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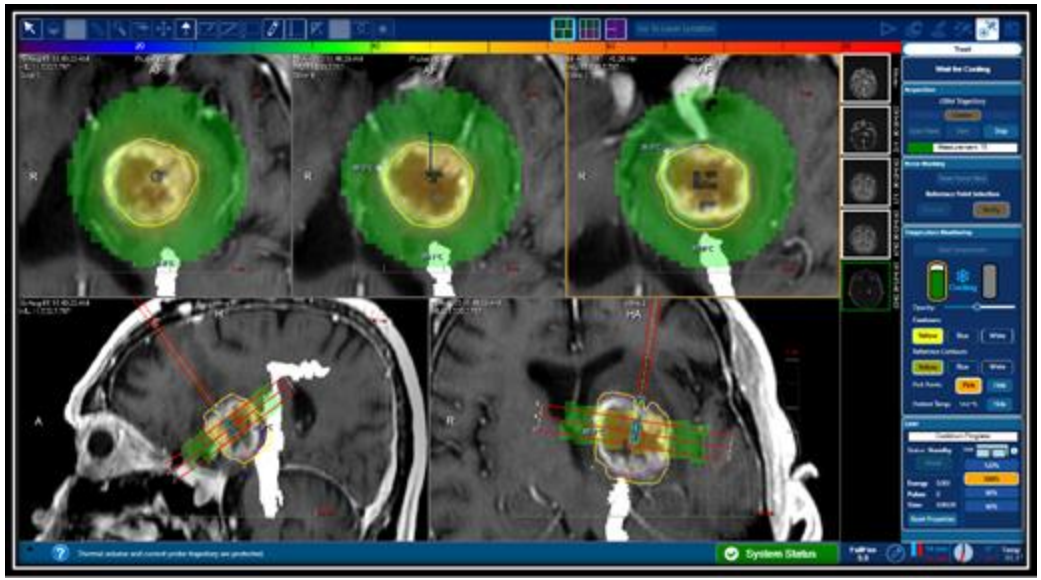
# System Software - Brain Tumor



Courtesy of Sujit Prabhu, M.D., MD Anderson

- Cell death is a function of temperature and time
- MRI Thermometry is used to calculate near real time temperature data in 3 planes
- Thermal dose (TDT) lines are contoured around heating areas and the user selects the dose to monitor while ablating
    - Tissue within the blue TDT lines is destroyed.
    - Tissue between the blue and yellow TDT lines may experience thermal damage; but cell death is uncertain.

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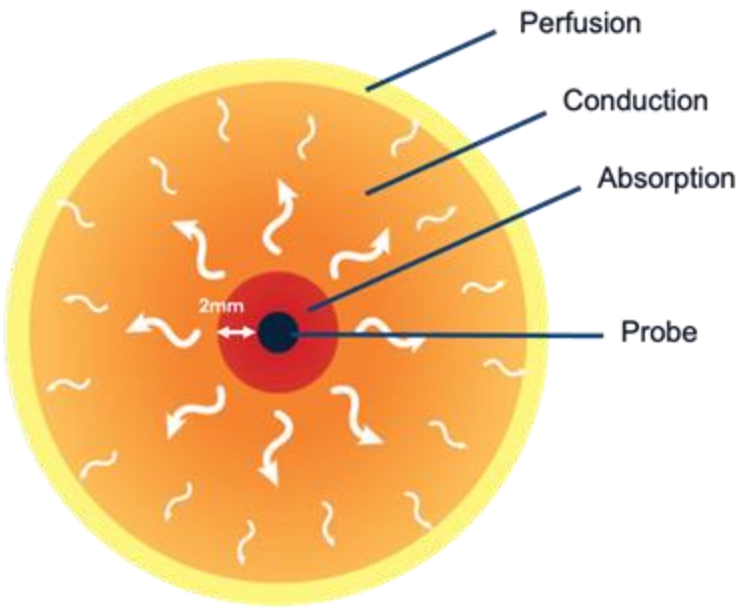
# How Laser Ablation Works




- Laser energy penetrates tissue ~2 mm and is converted to heat, progressing by thermal conduction away from the source (probe)
- Thermal exposure of tissue at the right temperature or time-temperature combination leads to tissue death (ablation)
- The goal of LITT is to produce controlled hyperthermia-induced necrosis at **43 - 85°C** within target tissue

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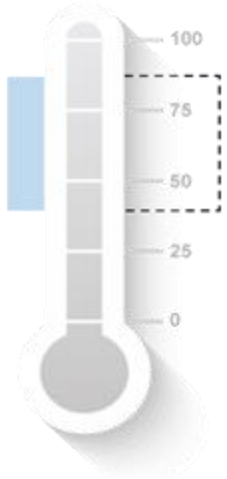
# How Laser Ablation Works




| | |
|---|---|
| **> 100° C** | Vaporization of intra- and extra-cellular water; rupture of cell membranes |
| **60° - 100° C** | Instant denaturation of proteins and cellular components; tissue coagulation |
| **44° - 59° C** | Time-dependent thermal damage; thermal denaturation of critical enzymes; cell death |
| **~ 43° C** | Critical temperature below which thermal damage does not occur regardless of exposure time |
| **37° C** | Normal body temperature |

# Procedure Overview

Offers an alternative to traditional, open surgery for patients diagnosed with brain tumors or drug-resistant epilepsy

Performed through a small hole in the skull where a bolt is placed. Bolt placement occurs in the OR or in an intraoperative MR

Robotic laser interface is used for precise, remote manipulation of laser probe position from the workstation in the MR suite

Ablation is visualized and controlled remotely

After the procedure, the skin is usually closed with one or two sutures, and the patient can return home after a short hospital stay

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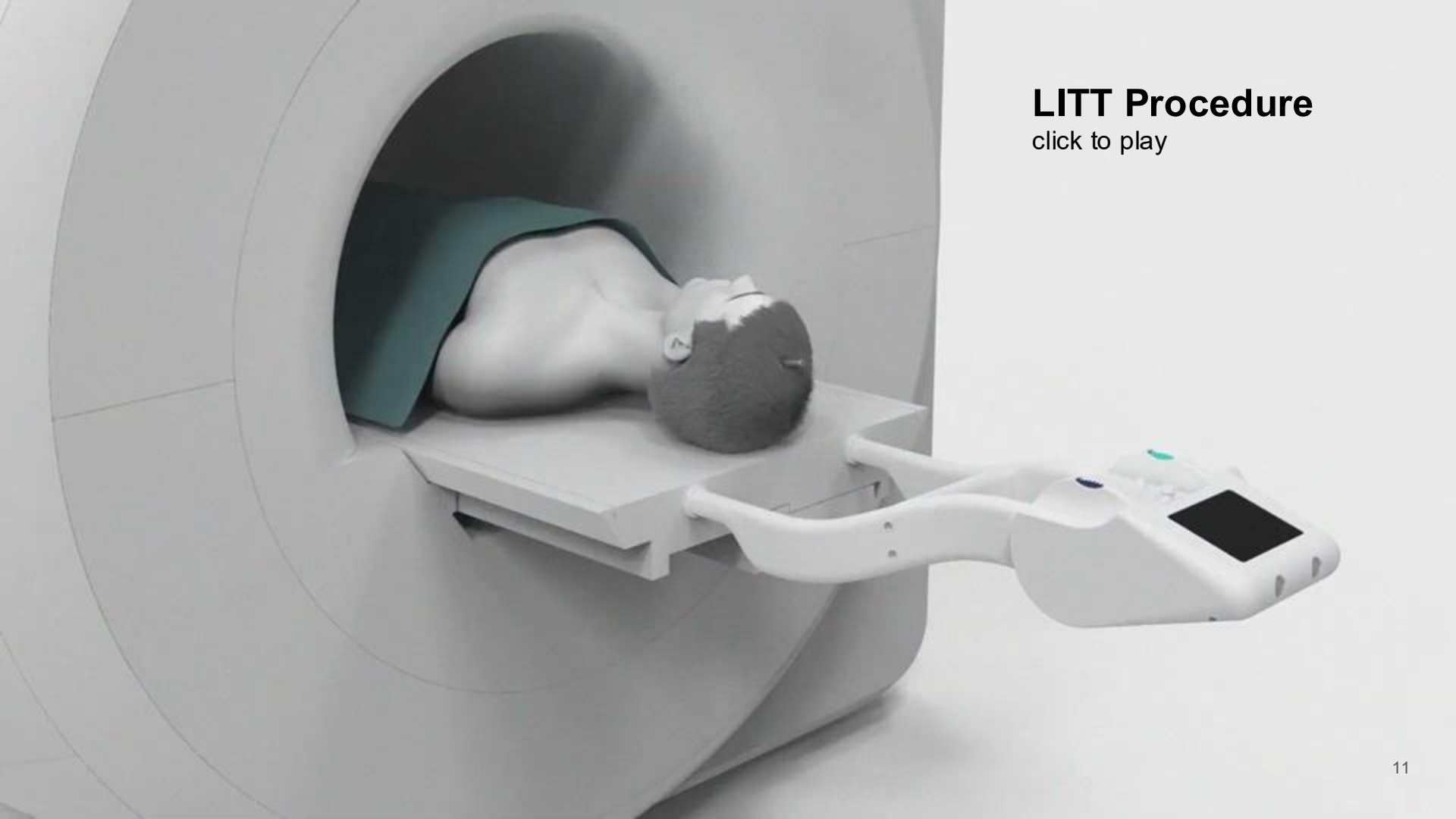
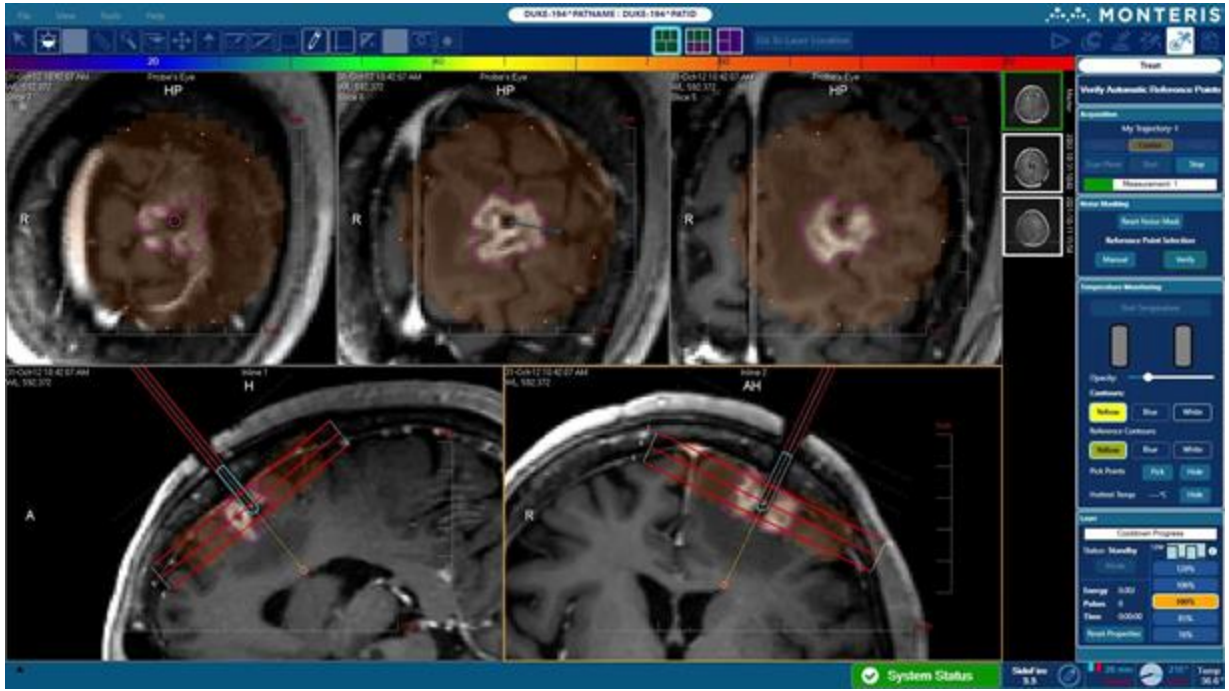


# LITT Procedure

click to play

# Case Example: Recurrent Brain Met - Radiation Necrosis




**Treatment Replay**
click to play

Courtesy of Peter Fecci, MD, PhD
Duke Health

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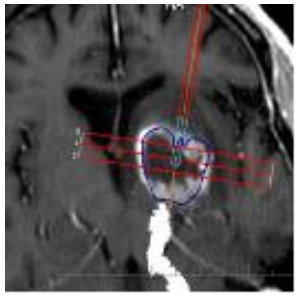
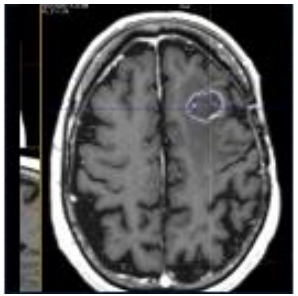
# LITT Applications in Neuro-oncology



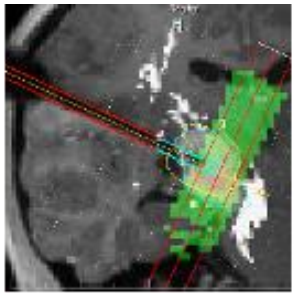
**Newly Diagnosed Glioma**

Glioblastoma



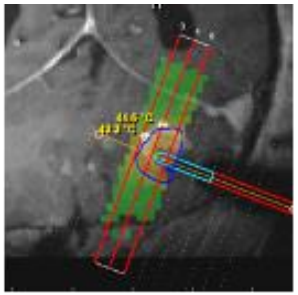
**Recurrent Glioma**
**(2nd, 3rd, 4th, etc. recurrence)**

Anaplastic Astrocytoma



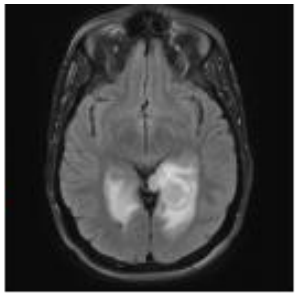
**Difficult to Access**

Pilocytic Astrocytoma



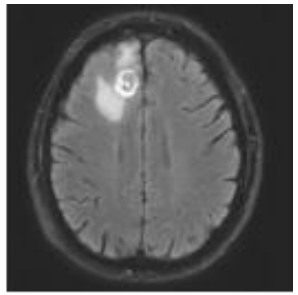
**Posterior Fossa**

Adenocarcinoma



**Multiple Lesions**

Recurrent Melanoma



**Early Radiographic Progression**

Radiation Necrosis
(no interruption of immunotherapy)

**LITT is used for:**

- Newly diagnosed and recurrent primary tumors
- Recurrent metastatic tumors and post-SRS progression
- Radiation necrosis

**Plus:**

- Patients with previous interventions
- Deep-seated and difficult to access tumors
- Fragile patients
- Patients who prefer a minimally invasive option

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# LITT is Supported by Societal Guidelines and Position Statements

**National Comprehensive Cancer Network (NCCN) Guidelines Version Central Nervous System Cancers (May 2024)1:**

“LITT may be considered for patients who are poor surgical candidates (craniotomy or resection). Potential indications include recurrent brain metastases, radiation necrosis, glioblastomas, and other gliomas.”

**September 2021: Joint CNS-AANS societies’ Position Statements on LITT for brain tumors and radiation necrosis considering LITT2:**

“For the management of primary brain tumors (gliomas/glioblastoma), recurrent tumors, brain metastases, and radiation necrosis.”

- “LITT is an appealing option because it offers a method of minimally invasive, targeted thermal ablation of a lesion with minimal damage to healthy tissue.”
- “Intracranial LITT is also an effective option for addressing radiation necrosis with an overall reduction in steroid dependence for these patients.”
- “Especially in instances where the therapeutic window is narrowed such that craniotomy is not a viable option, LITT can play an important role in treatment for glioma or metastatic brain cancer.”


**1** NCCN Guidelines Version 1.2024, 05/31/24. Central Nervous System Cancers. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

**2** American Association of Neurological Surgeons and Congress of Neurological Surgeons Position Statement on Laser Interstitial Thermal Therapy for the Treatment of Brain Tumors and Radiation Necrosis. AANS-CNS_Position_Statement_Paper_LITT_Tumor-Oncology_090721.ashx

# LAANTERN Registry Overview

Laser Ablation of Abnormal Neurological Tissue using LITT (NCT02392078)

## Study Design

- Prospective, multi-center, “real world” outcomes registry. All patients undergoing LITT were eligible.
- Over 1,000 patients enrolled

## Study Objectives

- Safety
- Procedural Outcomes: Local Control, Progression Free Survival, Overall Survival, Seizure Freedom
- Quality of Life (QoL)

**LAANTERN Publications**


Kim AH, et al., Laser interstitial thermal therapy for new and recurrent meningioma: a prospective and retrospective case series. Journal of Neurosurgery (published online ahead of print 2024).

Chan M, et al. Efficacy of laser interstitial thermal therapy for biopsy-proven radiation necrosis in radiographically recurrent brain metastases, Neuro-Oncology Advances. 2023.

de Groot J, et al. Efficacy of laser interstitial thermal therapy (LITT) for newly diagnosed and recurrent IDH wild-type glioblastoma, Neuro-Oncology Advances. 2022.

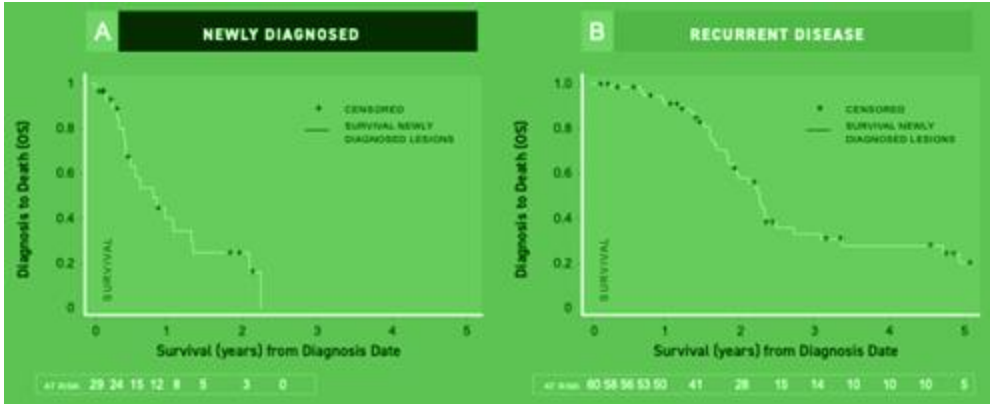
Kim AH, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN): 12-month outcomes and quality of life after brain tumor ablation, Neurosurgery. 2020.

Rennert RC, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN): procedural safety and Hospitalization. Neurosurgery. May 2019.

Landazuri P, et al. A prospective multicenter study of laser ablation for drug resistant epilepsy – One-year outcomes, Epilepsy Research. 2020.

Rennert RC, et al. Patterns of clinical use of stereotactic laser ablation: analysis of a multicenter prospective registry. World Neurosurg. 2018.

# Efficacy of LITT for Newly Diagnosed + Recurrent IDH Wild-type Glioblastoma




**Survival outcomes for LITT are comparable to those of traditional resection.**

**Newly diagnosed** patients followed with standard of care chemoradiation

- OS: **16.14** mo
- PFS: **11.93** mo.

Published resection outcomes:

- OS:10-21 mo
- PFS: 6-8 mo

*** Recurrent disease:**

- OS: 8.97 mo
- PFS: 4.83 mo
- Comparable to the overall survival range of 5-13 months observed with resection
- Number of recurrences at the time of LITT is not known

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de Groot J, et al., Neuro-Oncology Advances, 2022

# LAANTERN: 12-month Outcomes + Quality of Life After Brain Tumor Ablation

NEUROSURGERY

THE REGISTER OF THE NEUROSURGICAL MIND

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## Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN): 12-Month Outcomes and Quality of Life After Brain Tumor Ablation

**BACKGROUND:** Laser Ablation of Abnormal Neurological Tissue using Robotic NeuroBlate System (LAANTERN) is an ongoing multicenter prospective NeuroBlate (Monteris Medical) LITT (laser interstitial thermal therapy) registry collecting real-world outcomes and quality-of-life (QoL) data.
**OBJECTIVE:** To compare 12-mo outcomes from all subjects undergoing LITT for intracranial tumors/neoplasms.
**METHODS:** Demographics, intraprocedural data, adverse events, QoL, hospitalizations, health economics, and survival data are collected; standard data management and monitoring occur.
**RESULTS:** A total of 14 centers enrolled 223 subjects; the median follow-up was 223 d. There

**Study Summary:**

- 14 centers prospectively enrolled 223 subjects
- Part of ongoing LAANTERN registry (Monteris Medical sponsored)
- Objective to compare 12-month outcomes from all subjects undergoing LITT for intracranial tumors / neoplasms

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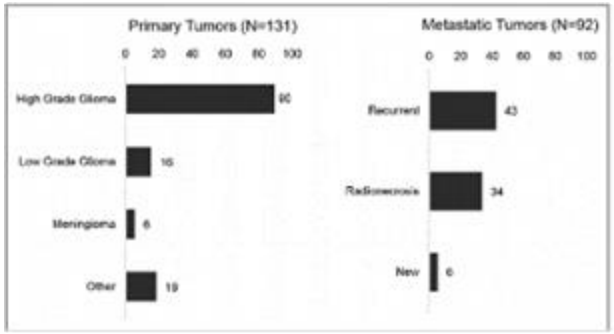
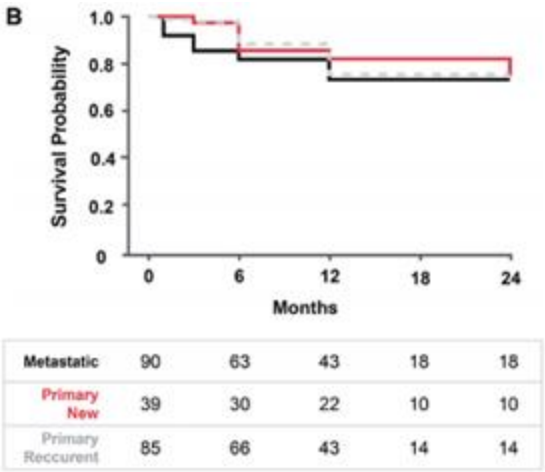
Kim AH, et al., Neurosurgery, 2020

# LAANTERN: 12-month Outcomes + Quality of Life After Brain Tumor Ablation




**Study Summary:**

- 33.4h median length of stay
- Most patients spent little or no time in the ICU
- Discharge to home 83.4%
- Repeat hospitalizations within 30 days – 1.8%

- Adverse events related to LITT / surgery – 4%
- Stable or improved KPS at 6 months – 50.5%
- QOL FACT_Br (brain tumor specific) and EQ-5D (whole person) data indicates that Qol is stabilized post LITT and that mobility, self care and ability to participate in usual activities are improved

Kim AH, et al., Neurosurgery, 2020

# LAANTERN: Procedural Safety + Hospitalization

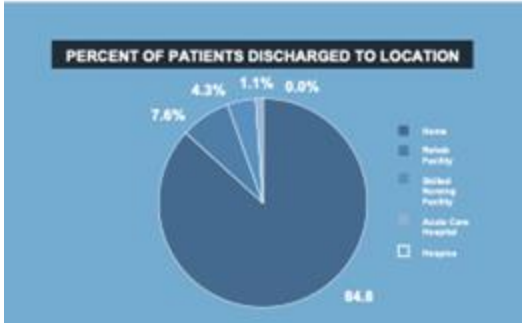
**Study Overview:**

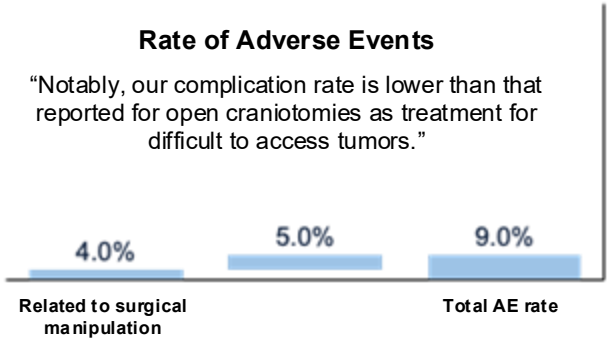
- Analysis of the procedural safety of LITT for intracranial lesions.

**Study Summary:**

- Little or no ICU time (25% no ICU; all others median 21 hours)
- Short hospitalization
- Upon discharge, 84.8% of patients went directly home
- 5% LITT-related complication rate
  (comparable to stereotactic biopsy alone)


**"Comparable or shorter than the ICU and hospital stays associated with open cranial surgery"**

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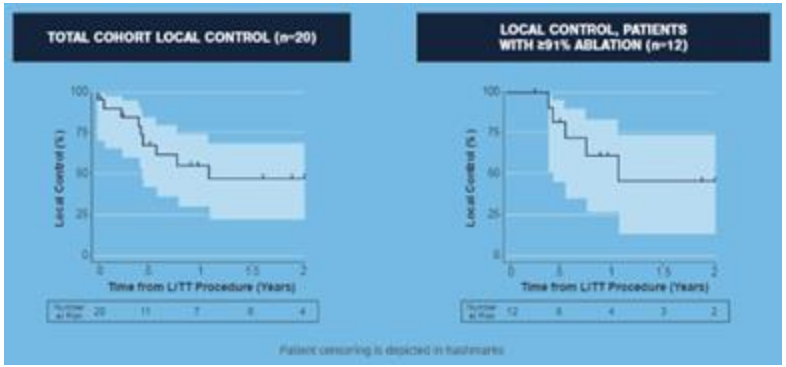
# LAANTERN: LITT for Meningioma

**Study Overview:**

- Largest cohort of LITT for meningioma to date (N=20)

**Key Points**

- LITT for meningioma serves an unmet need in neuro/surgical oncology
- Treatment options for malignant meningiomas are extremely limited and are comprised of surgery and radiation
- LITT for meningioma is a safe and well-tolerated procedure




- 1-year local control was 61.4% for patients with ≥91% ablation
- The majority of patients and providers reported a preference for a minimally invasive procedure
- LITT is a safe and useful tool in the limited armamentarium against meningioma, particularly when other options are exhausted

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Kim AH, et al., Journal of Neurosurgery (published online ahead of print 2024)

# LAANTERN Registry Publications

## What do these studies mean for your patients?

### LITT survival outcomes comparable to those published for traditional resection affords patients

- A minimally invasive procedure with survival outcomes comparable to an open resection
- The possibility of resuming cancer treatment sooner

### A minimally invasive procedure means

- Little hair removal
- Less scarring compared to open resection
- Optimize time and quality of life with a short recovery compared to an open craniotomy

### Little to no time in the ICU, short hospitalization, and low complication rates offer patients possible options

- Go directly home rather than being discharged to a rehab facility
- Resume regular activities within a shorter period compared to an open resection
- Benefit from a LITT procedure rather than biopsy alone with potential additional benefits

**While LITT and craniotomy have not been studied head-to-head in a randomized trial, when compared to published literature, LITT has shown significant benefits.**

# LITT for Recurrent Brain Metastases

| Publications | Study Overview |
|---|---|
| **Efficacy of Laser Interstitial Thermal Therapy (LITT) for Biopsy-Proven Radiation Necrosis in Radiographically Recurrent Brain Metastases**<br>Chan M, Tatter S, Chiang V, et al. Neuro-Oncology Advances, 2023;, vdad031.<br>doi: 10.1093/noajnl/vdad031 | This publication of 90 patients represents the largest prospective series to date of LITT for pathologically proven radiation necrosis (RN) after prior stereotactic radiosurgery (SRS) for brain metastases. |
| **Stereotactic Laser Ablation (SLA) followed by consolidation stereotactic radiosurgery (cSRS) as treatment for brain metastasis that recurred locally after initial radiosurgery (BMRS): a multi-institutional experience**<br>Peña Pino I, Ma J, Hori YS, et al. *J Neurooncol.* 2022 Jan;156(2):295-306. Epub 2022 Jan 10.<br>doi: 10.1007/s11060-021-03893-6 | Clinical outcomes of 20 patients with 21 histologically confirmed progressive tumor brain mets (post initial SRS) were treated with LITT followed by consolidation SRS. |
| **Combination laser interstitial thermal therapy plus stereotactic radiotherapy increases time to progression for biopsy-proven recurrent brain metastases**<br>Grabowski M, Srinivasan E, Vaios E, et al. Neuro-Oncology Advances, Volume 4, Issue 1, January-December 2022, vdac086.<br>doi: 10.1093/noajnl/vdac086 | A study to evaluate the efficacy of LITT followed by SRS (LITT+SRS) in recurrent SRS-treated BM, and to compare outcomes to LITT alone vs. repeat SRS alone. |
| **Time to Steroid Independence After Laser Interstitial Thermal Therapy vs Medical Management for Treatment of Biopsy-Proven Radiation Necrosis Secondary to Stereotactic Radiosurgery for Brain Metastasis**<br>Sankey E, Grabowski M, Srinivasa E, et al. Neurosurgery. Epub 2022 March 23;90(6):684-0690.<br>doi: 10.1227/neu.0000000000001922 | Multi-center, retrospective cohort study of SRS-treated patients with brain metastases who developed biopsy proven radiation necrosis and were treated with LITT vs medical management (steroids). |

# Efficacy of LITT for Biopsy-Proven Radiation Necrosis in Radiographically Progressive Brain Metastasis


**Study Overview:**

- 90 patients across 14 US centers
- The largest series to date of LITT for radiation necrosis
- Biopsy-proven pure radiation necrosis
- Patients required to be eligible for 2-yr follow up

**Outcomes:**

- Time to steroid cessation
- Continuation of systemic therapy
- Survival
- Symptom control
- Safety
- KPS over time

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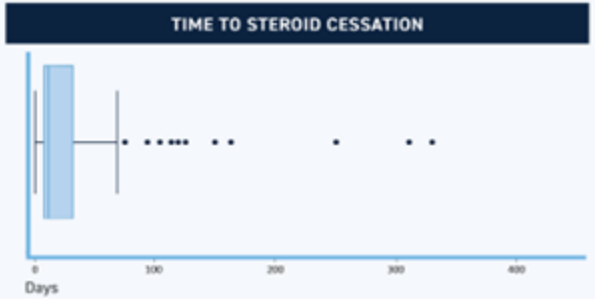
# Efficacy of LITT for Biopsy-Proven Radiation Necrosis in Radiographically Progressive Brain Metastasis: Study Findings

- Patients discontinued steroid use a median time of 13 days
- Symptom control: Seizure prevalence decreased by 34.4% from baseline
- KPS remained stable at 80 throughout 2-year follow up

| Characteristics and Measures* | All subjects (N=90) |
|---|---|
| Time on Steroids after Procedure, days | N=79 |
| Mean (SD) | 62.1 (166.8) |
| Median (Min, Max) | 13 (0.0, 1229.0) |

*Baseline steroid use includes patients who were started on steroids within 6 weeks before or 2 weeks after LITT procedure.




- Patients who had LITT experienced little or no interruption to systemic therapy regimens

| Characteristics and Measures* | All subjects (N=90) |
|---|---|
| Never stopped chemotherapy, No. (%) | 11/27 (40.7) |
| Never stopped immunotherapy, No. (%) | 3/17 (17.6) |

*Chemotherapy and immunotherapy baseline use was defined as therapy delivered within three months prior to the LITT procedure.

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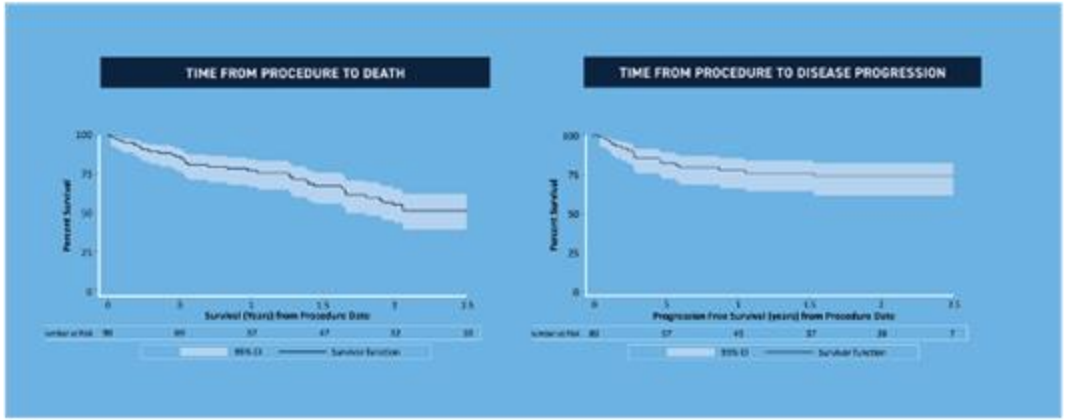
Chan, M. et al., Neuro-Oncology Advances, 2023

# Efficacy of LITT for Biopsy-Proven Radiation Necrosis in Radiographically Progressive Brain Metastasis: Study Findings

**LITT for RN was found to be a durable, safe procedure with low patient morbidity**

- Median post-procedure overall survival was 2.55 years [1.66, infinity] and 77.1% at one year
- No significant difference in risk of disease progression in those with total and near-total ablations (91% or greater ablative coverage) versus those with sub-total ablations (<90%)
- 75% of patients did not require any further treatment for the duration of follow up

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Chan, M. et al., Neuro-Oncology Advances, 2023

# Recurrent Metastatic Tumor Studies

## What do these studies mean for your patients?

### LITT+SRS study:

- Biopsy at the time of LITT allows for diagnostic confirmation, e**nsuring the most appropriate treatment** is being utilized.[1]
- For recurrent brain metastasis patients, the **combination of LITT+SRS** for recurrent tumor may offer superior local control and an overall survival advantage.[2]
- LITT+SRS may help prevent future incidence of radiation necrosis.[1]

### Time to Steroids Independence[3]:

- Long term steroid use can cause many different side effects and can make immunotherapy less efficacious.
- Brain metastasis patients with radiation necrosis are able to **stop steroids much sooner when LITT** is used as an intervention.


[1] Chan M, Tatter S, Chiang V, et al., Efficacy of Laser Interstitial Thermal Therapy (LITT) for Biopsy-Proven Radiation Necrosis in Radiographically Recurrent Brain Metastases, Neuro-Oncology Advances, 2023; vdad031. doi: 10.1093/noajnl/vdad031

[2] Grabowski M, Srinivasan E, Vaios E, et al., Combination laser interstitial thermal therapy plus stereotactic radiotherapy increases time to progression for biopsy-proven recurrent brain metastases, Neuro-Oncology Advances, Volume 4, Issue 1, January-December 2022, vdac086. doi: 10.1093/noajnl/vdac086

[3] Sankey E, Grabowski M, Srinivasa E, et al., Time to Steroid Independence After Laser Interstitial Thermal Therapy vs Medical Management for Treatment of Biopsy-Proven Radiation Necrosis Secondary to Stereotactic Radiosurgery for Brain Metastasis, Neurosurgery. Epub 2022 March 23;90(6):684-0690. doi: 10.1227/neu.0000000000001922

# Oncology Summary

Extensive prospective multi-center registry data (LAANTERN NCT02392078) and multiple retrospective publications suggest that **LITT** is safe and highly effective

| | |
|---|---|
| Favorable hospitalization data | • Little or no ICU stay[1]<br>• 33.4 hours median length of stay[2]<br>• 83.4% of patients discharged directly to home[2]<br>• 1.8% 30-day readmission rate[2]<br>• 5-7% complication rate comparable to biopsy alone[1] |
| Most patients reported an improvement or stabilization in quality-of-life post-LITT | QoL results showed better than anticipated outcomes in patient population with predominantly recurrent disease and a short life expectancy.[2] |

LITT allows for the prompt cessation of steroids and the continuation of chemotherapy and/or immunotherapy[3]

LAANTERN 12-month outcomes reports 73% 12-month overall survival[2]

**Over 11,000 LITT patient experiences have been studied and documented in peer-reviewed publications.**

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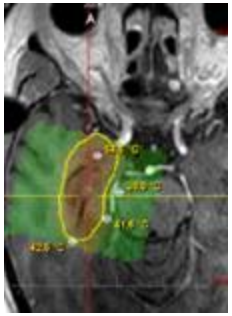
[1] Rennert RC, Khan U, Bartek J, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic Neuroblate System (LAANTERN): procedural safety and hospitalization. Neurosurgery. May 2019. doi: 10.1093/neuros/nyz141

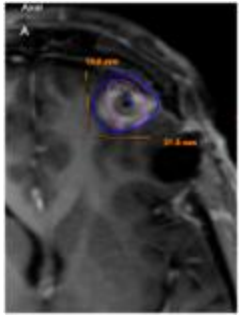
[2] Kim AH, Tatter S, Rao G, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN): 12- month outcomes and quality of life after brain tumor ablation. Neurosurgery. 2020 April 21: nyaa071. doi: 10.1093/neuros/nyaa071

[3] Chan M, Tatter S, Chiang V, et al. Efficacy of laser interstitial thermal therapy for biopsy-proven radiation necrosis in radiographically recurrent brain metastases. Neurooncol Adv. 2023 Mar 28;5(1):vdad031. doi: 10.1093/noajnl/vdad031. PMID: 37114245; PMCID: PMC10129388.

# LITT Applications in Neuro-oncology



MTLE



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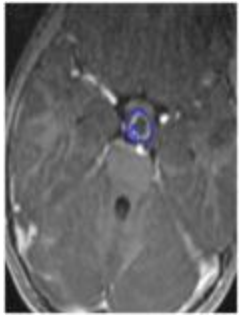
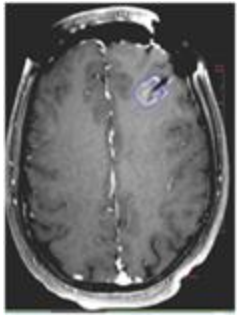
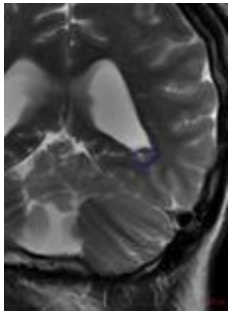


Hypothalamic Hamartoma

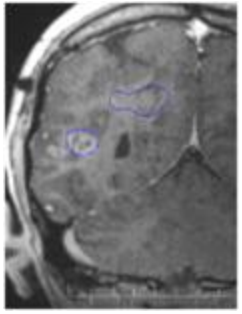


Cavernous Malformation

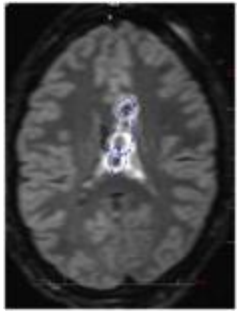


Periventricular Heterotopia

Tuberous Sclerosis



Non-Lesonal
Multi-Focal



Corpus Callosotomy

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# Thank You.

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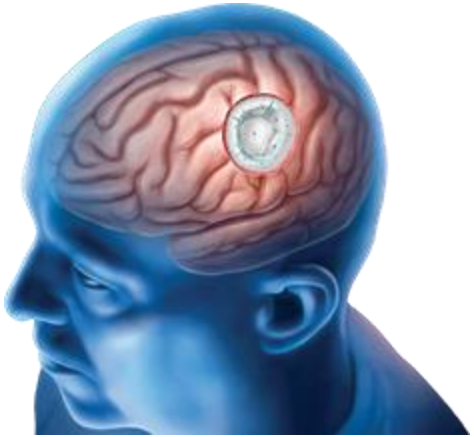
# A New Way to Treat Brain Tumors: Surgery and Radiation in One Procedure

**VMFH Neurosciences and Spine Symposium**
**Meydenbauer Center, Bellevue, WA**
**May 9, 2026**

**Roby Ryan, MD, Neurosurgery**
**Virginia Mason Franciscan Health**
**roby.ryan@commonspirit.org**



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# Disclosures

- No financial disclosures

- Virginia Mason is a participating site for the STaRT Registry, participated in the ROADS RCT, and is undergoing site selection for the BRIDGES RCT evaluating GammaTile

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# Objectives

- Review the rationale and design of the GammaTile surgically targeted radiation implant

- Evaluate the workflow and application of the implant

- Discuss current data and ongoing evaluations of the efficacy of surgically targeted radiation for primary and recurrent tumors
    - STaRT Registry, ROADS, BRIDGES

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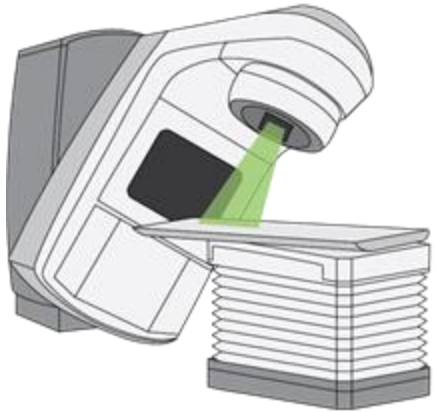
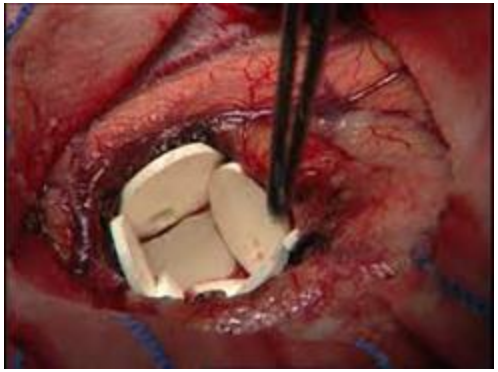
# Local recurrence – The Problem

- Both primary and metastatic brain tumors have high local recurrence rates, especially in the absence of adjuvant therapy

- Options:
  - Systemic therapy
  - EBRT
  - Local/cavity chemotherapy
  - Brachytherapy



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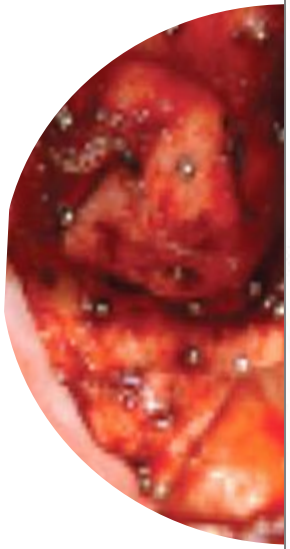
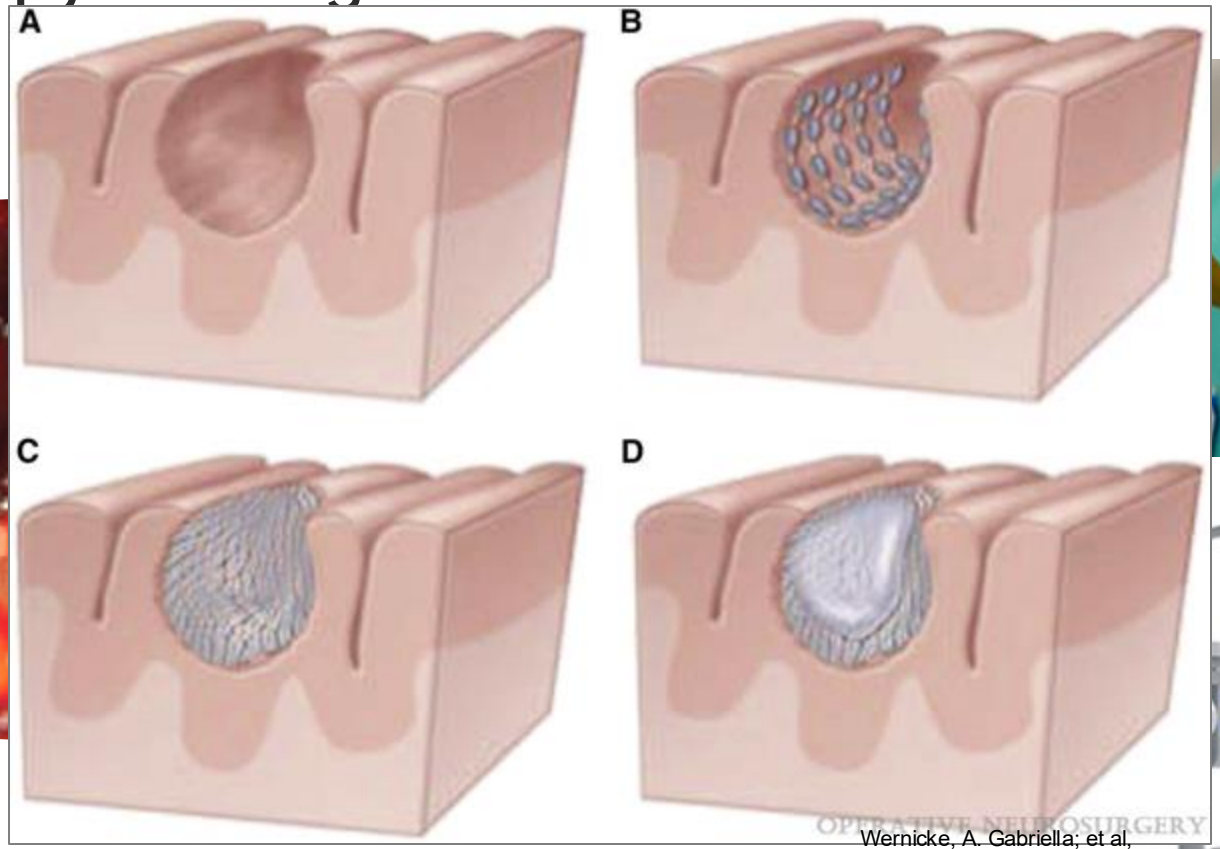
# Brachytherapy Challenges



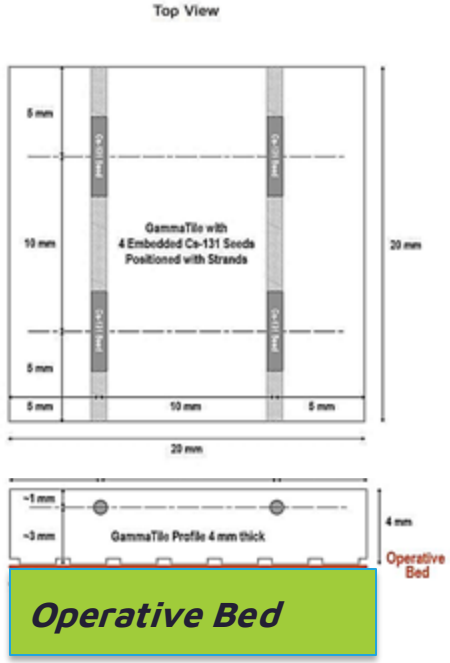


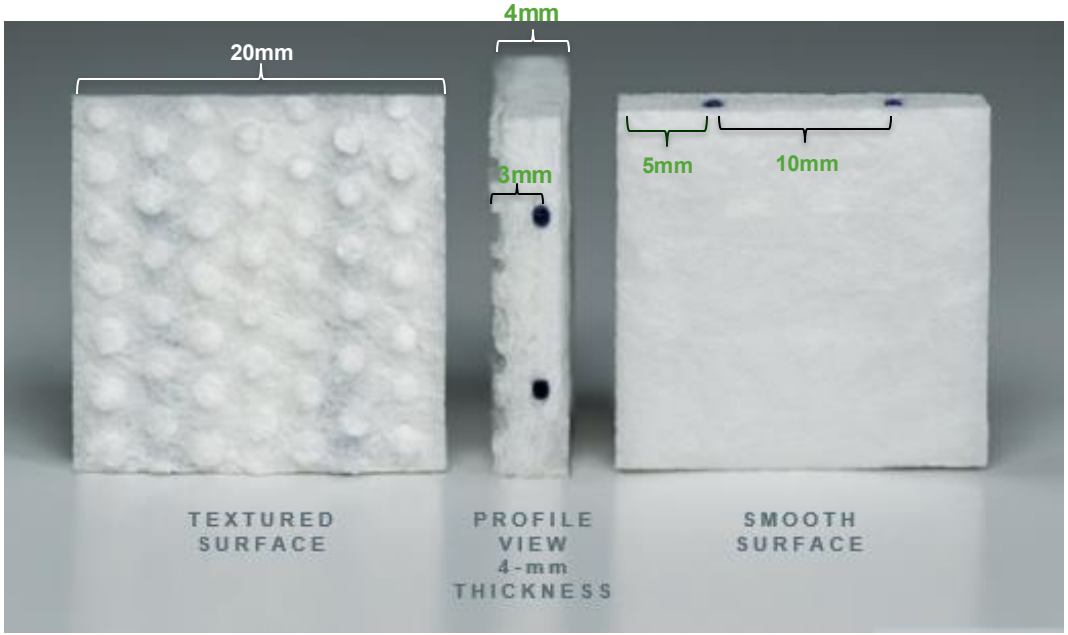

Wernicke, A. Gabriella; et al, Operative Neurosurgery12(1):49-60, March 2016.

Selker, *et al, Neurosurgery* 51(2):p 343-357, August 2002.

Lapperierre, et al, *Int J Radiat Oncol Biology Phys.* 1998;41(5):1005–1011.

# GammaTile Therapy | THE DEVICE – 4 Cs-131 Seeds in Collagen Tile

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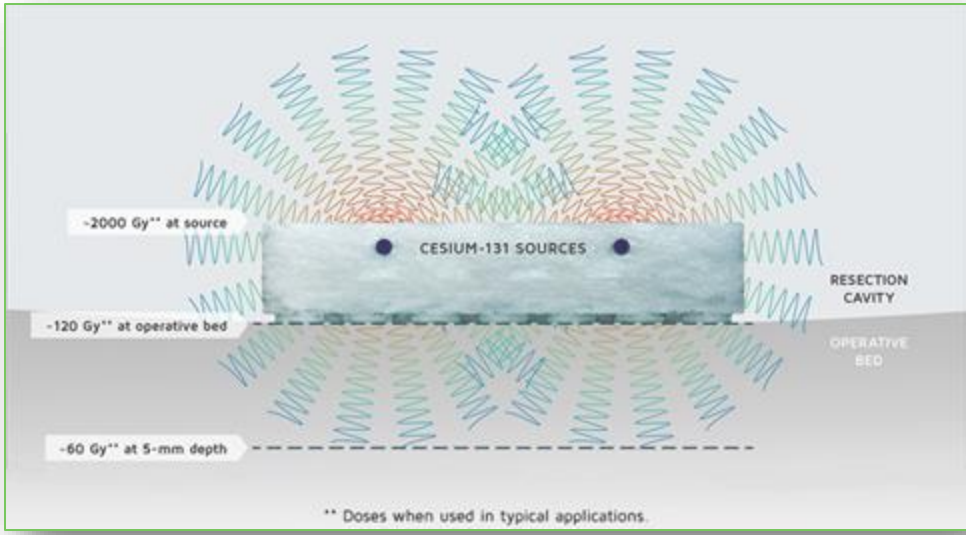
GammaTile

# Cesium-131 Dose Distribution And Intensity

- Like other radiation therapies, GammaTile Therapy works by disrupting the tumor cell replication process.
- The collagen tile keeps the sources in place while the radiation is delivered.

  The half-life of the Cs-131 sources is 9.7 days; 90% of the dose is delivered over the first month.

  After 100 days, the tiles are considered inert
- The collagen is broken down and absorbed over time
- The small titanium sources remain in the brain, and do not need to be removed




**Designed to achieve *60 Gy dose of radiation at 5mm depth* when 3+ seeds are implanted**

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**Chiu-Tsao ST, Napoli JJ, Davis SD, et al. Dosimetry for 131Cs and 125I seeds in solid water phantom using radiochromic EBT film. *Appl Radiat Isot.* 2014;92:102-114.

# Overview of BNI Trial That Led to FDA Clearance of GammaTile®

## Study type

- Prospective, multiple-histology basket design, single arm, single institution (NCT03088579). Opened 2/2013, closed 2/2018

## Treated patients

- 108 implants in 96 adult patients with aggressive intracranial neoplasms for whom surgery alone was considered not likely to be curative; most patients had failed ≥ 2 times (range 1–4) before enrolling

## Trial intervention

- Maximum safe resection (R) + Cs-131 collagen carrier tile brachytherapy (CTBT, GammaTile) implantation; prescribed 60 to 80 Gy at 5 mm into tumor bed

## Endpoints

- Included local control (LC); overall survival (OS); toxicity

| Histologies Treated |
| --- |
| 52 Glioma (Incl. 28 rGBM) |
| 35 Meningioma |
| 16 Mets |
| 5 Other |

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Nakaji P, Youssef E, Dardis C, et al: Surgically targeted radiation therapy: a prospective trial in 79 recurrent, previously irradiated intracranial neoplasms. Oral presentation at: American Association of Neurological Surgeons Annual Meeting; April 2019; San Diego, CA.

# GammaTile® Therapy – Workflow


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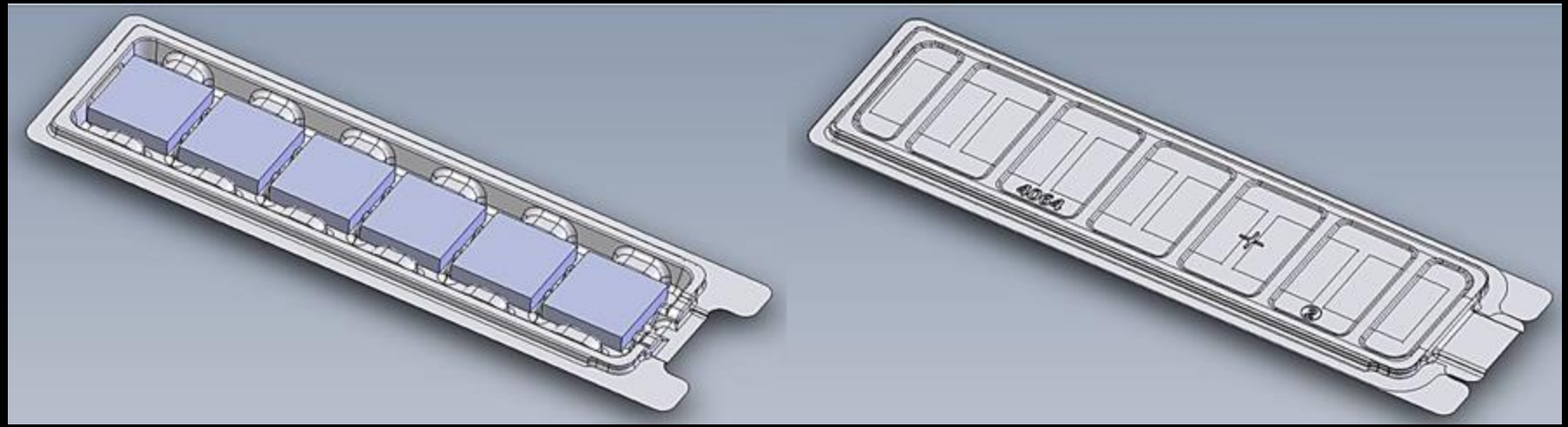

# Case Review – 43 yo man with recurrent GBM

- Previously healthy, left handed business executive had presented with new onset seizure
- Right parietal tumor, IDH WT, MGMT unmethylyated, complete contrast enhancing resection
- Received standard Stupp, and continued with Optune

- 11 months after initial resection developed increasing simple partial seizures
- Surveillance imaging showed locally recurrent disease

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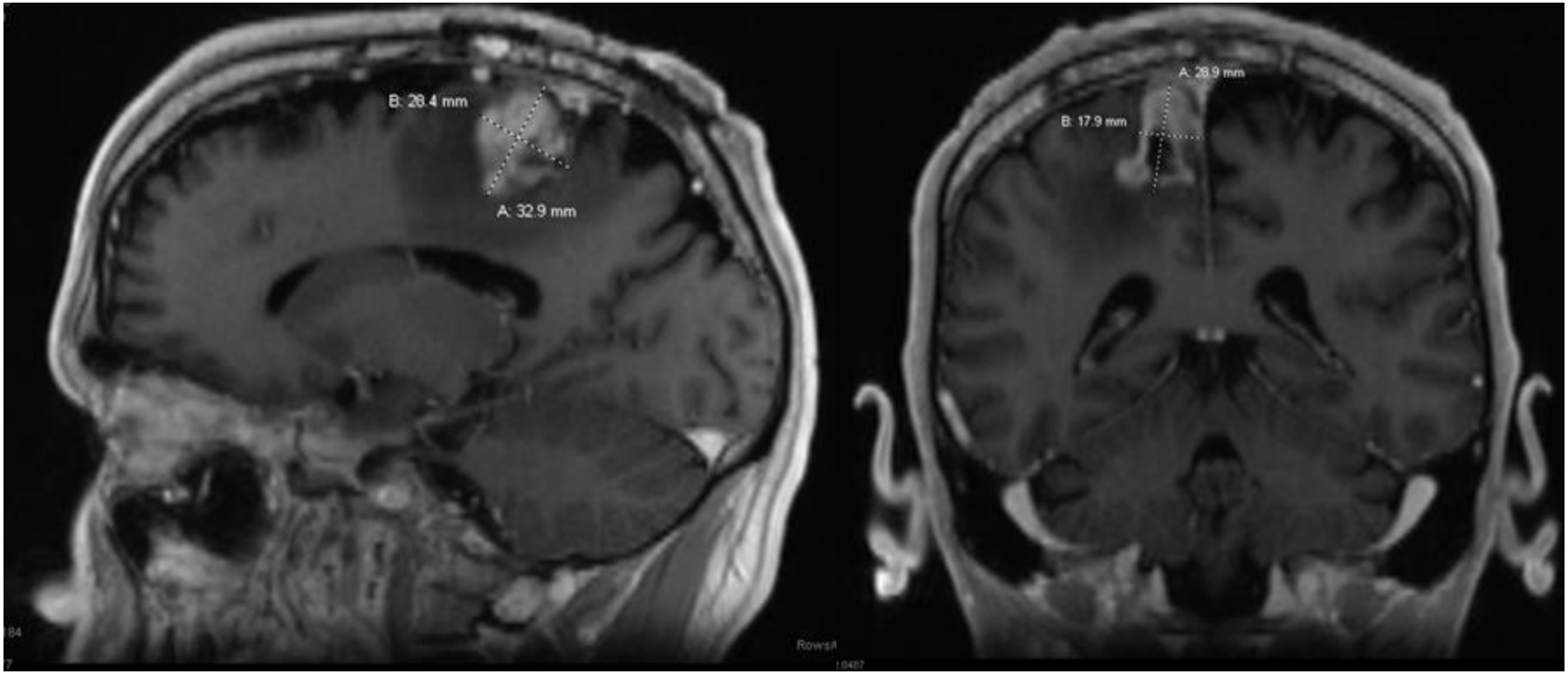


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# Treatment planning

- Patient highly informed of standard and experimental treatment options

- Considering vaccine trial vs implanted therapy (chemo vs brachytherapy)

- Decision to proceed with:

Gleolan(5-ALA) fluorescent guidance; GA and motor mapping; additional specimen for UK vaccine trial protocol; GammaTile implant

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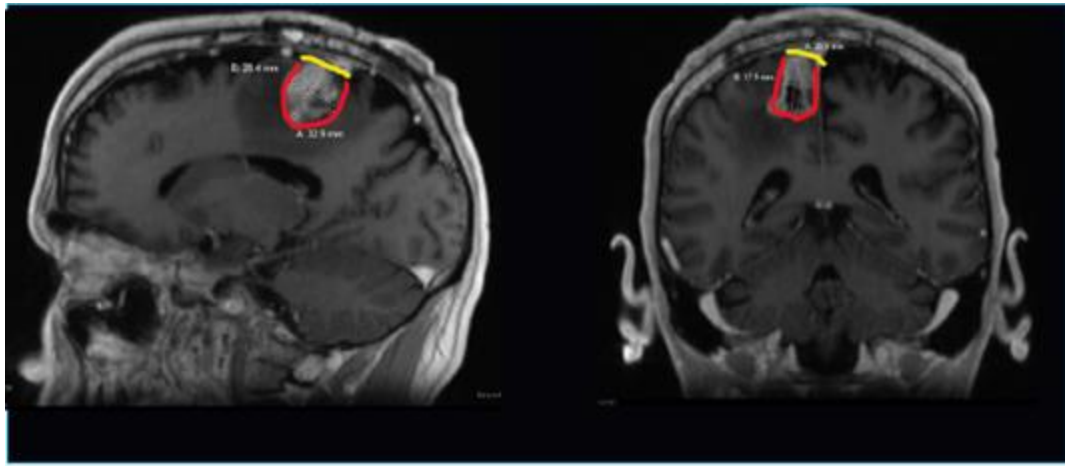
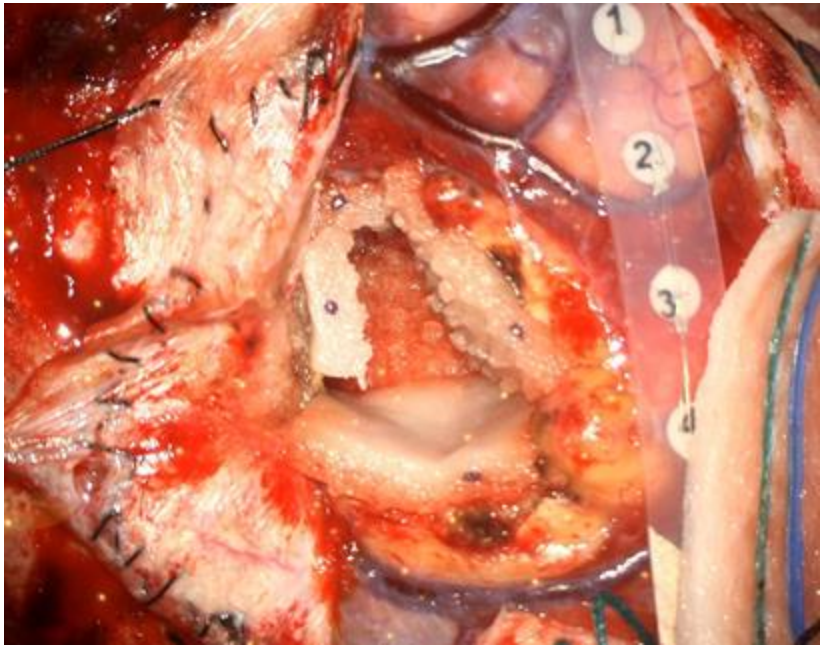
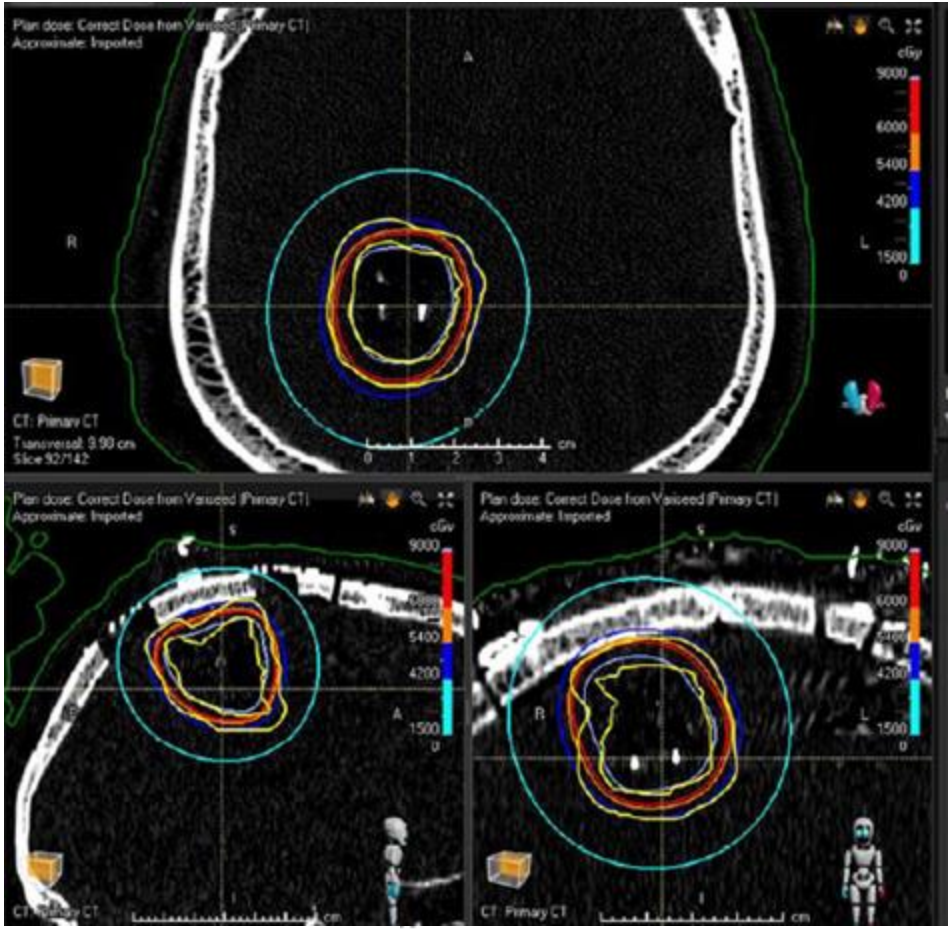





4 Tiles ordered based on surface area calculations

Resection limited anteriorly by activation of motor fibers – Tiles placed “smooth side out” for increased dose (~ 8 mm 60 Gy)



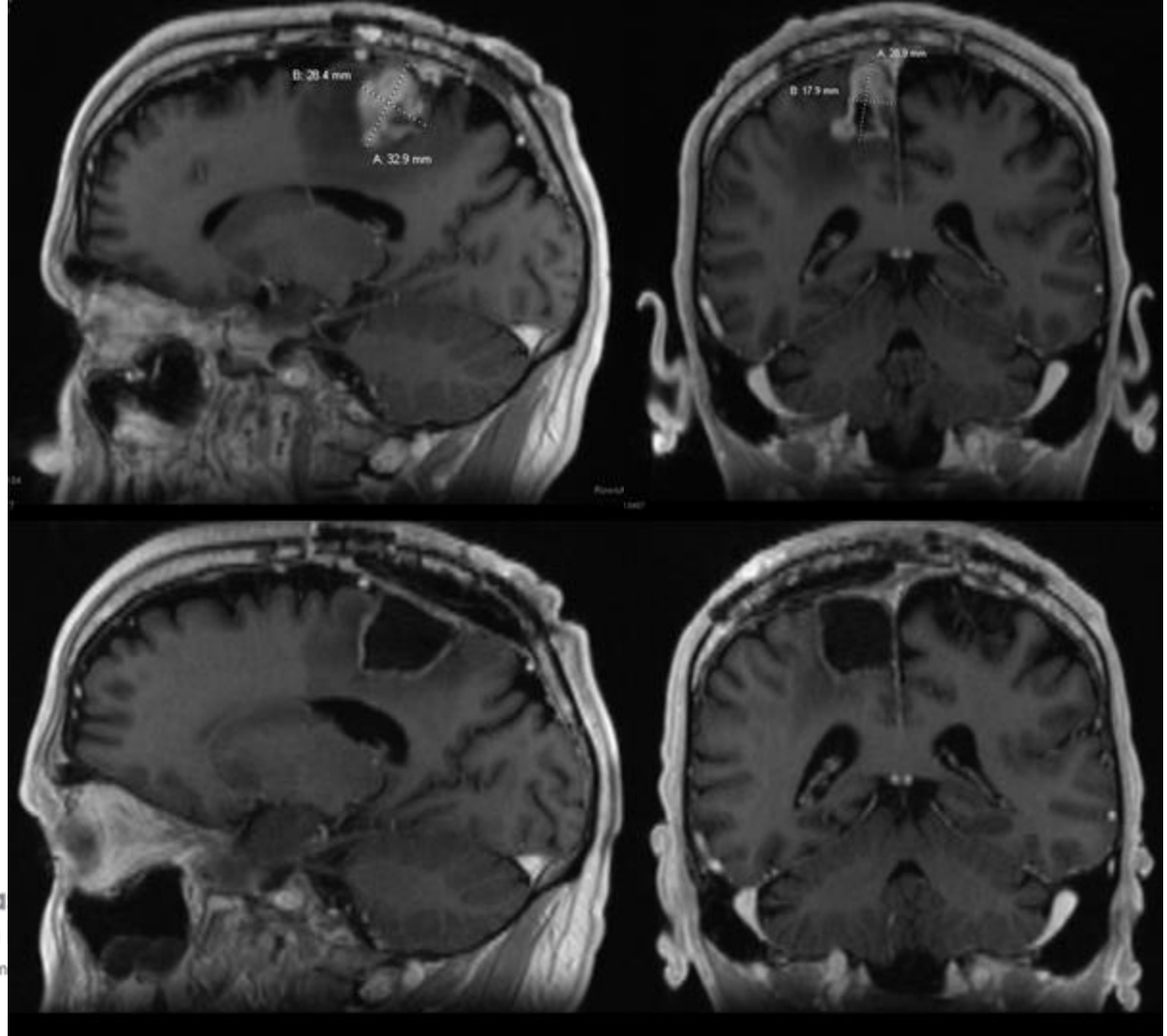

Tolerated the operation well; mild L sided symptoms that improved with PT

Discharged home on POD 3

Post op Dosimetry confirmed full coverage of residual anterior enhancement to 60 Gy

Returned with fluid collection under scalp that required lumbar drainage, with resolution

Back to full activity and able to resume adjuvant chemotherapy regime




6 month post-op imaging stable

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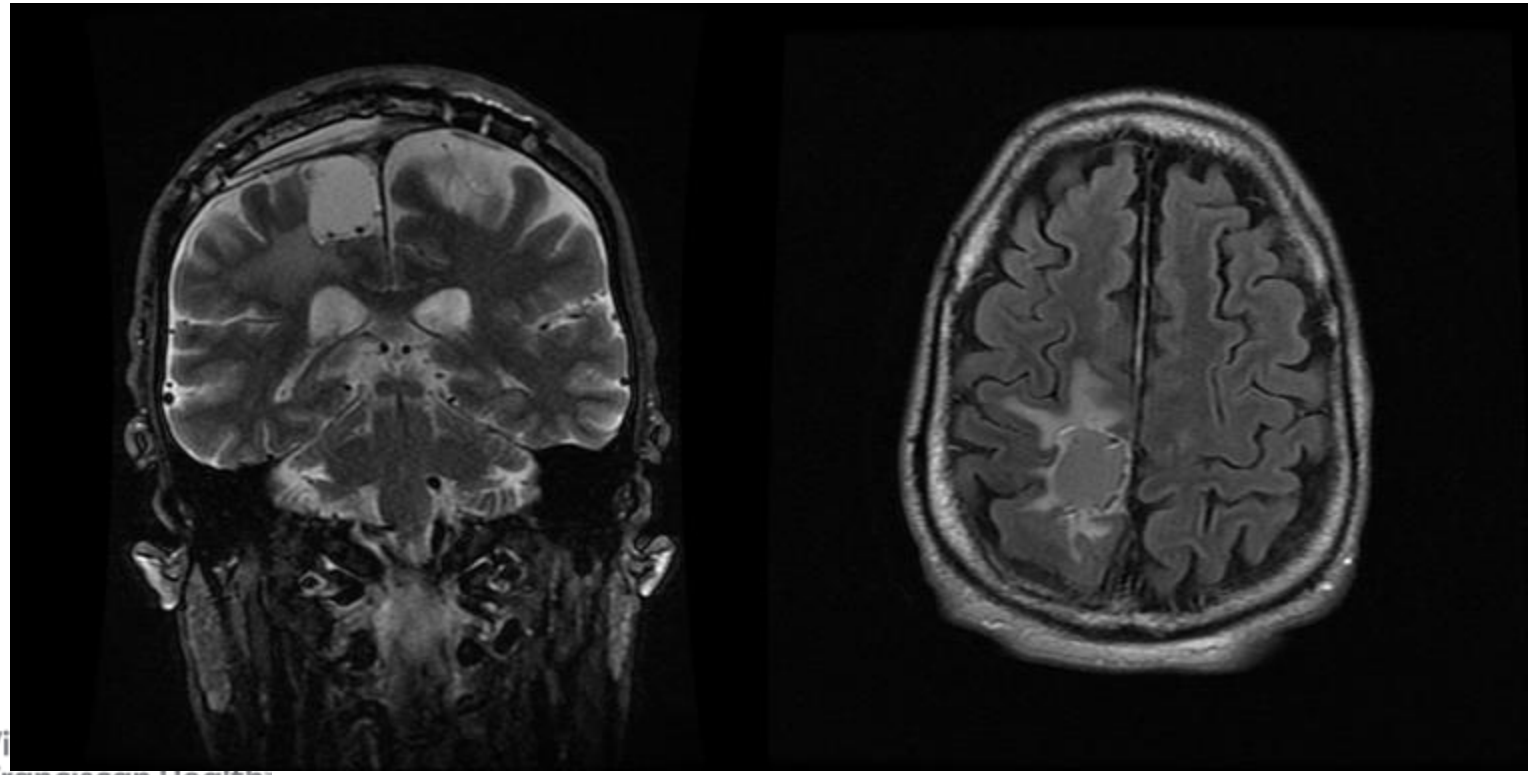
# Stable position of tiles at 6 months – continuing adjuvant



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# Current Studies 1. GammaTile STaRT Registry

- NCT04427384: A Multicenter Observational Study of GammaTile Surgically Targeted Radiation Therapy (STaRT) in Intracranial Brain Neoplasms
- Multi-center, prospectively maintained database, started 9/11/2020
- Objective: Evaluate real world clinical and patient reported outcomes
- Patients (N=600) with surgically resected tumors of any pathology and treated with STaRT

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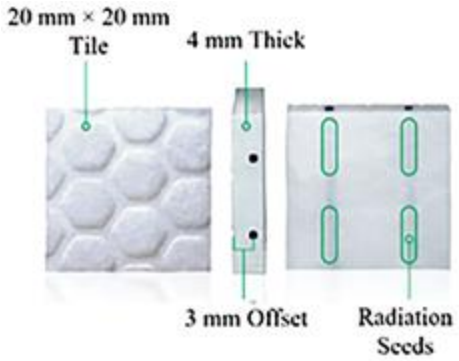
# Registry of Patients With Brain Tumors Treated With STaRT (GammaTiles)

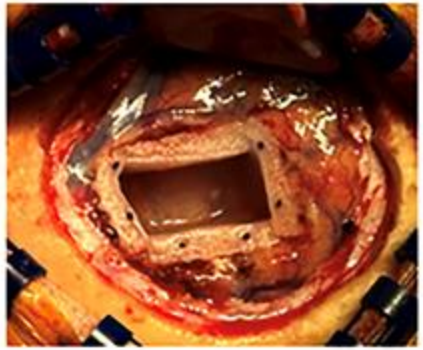
ClinicalTrials.gov ID NCT04427384

- Data Collected:
  - Local control
  - Overall Survival
  - QOL, neurocognition, functional decline
  - Surgical and radiation AEs
- Time points: 1, 3, 6, 9, 12, 18, 24 months then every 6 months

Results:

Data will be used to benchmark clinical outcomes and compare to existing standard of care treatments



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# Results from the registry

Journal of Neuro-Oncology (2026) 176:199
https://doi.org/10.1007/s11060-026-05455-0

RESEARCH

## Local control and leptomeningeal disease after resection and GammaTile brachytherapy for newly diagnosed brain metastases: results from a prospective registry

Trent Kite[1] · Simon Hanft[2] · Sabrina Zeller[2] · Stuart Lee[3] · M. Sean Peach[4] · Lindsey Sloan[5] · Clark C. Chen[6] · Vincent DiNapoli[7] · Parag Sevak[8] · Colette J. Shen[9] · Rupesh Kotecha[10] · Michael A. Garcia[11] · David Brachman[11] · Sita Patel[11] · Adam Robin[12] · Ian Lee[12] · Huong Pham[13] · Robert Ryan[14] · William H. Smith[15] · Andrea Wasilewski[16] · Daniel Pavord[17] · Rodney E. Wegner[17] · Eugene C. Poggio[18] · Matthew J. Shepard[1]

Received: 29 December 2025 / Accepted: 30 January 2026 / Published online: 7 February 2026


- Analyzed rates of leptomeningeal disease in newly diagnosed brain mets
- 55 BM in 51 patients analyzed
- Clinical Outcomes (LMD, LC, radiation toxicity, distant control, OS) collected and compared with historical control

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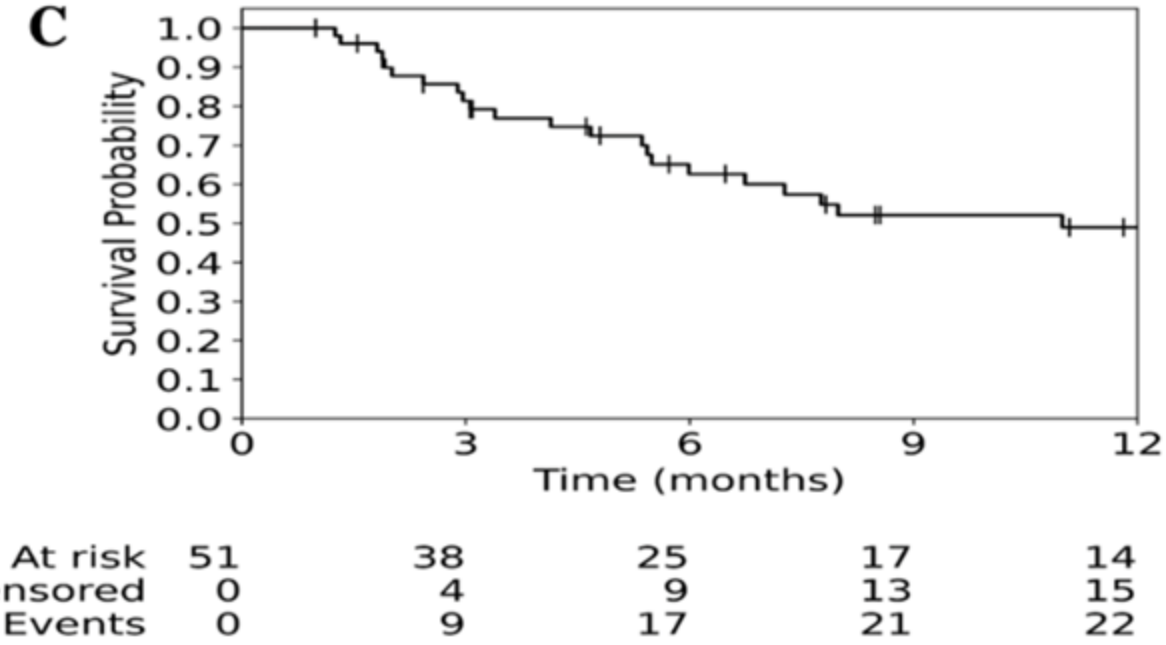


- Very low rates of LMD and AEs
- Favorable 12 month LC vs post-op SRS (92% vs 72% from phase III SRS trial)

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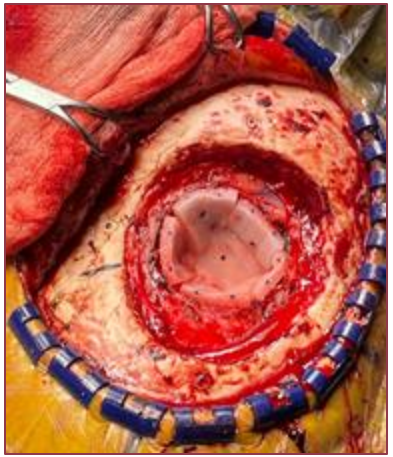
# Current Studies 2. ROADS Trial

- Phase 3, RCT comparing surgical resection of newly diagnosed brain met followed by:
  - Standard of care external beam SRS vs.
  - Surgically targeted radiation with GammaTile



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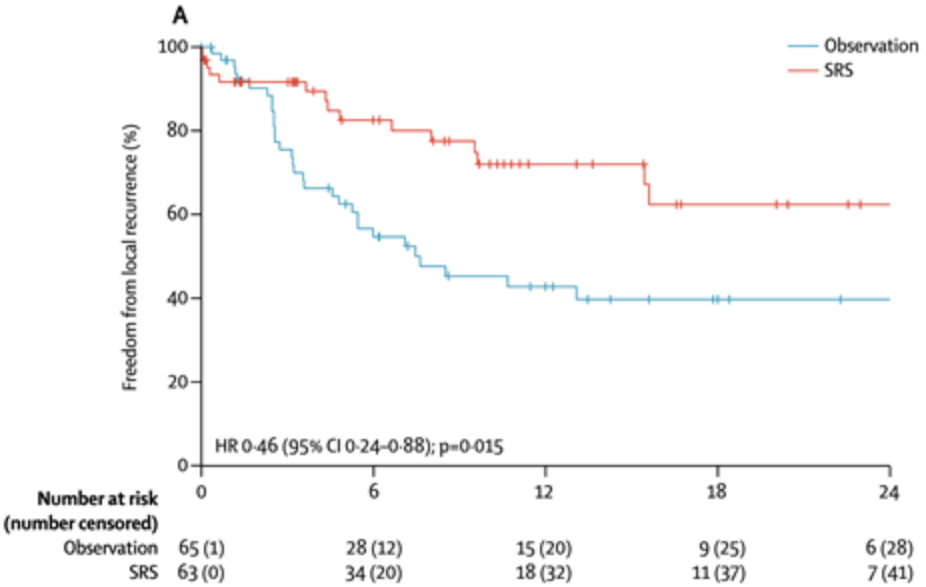
# Current standard of care results in 72% 12-month local control, driving the need for better outcomes[1,2]

- **Surgery → Post-operative SRS/SRT**[1]
  (Mahajan et al., *Lancet Oncol.* 2017)

- 12-month local control:
  - **Surgery alone: 43%**
  - **Surgery + SRT: 72%**

- **Limitations:**
- Typically delayed by several weeks for post-op recovery
- Dose limits by lesion size




1. Mahajan A, et al. *Lancet Oncol.* 18(8):1040-1048 (2017). 2. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

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# ROADS – A Phase 3 Randomized Controlled Multicenter Trial for Newly Diagnosed Brain Metastases[1]

## Objective

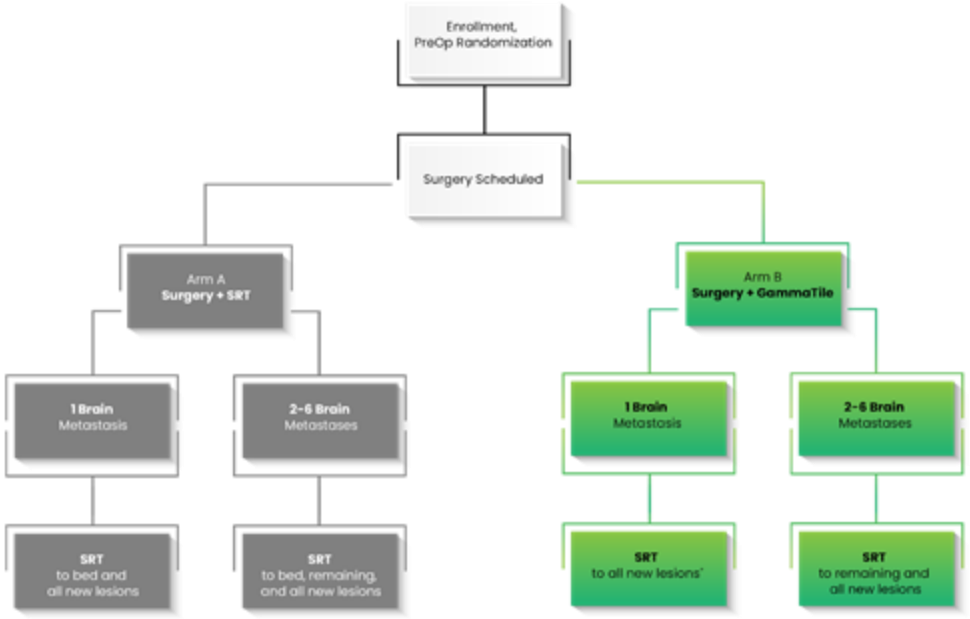
Compare outcomes between surgery + stereotactic radiotherapy (SRT) (Arm A) versus surgery + GammaTile (Arm B).

## Primary Outcome

- Surgical bed recurrence-free survival (SB-RFS)
  - *Recurrences were centrally and independently reviewed*

## Secondary Outcomes

- Rates of leptomeningeal disease
  - *LMD incidence/types were centrally and independently reviewed*
- Overall survival
- Toxicities
- Neurocognitive Status
- Quality of life (FACT-Br)
- Functional status (KPS)
- Factors that cause delays in SRT/SRS




Index Lesion: 2.0-7.0 cm
Up to 5 non-index lesions allowed

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1. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

# Interim patient demographics and characteristics were similar between arms (n=168, median follow-up: 8.9 months)[1]

| Parameter | Surgery plus SRT | Surgery plus GammaTile |
|---|---|---|
| Number of patients (n) | 81 | 87 |
| Median age in years (range) | 63 (34-83) | 63 (34-89) |
| Sex (M:F) | 40:41 | 34:53 |
| Ethnicity, predominantly Non-Hispanic (%) | 73% | 76% |
| Race, predominantly White (%) | 66% | 68% |
| Median resected tumor diameter in cm (range) | 3.2 (2.1 – 5.8) | 3.3 (2.0 – 5.0) |
| Median number of brain metastases (range) | 1 (1-6) | 1 (1-6) |

| Surgery plus SRT | |
|---|---|
| Median days to SRT (range) | 26 (5 – 62) |
| Reasons for radiation delay include (if past the protocol-specified 28 days) | Rehabilitation<br>Prolonged hospitalization<br>Weather |

| Histology | SRT (%) | TBRT (%) |
|---|---|---|
| Lung | 48.1 | 42.5 |
| Melanoma | 11.1 | 11.5 |
| Breast | 8.6 | 14.9 |
| Colon | 4.9 | 3.4 |
| Other | 23.5 | 23.0 |
| Renal | 2.5 | 1.1 |
| Unknown | 1.2 | 3.4 |
| Total | 100 | 100 |

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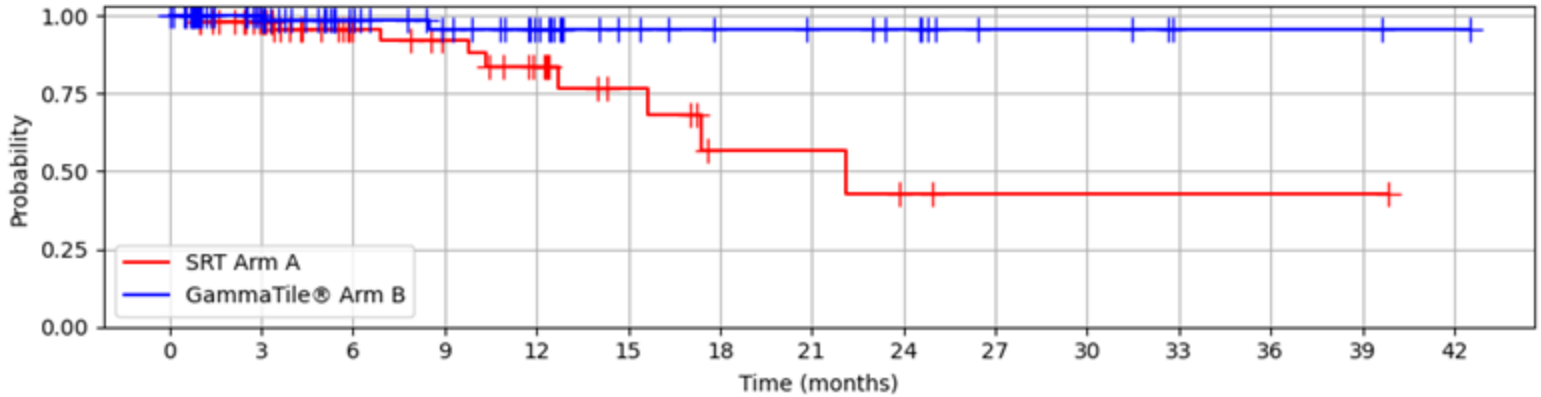
1. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

# Surgery plus GammaTile leads to superior surgical bed control compared to surgery plus SRT[1]

Time to surgical bed recurrence is defined as *time to recurrence at the surgical bed*, with patient deaths censored.

Median time to surgical bed recurrence was 22.1 months (Arm A: SRT) versus not yet met (Arm B: GammaTile) (HR: 0.13, 95% CI: 0.03-0.62, *p*=0.010).[1]




**GammaTile showed superiority in surgical bed control compared to SOC.**
*All recurrences were centrally and independently reviewed.*

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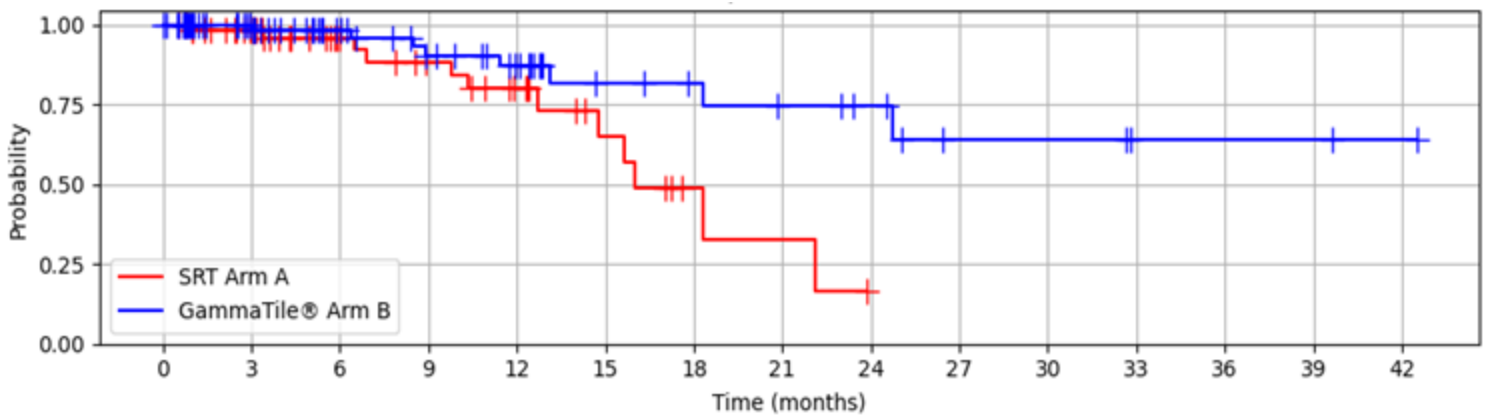
1. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

# Surgery plus GammaTile demonstrates superior freedom from either surgical bed recurrence or radiation necrosis compared to surgery plus SRT[1]

This composite endpoint is *time to surgical bed recurrence or necrosis, whichever occurs first.*

Median time to freedom from SBR or RN was 16.0 months (Arm A: SRT) versus not yet met (Arm B: GammaTile) (HR: 0.32, 95% CI: 0.12-0.82, *p*=0.018)[1]



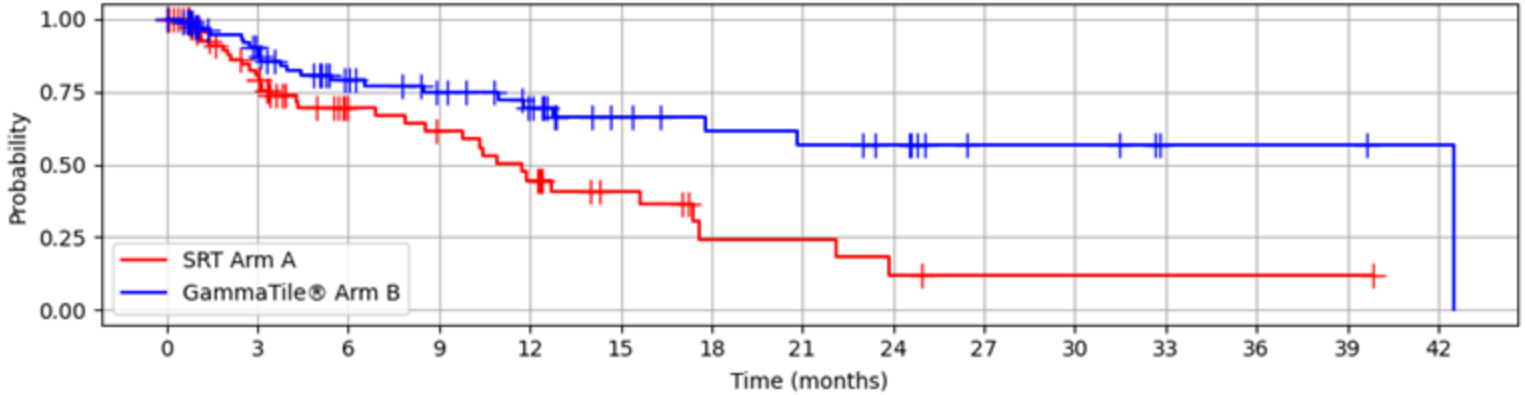

**GammaTile showed superiority in overall protection from worrisome radiographic brain changes (both SBR and RN).** At the time of analysis, more than half of GammaTile patients remained free from both tumor regrowth and radiation-related tissue damage, while in the SRT group, half of patients had one or the other by 16.0 months (HR:0.32).

1. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

# Surgery plus GammaTile demonstrates superior surgical bed recurrence-free survival (SB-RFS) compared to surgery plus SRT[1]

SB-RFS is defined as *time to recurrence at the surgical bed or patient death, whichever occurs first.*

Median SB-RFS was 11.7 months (Arm A: SRT) versus 42.5 months (Arm B: GammaTile) (HR: 0.42, 95% CI: 0.24-0.73, *p*=0.0024).[1]




**GammaTile showed superiority in the primary endpoint of the study compared to SOC.**
Patients who received GammaTile lived longer without tumor regrowth and there was a greater than 50% in risk of either tumor recurrence or death (HR: 0.42).

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1. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

# GammaTile demonstrated significant gains in efficacy with no increase in safety concerns[1]

**Across both Arms, leptomeningeal disease and radiation necrosis rates were low, as well as ≥Grade 3 TRAEs[1]**

| | Surgery + SRT | |
|---|---|---|
| Leptomeningeal disease (LMD), *p = 0.402* | 0% | 3.4% |
| Radiation necrosis (RN) | 6.8% | 6.8% |
| ≥Grade 3 treatment-related adverse events (TRAEs ) | 21.0% | 20.7% |

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1. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

# Conclusion: GammaTile tile-based radiation delivers superior tumor control compared to standard of care[1]

## Efficacy[1]

- **Surgery plus GammaTile provides significantly longer time-to-surgical bed recurrence** compared to surgery plus SRT (HR: 0.13, 95% CI: 0.03-0.62, *p=0.010*).
- **Surgery plus GammaTile provides superior freedom from surgical bed recurrence or radiation necrosis** compared to surgery plus SRT (HR: 0.32, 95% CI: 0.12-0.82, *p=0.018*).

**Primary Endpoint: Surgery plus GammaTile provides superior SB-RFS** compared to surgery plus SRT, with a risk reduction of >50% (HR:0.42 CI:0.24-0.73, *p=0.0024*).

## Safety[1]

- **Low incidence** of LMD and RN in both Arms.
- **Similar rates** of ≥Grade 3 TRAEs in both Arms.

## Next Steps[1]

- Accrual of 230 randomized patients now complete.
- Final analysis to be presented in 2026.

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1. Weinberg J, Beckham TH, Lin H, et al. Interim analysis of a phase 3 randomized controlled trial for treatment of newly diagnosed metastatic brain tumors (ROADS, NCT04365374). Presented at: Congress of Neurological Surgeons (CNS) Annual Meeting; October 15, 2025; Los Angeles, CA.

# Current Studies 3. BRIDGES Trial

- Phase 3 RCT for newly diagnosed Glioblastoma comparing surgical resection and:
  - Standard Stupp protocol post-op external beam radiation/TMZ vs:
  - Placement of GammaTile and post-op radiation boost during concurrent TMZ

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# The Current Standard of Care for Newly Diagnosed GBM "Stupp Protocol"


"Maximum safe resection"

6 weeks of concurrent external beam radiation (60 Gy) and oral chemo with temozolomide

Maintenance therapy – monthly oral chemo

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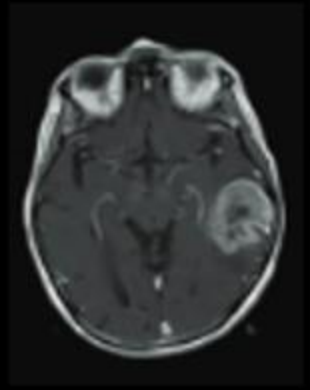
*Stupp et al, NEJM 2005*

# Rapid Early Progression (REP): Any Tumor Regrowth Between Surgery and EBRT

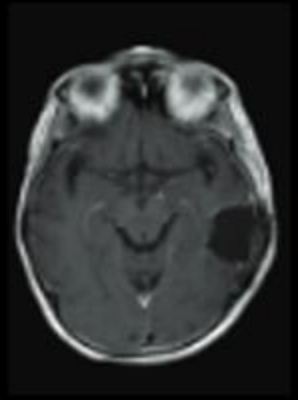
Rapid early progression in glioblastoma

Incidence rate of REP: 45.9%[1]

Pre-Surgery

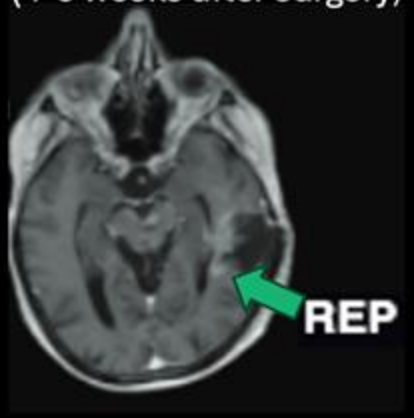


Post-surgery (≤48 hours)



Post-op recovery time

Pre-radiotherapy
(4-6 weeks after surgery)

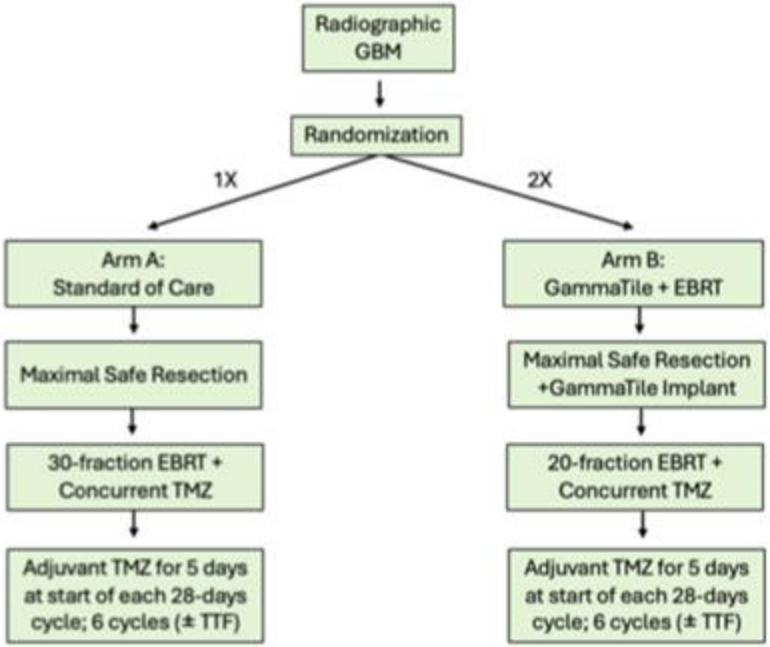



Waqar, M. *et al*. Rapid early progression (REP) of glioblastoma is an independent negative prognostic factor: Results from a systematic review and meta-analysis. *Neuro-oncology Adv* **4**, vdac075 (2022).

## Current Standard of Care


Can starting radiation immediately at surgery address rapid early progression and improve outcome?

**Randomized Study of Resection and GammaTile® Followed by Concurrent External Beam Radiation Therapy (EBRT) and Temozolomide (TMZ) and Adjuvant TMZ versus Standard of Care in Newly Diagnosed Glioblastoma (GBM)**




Abbreviations: EBRT = external beam radiation therapy; TMZ = temozolomide; TTF = tumor treating fields

**Short title: Beginning Radiation Immediately with GammaTile at GBM Excision versus Standard of Care (BRIDGES)**

Protocol Number: GTM-105
NCT07195591
Number of Study Sites: Up to 80

**Primary endpoint (superiority):**

- Overall survival

**Secondary endpoints (superiority):**

- Progression free survival
- Quality of life
- Financial toxicity
- Time toxicity
- Time to next unplanned treatment
- Safety

Maximum number of patients: 766
Two planned interim analyses:
1) At 155 events (~404 patients)
2) At 310 events (~620 patients)

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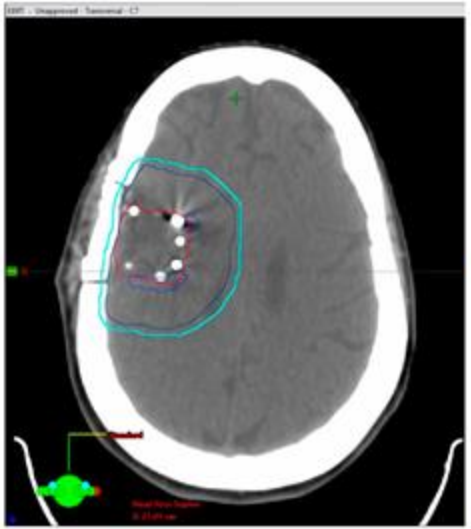
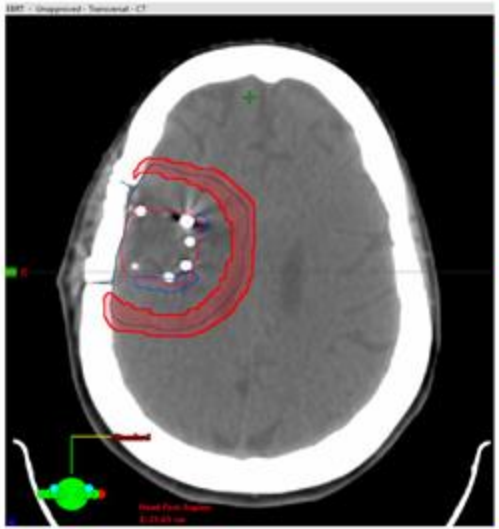
# Arm B RT Planning: GammaTile + EBRT

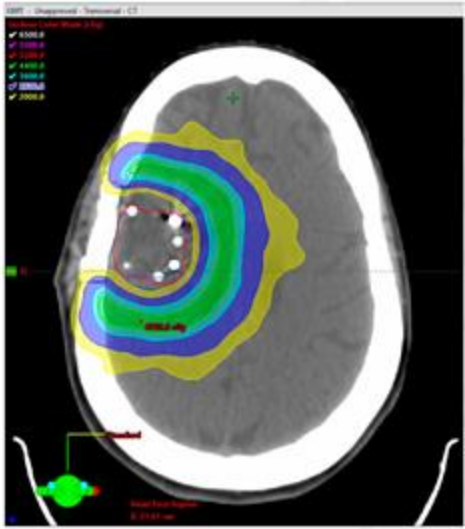
Calculate brachytherapy dose on EBRT planning CT



Generate Target Volumes and Organs at Risk



PTV_4400 = Total Treatment Volume – 40Gy_GT



Optimize a 20-fraction EBRT plan to deliver 4400 cGy to PTV_4400

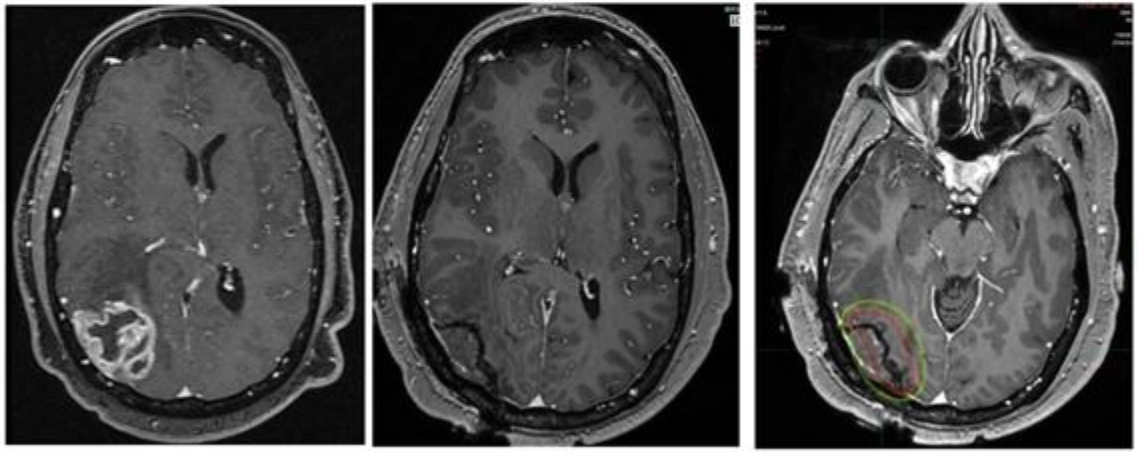
OAR constraints depend on dose received from GammaTile (obtained via online calculator)

# GESTALT—Newly Diagnosed GBM (GammaTile + Stupp) (NCT05342883)

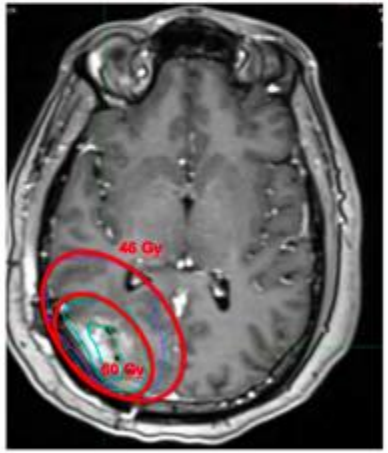
gestalt
CLINICAL TRIAL

Feasibility study

- Enrollment complete August 2025
- Primary aim: Feasibility of starting EBRT in timely fashion
- Secondary aim: Safety
- Tracking OS, PFS, LC, KPS



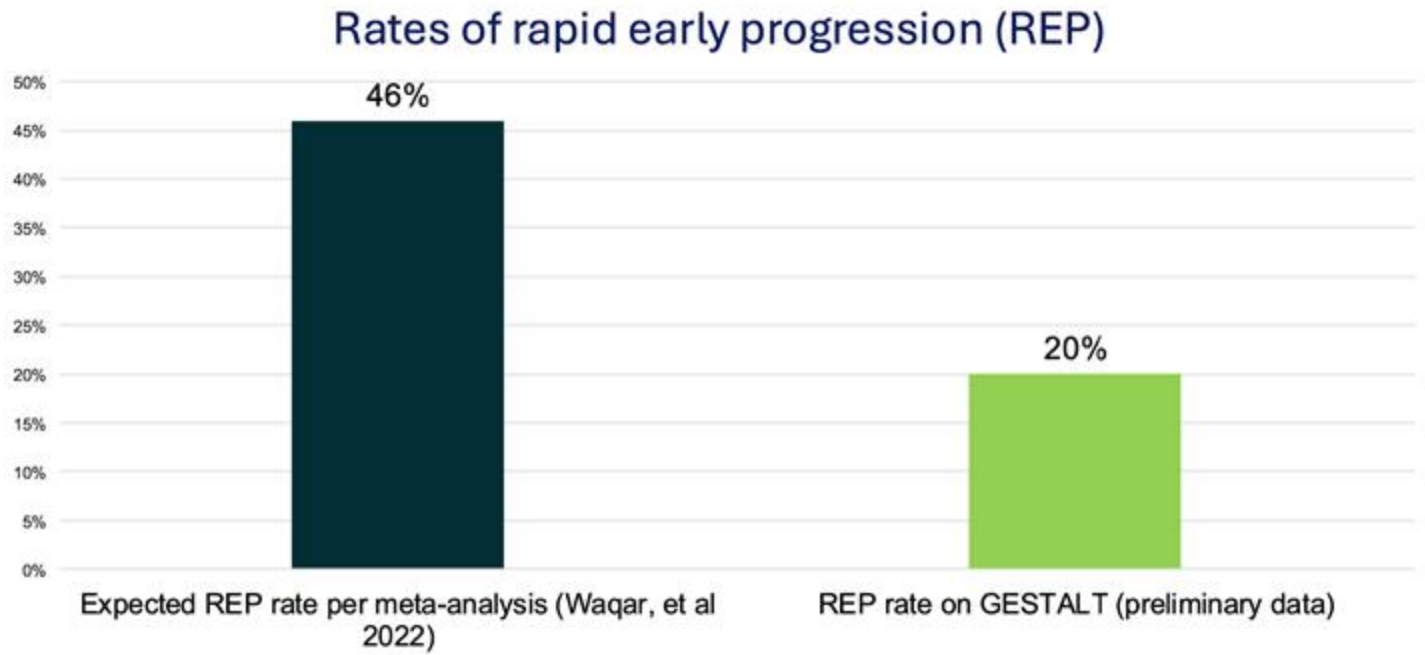
Post-op recovery time




Radiographic diagnosis → Resection + GammaTile ⇝ IMRT + Temozolomide

Case images courtesy of Dr. Jay McCracken and Dr. Nowlan

# Early GESTALT (NCT05342883) data: REP rate at 30 patients




Sloan L, Ferreira C, Neil E, Nowlan A, McCracken DJ, Wanebo J, Smith K, Block O, Zada G, Shah M, Richardson A, Khattab M, David J, Lee S, Peach MS, Hoeprich M, Chang E, Turner A, Brachman D, Garcia MA. Incidence of rapid early progression (REP) and rapid early response (RER) in patients with newly diagnosed GBM undergoing resection and im mediate post resection brachytherapy on a prospective tria. Proceedings of the American Radium Society® 107th Annual Meeting. American Journal of Clinical Oncology ():10.1097/COC.0000000000001223, June 13, 2025. | DOI: 10.1097/COC.0000000000001223

# GammaTile | Enrolling Clinical Studies

| | GammaTile Registry | ROADS (enrollment complete) | Memorial Sloan Kettering Investigator Initiated Study | GESTALT (enrollment complete) | BRIDGES |
|---|---|---|---|---|---|
| **Tumor Type** | Multi-tumor types | Newly Diagnosed Brain Metastases | Recurrent Brain Metastases | Newly diagnosed GBM | Newly Diagnosed GBM |
| **Design** | Observational Registry | Phase 3 Randomized | Phase 2 Randomized | Feasibility | Phase 3 Randomized |

# Thank you

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# Revascularizing the Occluded Brain: Contemporary Results of Moyamoya Bypass Surgery

Jason Lee Choi, MD
Cerebrovascular Endovascular Neurosurgeon
5/9/2026

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# Moyamoya Vasculopathy

- Rare steno-occlusive disease with progressive intimal thinking of the internal carotid arteries and its proximal branches
- Disease progression in a majority of patients
- 2/3 of patients have symptomatic progression over 5 years with poor outcome without treatment
- 5 year stroke risk ranges from 25-75%

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Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med. 2009; *360*:1226–1237. doi: 10.1056/NEJMra0804622.
Kronenburg A, Braun KP, van der Zwan A, Klijn CJ. Recent advances in moyamoya disease: pathophysiology and treatment. Curr Neurol Neurosci Rep. 2014; *14*:423. doi: 10.1007/s11910-013-0423-7.

Zipfel GJ, Sagar J, Miller JP, Videen TO, Grubb RL Jr, Dacey RG Jr, Derdeyn CP. Cerebral hemodynamics as a predictor of stroke in adult patients with moyamoya disease: a prospective observational study. Neurosurg Focus. 2009 Apr;26(4):E6. doi: 10.3171/2009.01.FOCUS08305. PMID: 19335132; PMCID: PMC2747517.

Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y. Incidence and clinical features of disease progression in adult moyamoya disease. Stroke. 2005 Oct;36(10):2148-53. doi: 10.1161/01.STR.0000182256.32489.99. Epub 2005 Sep 22. PMID: 16179571.

# Moyamoya Vasculopathy

- There is currently no medical treatment that can halt progression or reverse the vasculopathy
- Asymptomatic Moyamoya disease may be a misnomer, as 20% have silent strokes
- Surgical revascularization is the only treatment

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Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med. 2009; *360*:1226–1237. doi: 10.1056/NEJMra0804622.
Kronenburg A, Braun KP, van der Zwan A, Klijn CJ. Recent advances in moyamoya disease: pathophysiology and treatment. Curr Neurol Neurosci Rep. 2014; *14*:423. doi: 10.1007/s11910-013-0423-7.

Zipfel GJ, Sagar J, Miller JP, Videen TO, Grubb RL Jr, Dacey RG Jr, Derdeyn CP. Cerebral hemodynamics as a predictor of stroke in adult patients with moyamoya disease: a prospective observational study. Neurosurg Focus. 2009 Apr;26(4):E6. doi: 10.3171/2009.01.FOCUS08305. PMID: 19335132; PMCID: PMC2747517.

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# Questions to consider

- When to Bypass?
- Indirect vs Direct?
- How much flow do we need?

JNS

CLINICAL ARTICLE

## Short- and long-term outcomes of moyamoya patients post-revascularization

Mario Teo, MD, FRCS(SN), Kumar Abhinav, MD, FRCS(SN), Teresa E. Bell-Stephens, BSN, RN, CNRN, Venkatesh S. Madhugiri, MBBS, MCh, Eric S. Sussman, MD, Tej Deepak Azad, MD, Rohaid Ali, MD, Rogelio Esparza, MD, Michael Zhang, MD, and Gary K. Steinberg, MD, PhD

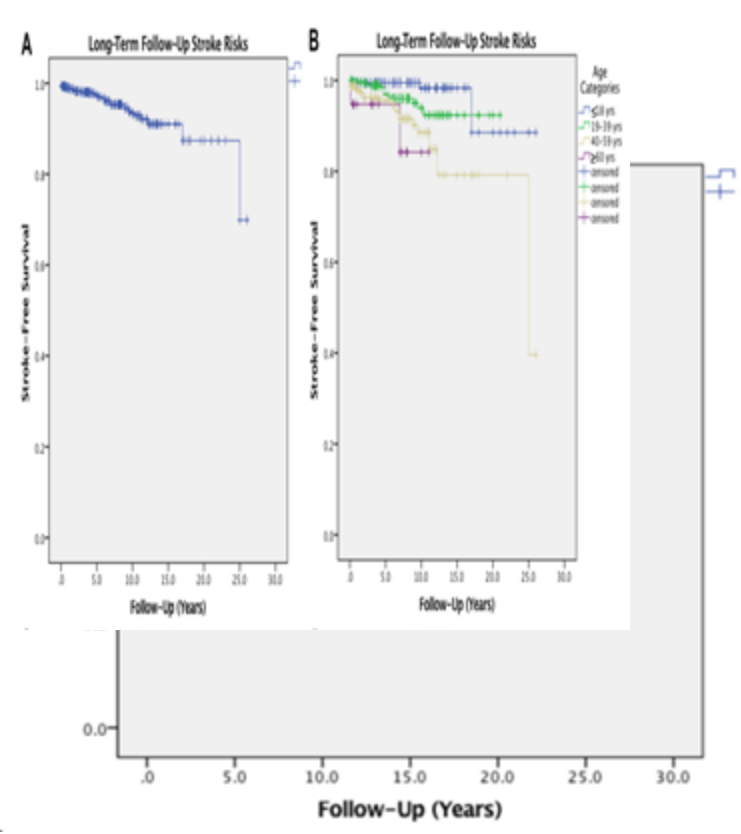
Department of Neurosurgery, Stanford University School of Medicine and Stanford Stroke Center, Stanford, California

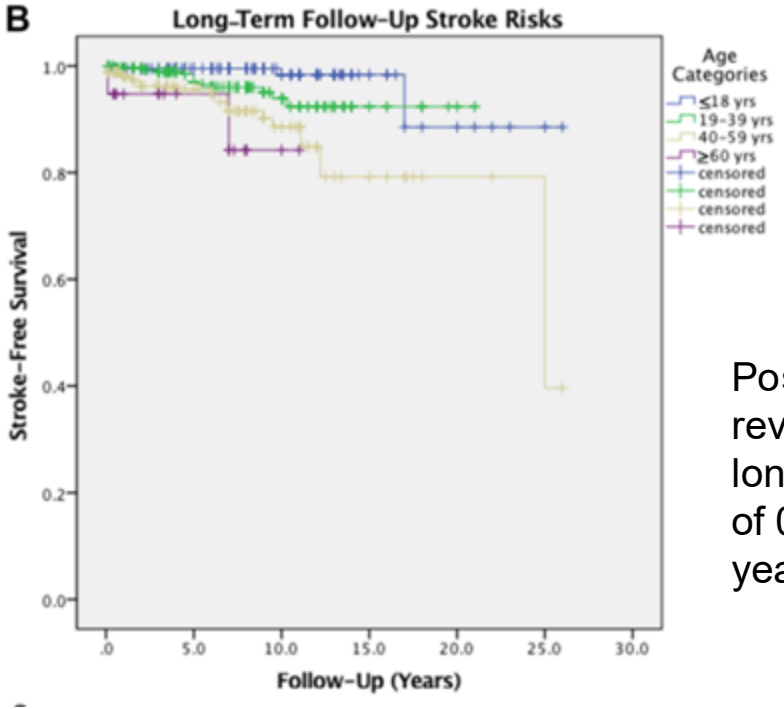
96% and 73% of the adult and pediatric cohorts, respectively, had direct revascularization, with a 4.2% per-bypass-procedure 30-day major stroke risk

Generally, the more advanced the disease prior to surgery, the higher the risk of complications after the surgery.

Younger patients do better than older patients

Post-revascularization long-term stroke risk of 0.6% per patient year




Post-revascularization long-term stroke risk of 0.6% per patient year

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# When to Bypass?

## Different Schools of Thought

Early Bypass

Bypass based on age, some imaging findings and minimal symptoms

Late Bypass

Bypass if there is an established flow deficit

JNS

CLINICAL ARTICLE

# Short- and long-term outcomes of moyamoya patients post-revascularization

Mario Teo, MD, FRCS(SN), Kumar Abhinav, MD, FRCS(SN), Teresa E. Bell-Stephens, BSN, RN, CNRN, Venkatesh S. Madhugiri, MBBS, MCh, Eric S. Sussman, MD, Tej Deepak Azad, MD, Rohaid Ali, MD, Rogelio Esparza, MD, Michael Zhang, MD, and Gary K. Steinberg, MD, PhD

Department of Neurosurgery, Stanford University School of Medicine and Stanford Stroke Center, Stanford, California

Retrospective case series of patients between 2005-2011
769 patients with 1250 bypasses (1118 direct, 132 indirect)
741/769 (96.4%) with 6 month follow up
205 pediatric patients vs 564 adult patients

# Strokes

The 30-day major stroke risk was 5.3% (41/769) and 2.4% (11/467) after the first and second bypasses, respectively.

4.2% per-procedure major stroke risk.

- 25/52 patients (52%) improved MRS $\geq$ 1 postoperatively

0.7% died of a stroke post operatively within 30 days

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# Most Significant Stroke Risk Factors

**Age**

Age <18, 19-39, 40-59, >60

**DSA Score**

1) stenosis/occlusion, 2) + IC-IC collateralization, 3) +EC Collateralization

**MRI Score** – within 1 mo prior to surgery

0) normal, 1) Ischemia/hemorrhage/atrophy, 2) DWI+ Infarct

**Hemodynamic Reserve**

0) normal augmentation, 1) impaired augmentation, 3) Steal

# Age

| Age | 30 Day Major postop stroke (↓ mRS) | | |
|---|---|---|---|
| | # of patients | %/pt | %/procedure |
| <18 yr | 4 | 1.9% | |
| 19-39 yr | 14 | 4.8% | |
| 40-59 yr | 29 | 11.3% | |
| >60 yr | 3 | 15.0% | |
| Total | 50 | 6.5% | 4.0% |


| | | | |
|---|---|---|---|
| >60 yr | 3 | 15.0% | |
| Total | 50 | 6.5% | 4.0% |


# DSA Score

| Variable | No. of Patients (row %) | | p Value |
|---|---|---|---|
| | No Stroke | Stroke | |
| DSA score | | | |
| 1 | 16 (100.0) | 0 (0) | **<0.0001** |
| 2 | 543 (95.3) | 27 (4.7) | |
| 3 | 138 (84.7) | 25 (15.3) | |

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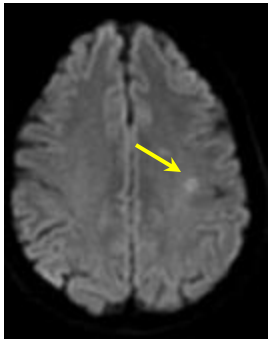
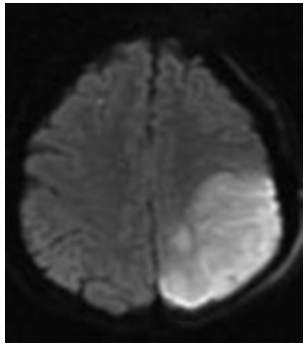
# Preoperative Risk Factors for Perioperative Stroke

## MRI score

Pre-bypass



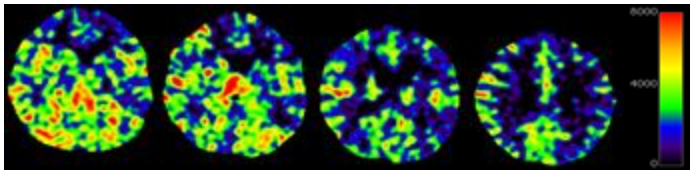
Post Lt bypass



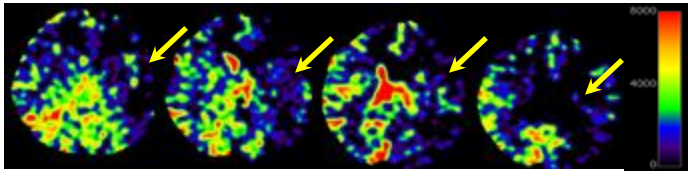
MRI brain score:

0) Normal 2%
1) Ischemia/hemorrhage/atrophy 6.3%
2) DWI+ infarct 36%

## Hemodynamic Reserve score



Pre-Diamox (Baseline)



Post-diamox

Hemodynamic Reserve (after Diamox) score:

0) Good augmentation **0.6%**
1) Impaired augmentation **6.0%**
2) Steal 22.5%

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# When to Bypass?

## Different Schools of Thought

Early Bypass

Bypass based on age, some imaging findings and minimal symptoms

- Patients with decreased perfusion have a higher risk of peri-operative complications
- Earlier development of iatrogenic collateralization, with maturity of the bypass over time

Late Bypass

Bypass if there is an established flow deficit

- Competing flows will decrease long-term patency of the bypass
- Bypasses beyond a stenosis may lead to complete occlusion of the parent vessel
- As cut flow index <0.5 there is an increase in risk of vessel occlusion

# Revascularization Techniques

Simple
Less Flow

Increasing
Complexity
More Flow

Burr holes

Bone Only Craniotomy

Craniotomy with Dural Inversion

Encephaloduromyosynangiosis (EDMS)

Encephaloduroarteriosynangiosis (EDAS)

EC-IC Bypass

EC-IC Bypass with Transposition Graft

Combination Bypass with Transposition

Introduces
Ischemic
Clamping

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# Indirect vs Direct = Controversial

**Direct versus indirect revascularization procedures for moyamoya disease: a comparative effectiveness study**

Luke Macyszyn, MD, MA, Mark Attiah, MD, MS, MBE, Tracy S. Ma, MD, Zarina Ali, MD, Ryan Faught, BA, Alisha Hossain, BA, Karen Man, BAS, Hiren Patel, BA, Rosanna Sobota, BA, Eric L. Zager, MD, and Sherman C. Stein, MD

Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

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Stroke

CLINICAL AND POPULATION SCIENCES

**Direct, Indirect, and Combined Extracranial-to-Intracranial Bypass for Adult Moyamoya Disease: An Updated Systematic Review and Meta-Analysis**

Vincent N. Nguyen, MD; Mustafa Motiwala, MD; Turki Elarjani, MD; Kenneth A. Moore, MD; L. Erin Miller, BA; Michael Barats, MS; Nitin Goyal, MD; Lucas Elijovich, MD; Paul Klimo, MD, MPH; Daniel A. Hoit, MD, MPH; Adam S. Arthur, MD, MPH; Jacques J. Morcos, MD; Nickalus R. Khan, MD

# Advantages of Direct

Augment flow immediately after surgery
More consistent higher extent of collateralization

The only multicentered, prospective, randomized, case controlled trial for MMD is the Japan Adult Moyamoya (JAM) Trial which compares outcomes of EC-IC vs no surgery for MMD, with significant benefit in the surgery group

Meta-analyses consistently show that direct bypass (as well as combined bypass) provides superior outcomes compared to indirect bypass alone in adult patients

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Lim, Y. C., Lee, E., & Song, J. (2024). Outcomes of Bypass Surgery in Adult Moyamoya Disease by Onset Type. *JAMA Network Open*, *7*, e2415102.
Lin, K., Sui, S., Zhao, J., Zhang, L., & Chen, K. (2021). A meta-analysis of comparisons of various surgical treatments for moyamoya diseases. *Brain and Behavior*, *11*.
Nguyen, V. N., Motiwala, M., Elarjani, T., et al. (2022). Direct, Indirect, and Combined Extracranial-to-Intracranial Bypass for Adult Moyamoya Disease: An Updated Systematic Review and Meta-Analysis. *Stroke*, *53*, 3572-3582. https://doi.org/10.1161/strokeaha.122.039584 Cited by: 90

# How much flow do we need?

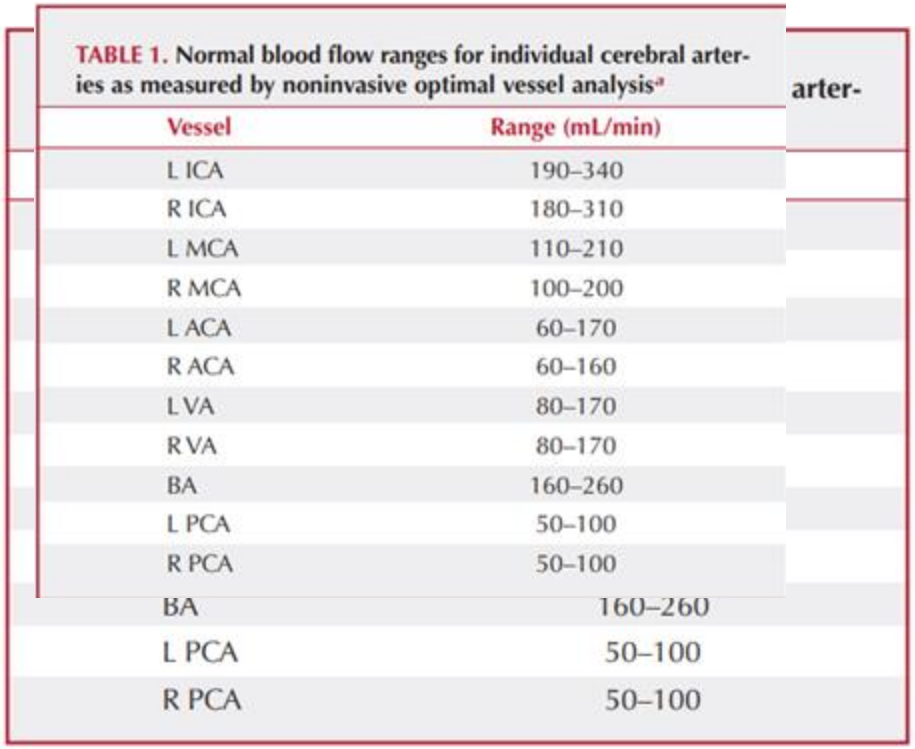

TABLE 1. Normal blood flow ranges for individual cerebral arteries as measured by noninvasive optimal vessel analysis[a]

| Vessel | Range (mL/min) |
|---|---|
| L ICA | 190–340 |
| R ICA | 180–310 |
| L MCA | 110–210 |
| R MCA | 100–200 |
| L ACA | 60–170 |
| R ACA | 60–160 |
| L VA | 80–170 |
| R VA | 80–170 |
| BA | 160–260 |
| L PCA | 50–100 |
| R PCA | 50–100 |

arter-

BA 160–260
L PCA 50–100
R PCA 50–100



M4 Vessel ~10-20 ml/min

Moyamoya M4 often 0.1-3ml/min

- Often times in the opposite direction via collaterals

# EC-IC Bypass

Donor
Superficial Temporal Artery
Occipital Artery
Posterior Auricular Artery

Recipient
M4, M3, M2, PCA, ACA

Transposition
Radial Artery
Saphenous Vein

Simple
Less Flow

Complex
More Flow

Technique
Single Vessel End to Side

Single Vessel Double Anastomosis
(E-S proximal STA, E-S Distal STA)

Double Barrel Bypass
(E-S Frontal and Parietal Branch)

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# The cut flow index revisited: utility of intraoperative blood flow measurements in extracranial-intracranial bypass surgery for ischemic cerebrovascular disease

Christopher J. Stapleton, MD, Gursant S. Atwal, MD, Ahmed E. Hussein, MD, Sepideh Amin-Hanjani, MD, and Fady T. Charbel, MD

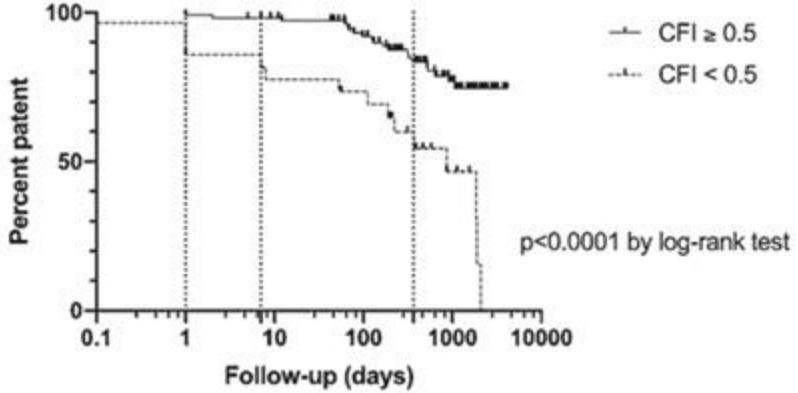
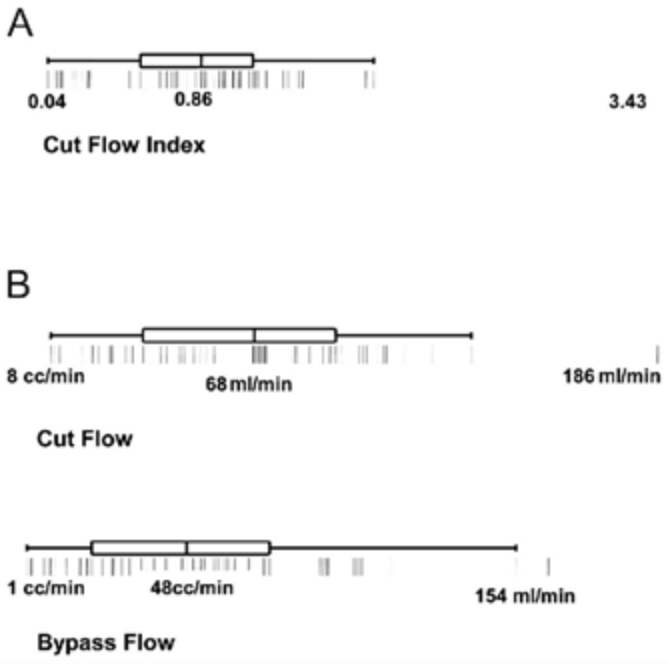
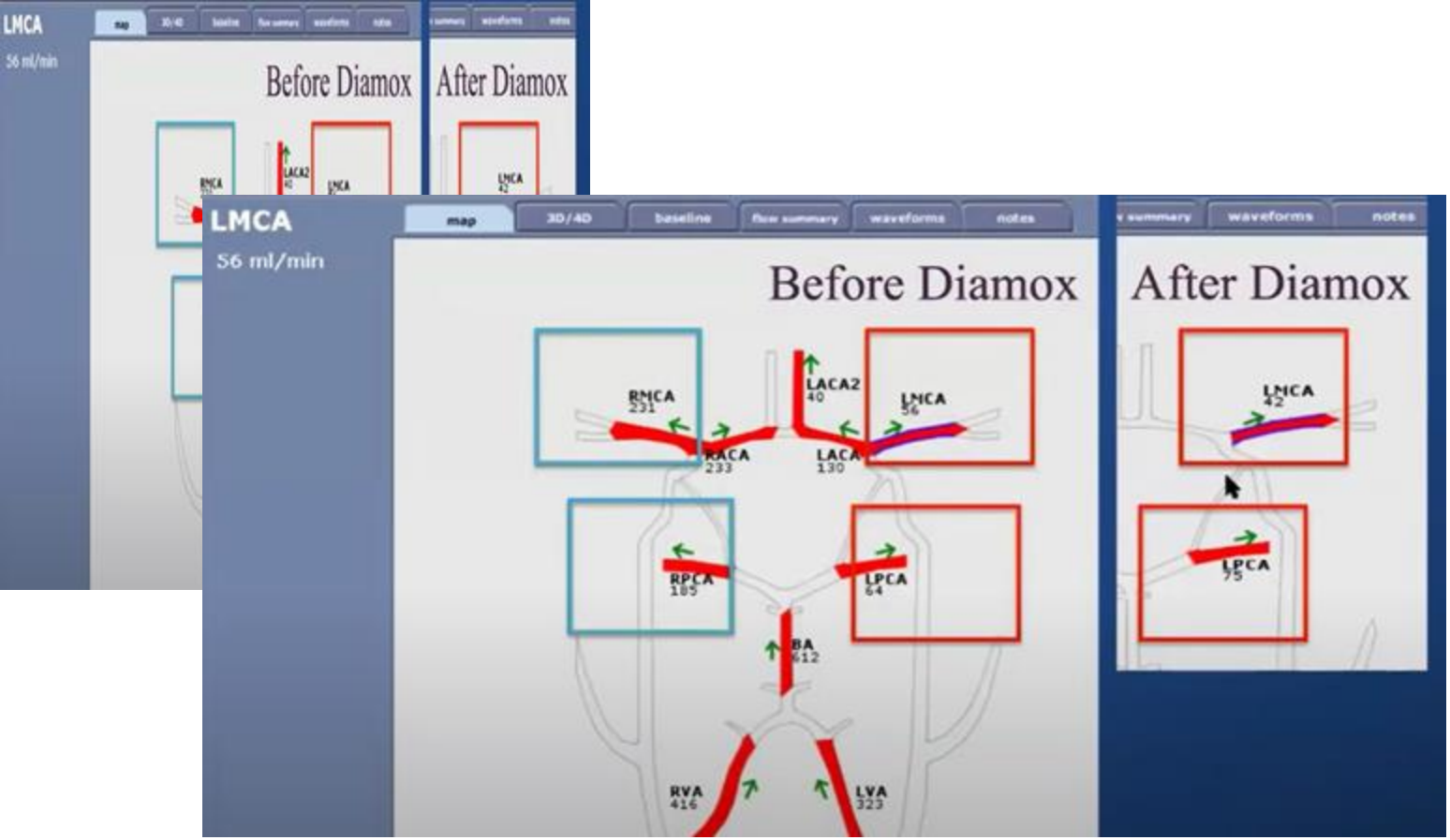



**FIG. 2.** Kaplan-Meier curves comparing patency over time for bypasses with a CFI ≥ 0.5 versus CFI < 0.5. Bypasses with a CFI ≥ 0.5 were significantly more likely to remain patent ($p < 0.0001$).

Follow-up (days)

FIG. 2. Kaplan-Meier curves comparing patency over time for bypasses with a CFI ≥ 0.5 versus CFI < 0.5. Bypasses with a CFI ≥ 0.5 were significantly more likely to remain patent (p < 0.0001).



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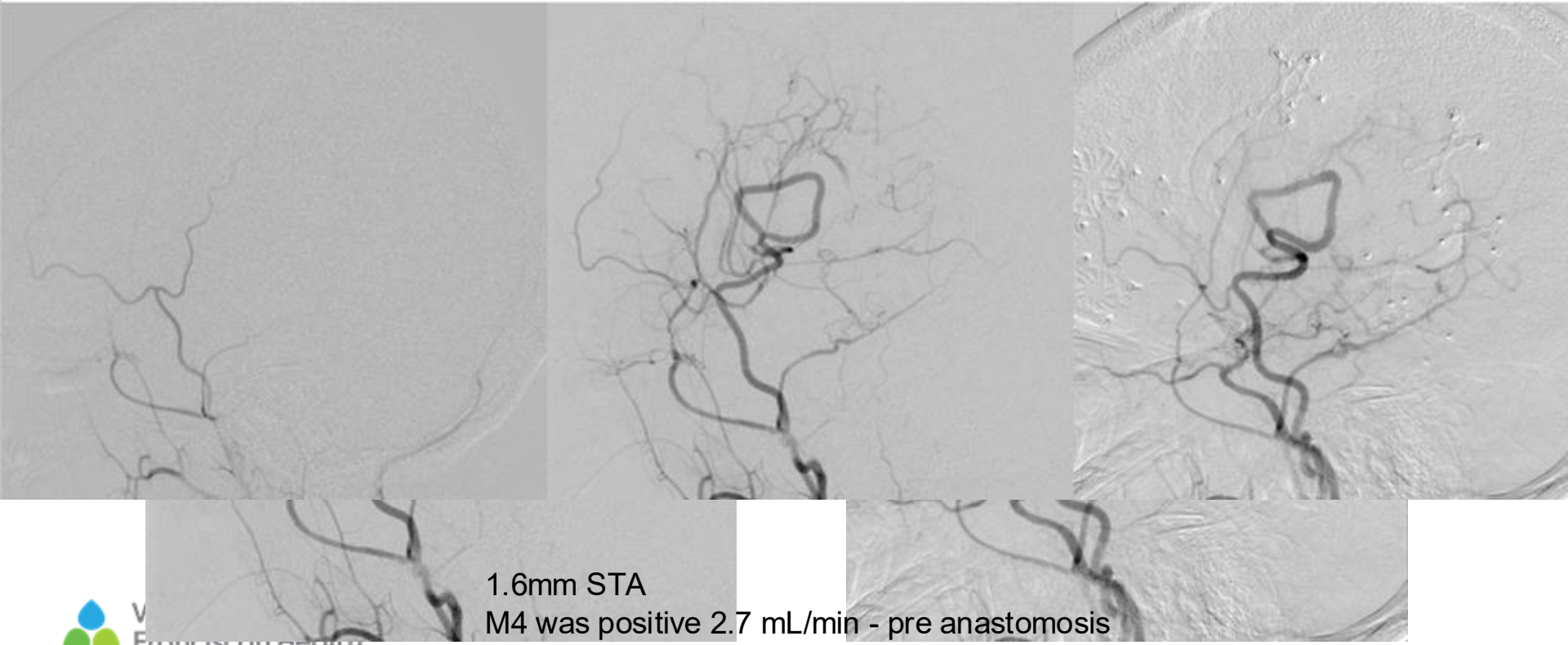
Pre-Op STA

6mo STA

3year STA



1.6mm STA
M4 was positive 2.7 mL/min - pre anastomosis
Post anastomosis  15.4 mL/min post anastomosis

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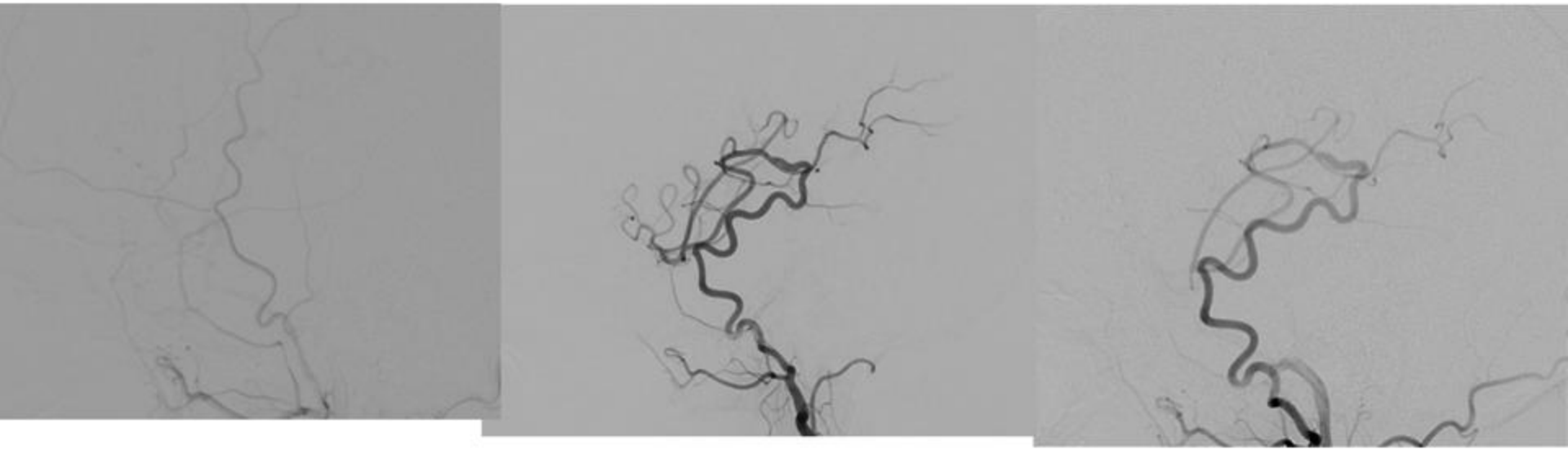
Pre-Op STA

6mo STA

3year STA



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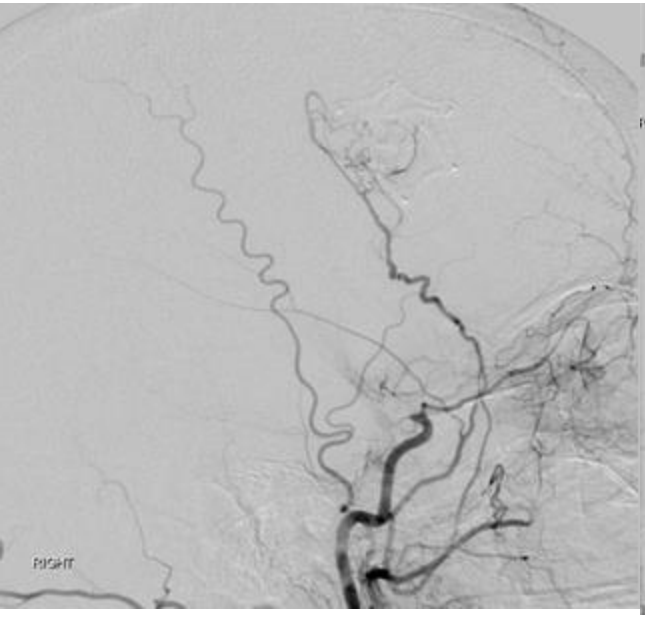
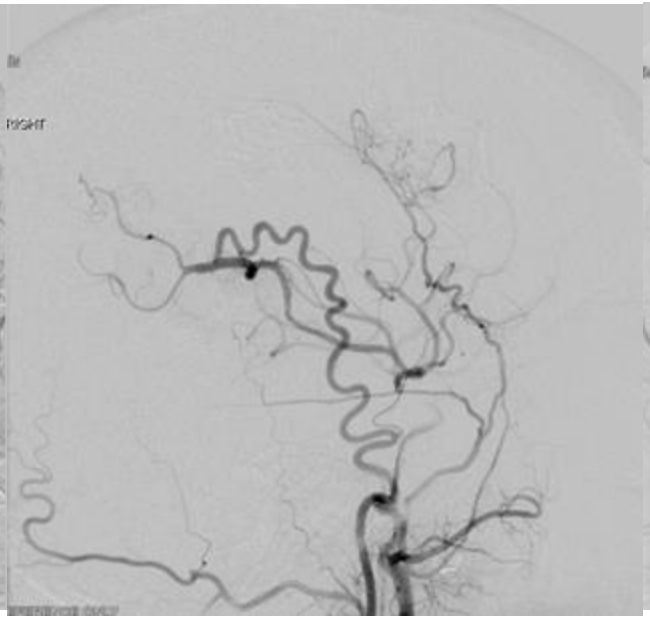
STA 1.4mm distal end
M4 was positive 1.6 mL/minute
Post Anastomosis: 40.8 mL/minute,

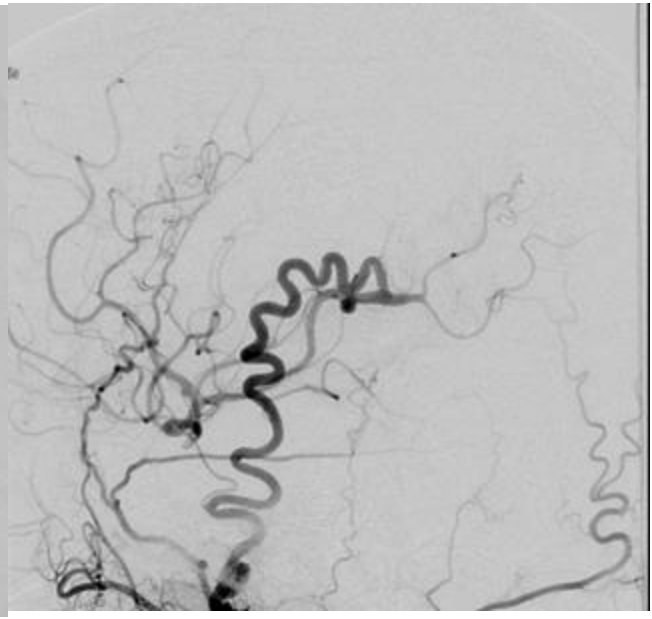
Pre-Op STA

6mo STA

3year STA







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1.8mm STA, Cut flow is 23.7 ml/min
M4 Flow: -5.8 ml/min
distal superficial temporal artery was positive 18.5 mL/min.

# Intraoperatively – My Approach

- Do the simplest direct bypass that decreases occlusion time
  - STA to M4 E-S
- Normocapnia
- MAP in the high normal range of the patient
- Anesthesia EEG monitoring
- Burst suppression for occlusion

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# In Summary – My Approach

- Earlier bypass with the right patient selection to reduce peri-operative complication risk
- STA-M4 direct and indirect bypass to allow for immediate blow flow augmentation, with the lowest introduction of ischemic time and peri-operative risk
- Aggressive peri-operative and post-operative management of blood pressure to reduce prevalence of transient neurologic deficits and delayed ischemia

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# Thank you

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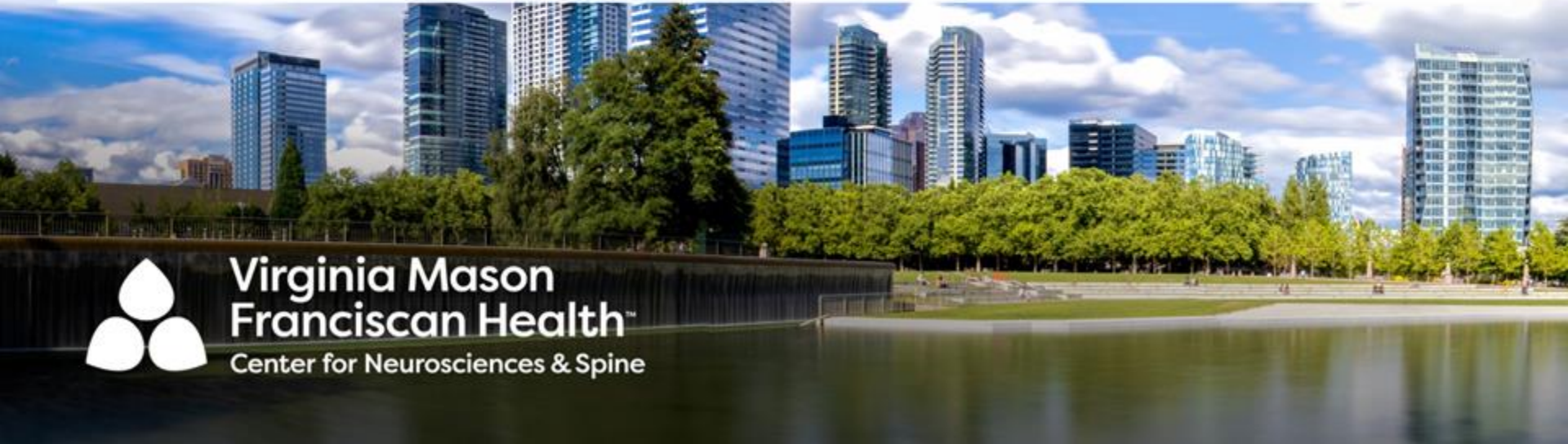
# Question & Answer

Audience - please raise hand for roaming mic

Virtual Attendees - please click on Q&A button



# Stroke Care Beyond the Acute Event

Virginia Mason Franciscan Health™

Center for Neurosciences & Spine

# Anticoagulation/Antiplatelet Indications and Management After Stroke (Ischemic and Hemorrhagic)

Fatima Milfred, MD
Neurohospitalist, Vascular Neurology
5/9/2026

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# No disclosures

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# Objectives

- Review the indications of antiplatelet use for ischemic stroke
- Review the indications of anticoagulation for ischemic stroke
- Timing for anticoagulation after stroke

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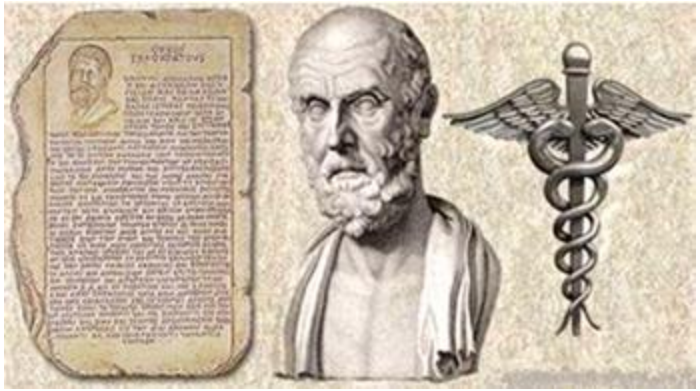
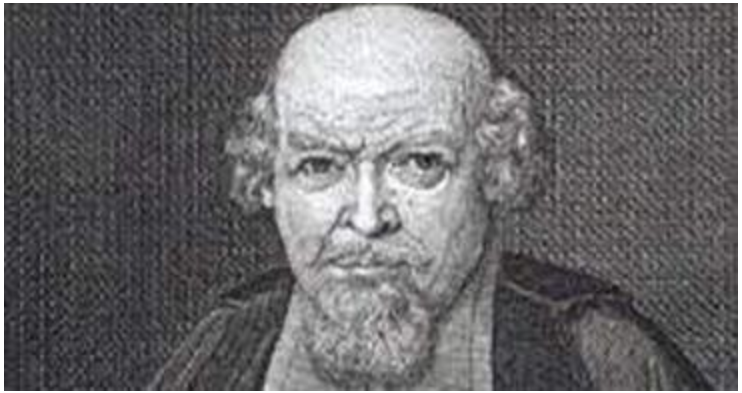
# History of Stroke



- Stroke was first documented by Hippocrates, the “the father of medicine” in the 5th century BC
- He named the condition “apoplexy” in Greek means “struck down by violence”



- In 1658, Dr. Johann Jacob Wepfer pathologist and pharmacologist performed post-mortem examinations and these patients' death was related to lack of blood supply to the brain (artery blockage by blood clots or bleeding in the brain)

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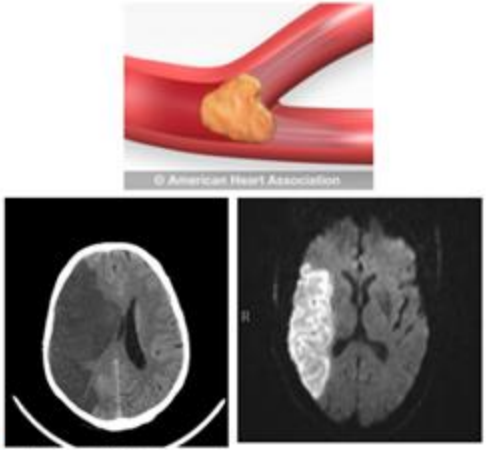
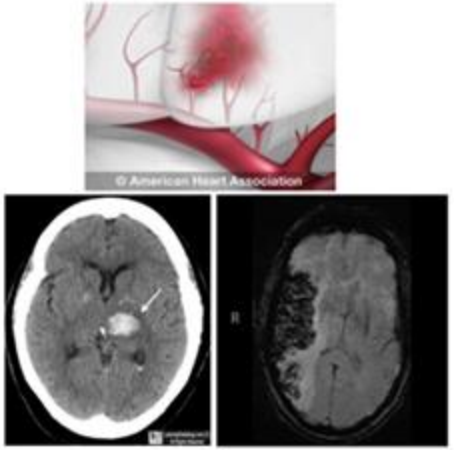
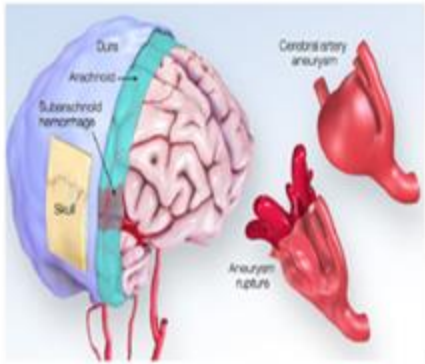
# Stroke

Ischemic




Hemorrhagic

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# Elements Associated with Elevated Stroke Risk

## Adverse Social Determinants of Health

- Poor Access to Care
- Socioeconomic Disadvantage
- Lack of Social and Community Support
- Poor Access to Education
- Racism and Discrimination

## Inadequate Management of Common Risk Factors

- Undiagnosed Risk Factors
- Untreated Risk Factors
- Best Practices Not Followed
- Lack of Shared Decision Making
- Health System Barriers
- De-Emphasis of Lifestyle Factors *(Life's Essential 8)*

## Commonly Unrecognized Risk-enhancing Factors

- Lipoprotein(a)
- Thrombophilias
- Endometriosis
- Early Menopause
- Complications of Pregnancy

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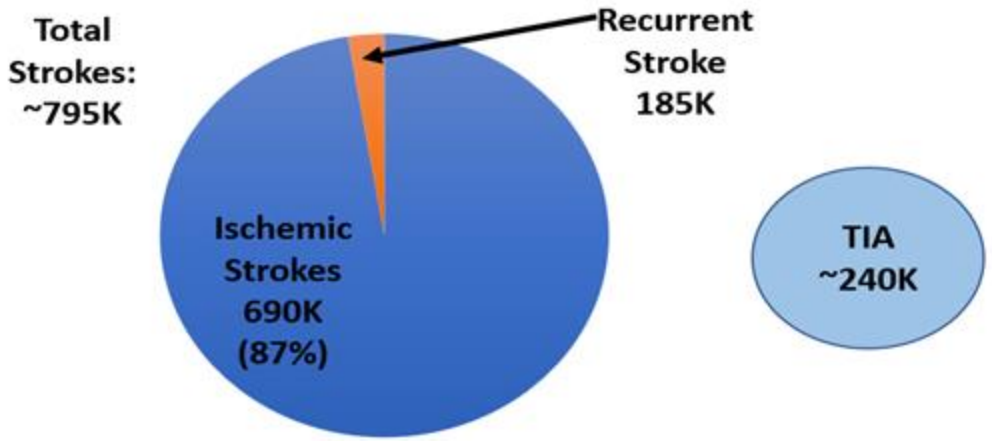
# Overview

## Annual Ischemic Stroke and TIA Incidence




## Pillars of Prevention

- Blood Pressure Control
- Diet
- Physical Activity
- Smoking Cessation

Guiding Principle: Secondary prevention for Stroke and TIA patients is identical!

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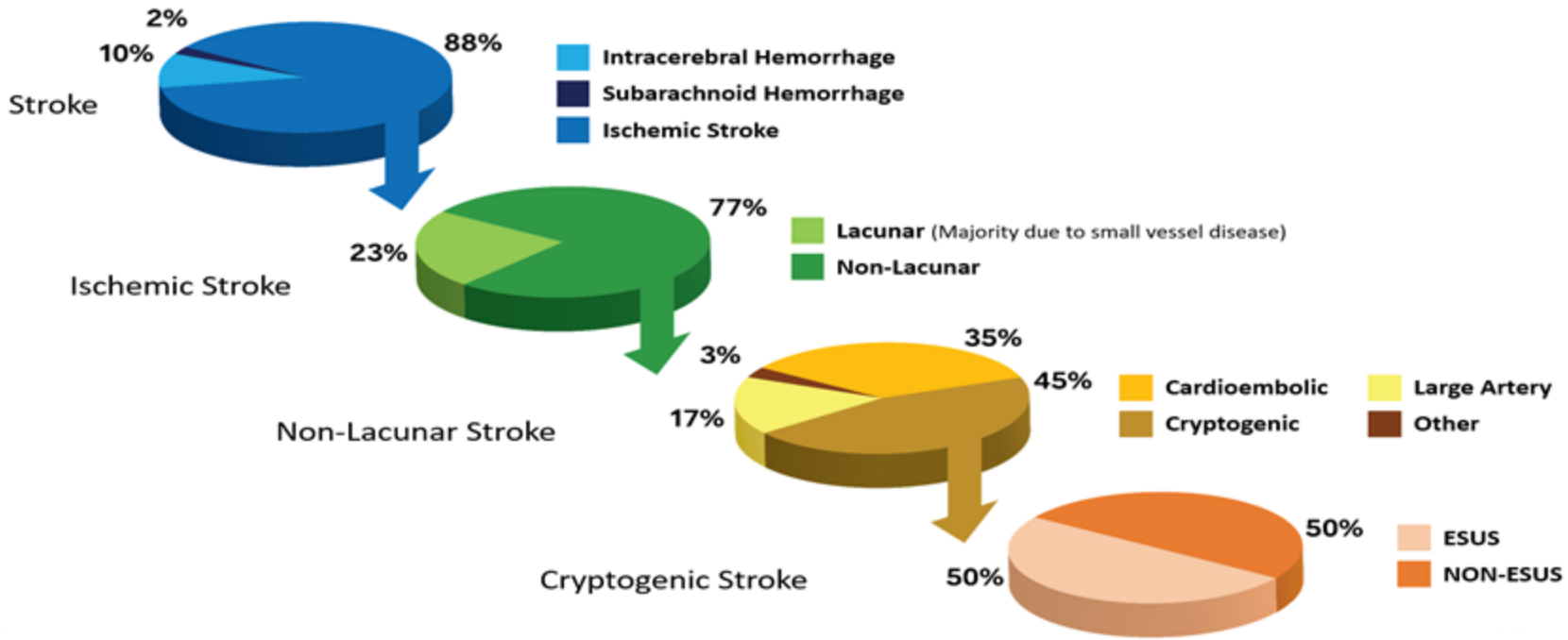
**Abbreviation:** TIA indicates transient ischemic attack.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Conceptual Representation of Strokes and Ischemic Strokes Subtype

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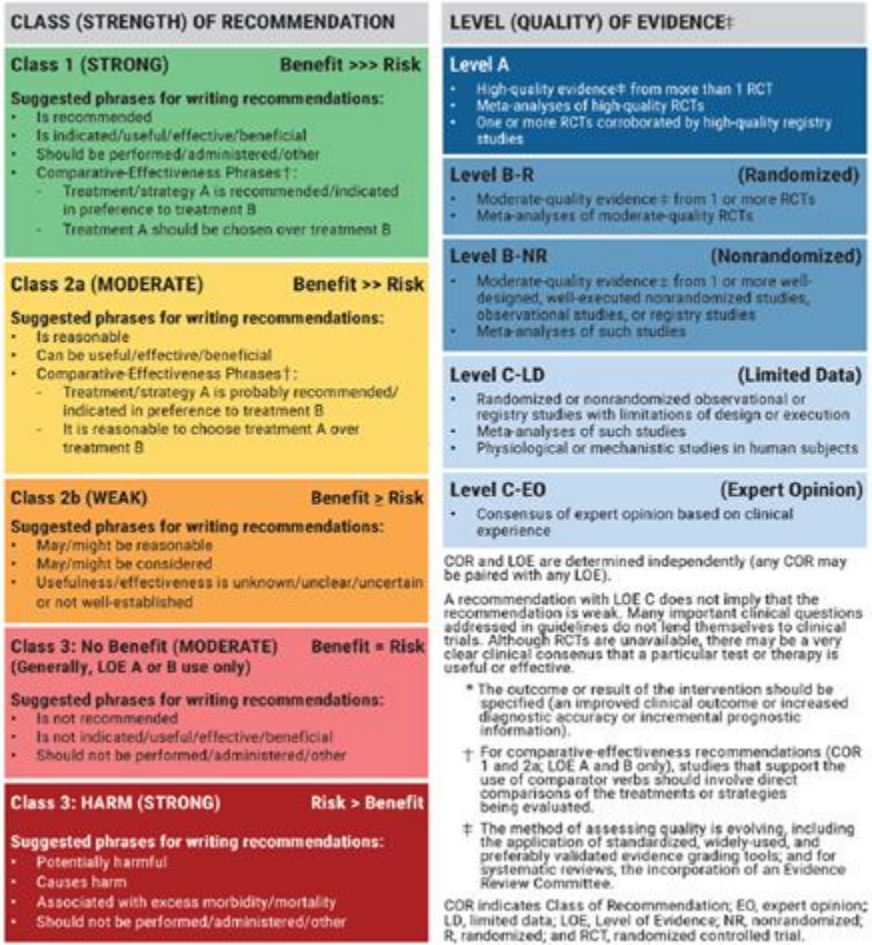
# Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care



**CLASS (STRENGTH) OF RECOMMENDATION**

**Class 1 (STRONG)** — **Benefit >>> Risk**

**Suggested phrases for writing recommendations:**
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

**Class 2a (MODERATE)** — **Benefit >> Risk**

**Suggested phrases for writing recommendations:**
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

**Class 2b (WEAK)** — **Benefit ≥ Risk**

**Suggested phrases for writing recommendations:**
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

**Class 3: No Benefit (MODERATE)** — **Benefit = Risk**
**(Generally, LOE A or B use only)**

**Suggested phrases for writing recommendations:**
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

**Class 3: HARM (STRONG)** — **Risk > Benefit**

**Suggested phrases for writing recommendations:**
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

**LEVEL (QUALITY) OF EVIDENCE‡**

**Level A**
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

**Level B-R (Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

**Level B-NR (Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

**Level C-LD (Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

**Level C-EO (Expert Opinion)**
- Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

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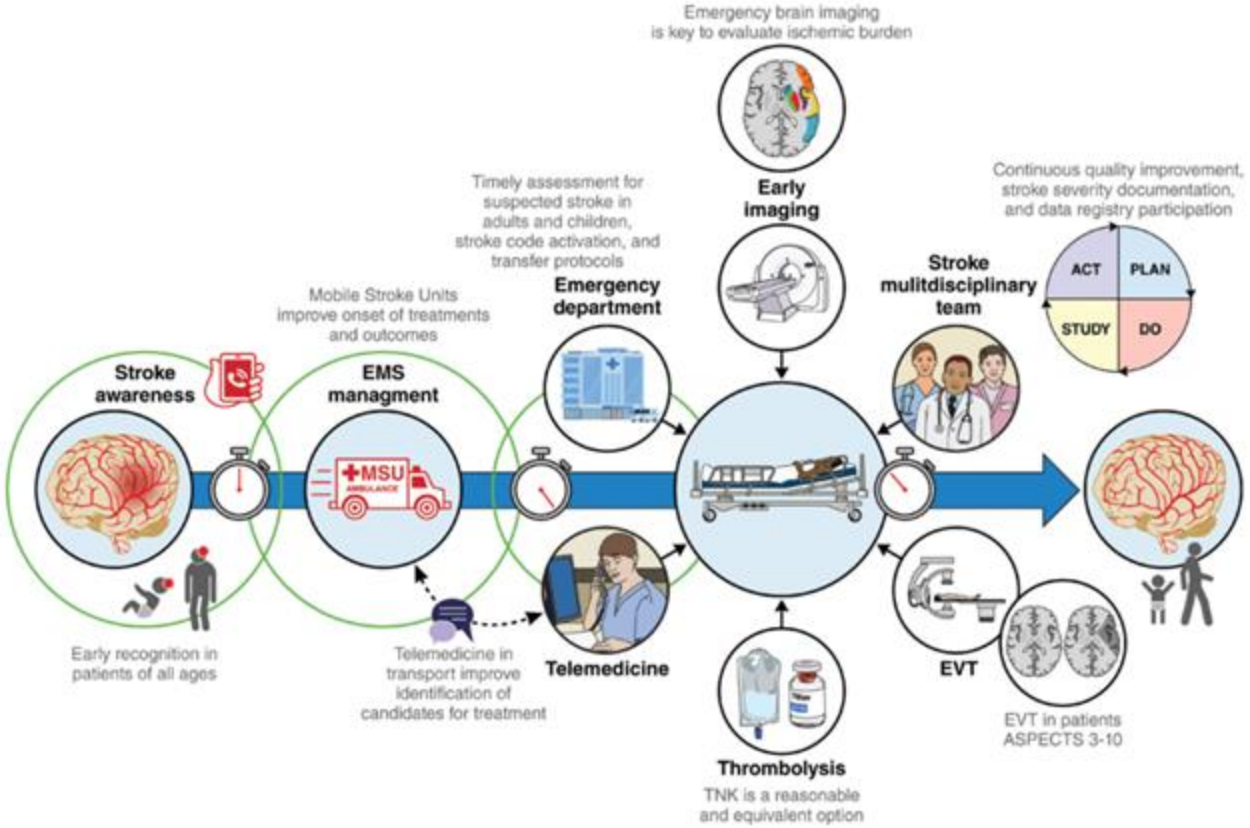
Prabhakaran, S., et al. 2026 AHA/ASA Guideline for the Early Management of Patients with AIS. *Stroke*

# Journey of a patient with AIS

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**Abbreviations:** AIS indicates acute ischemic stroke; EMS, emergency medical services; EVT, endovascular thrombectomy; MSU, mobile stroke unit; and TNK, tenecteplase

Prabhakaran, S., et al. 2026 AHA/ASA Guideline for the Early Management of Patients

# Stroke severity assessment

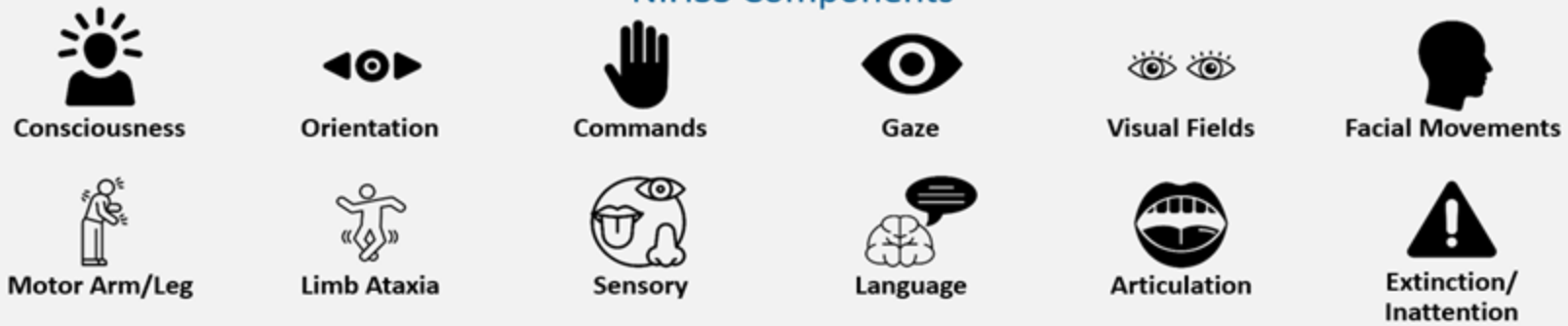
| COR | RECOMMENDATIONS |
|---|---|
| 1 | In patients with suspected AIS, the use of a stroke severity rating scale, preferably the **NIHSS,** is recommended for measuring clinical deficits at baseline and after reperfusion therapies. |

## Why NIHSS?

- Rapid, reproducible assessment
- Quantifies neurological deficit
- Facilitates communication across teams
- Identifies candidates for IV thrombolysis & thrombectomy
- Tracks change over time
- Predicts complication risk (e.g. ICH)

| Score | Stroke Severity |
|---|---|
| 0 | No stroke symptoms |
| 1-4 | Minor stroke |
| 5-15 | Moderate stroke |
| 16-20 | Moderate to severe stroke |
| 21-42 | Severe stroke |

## NIHSS Components

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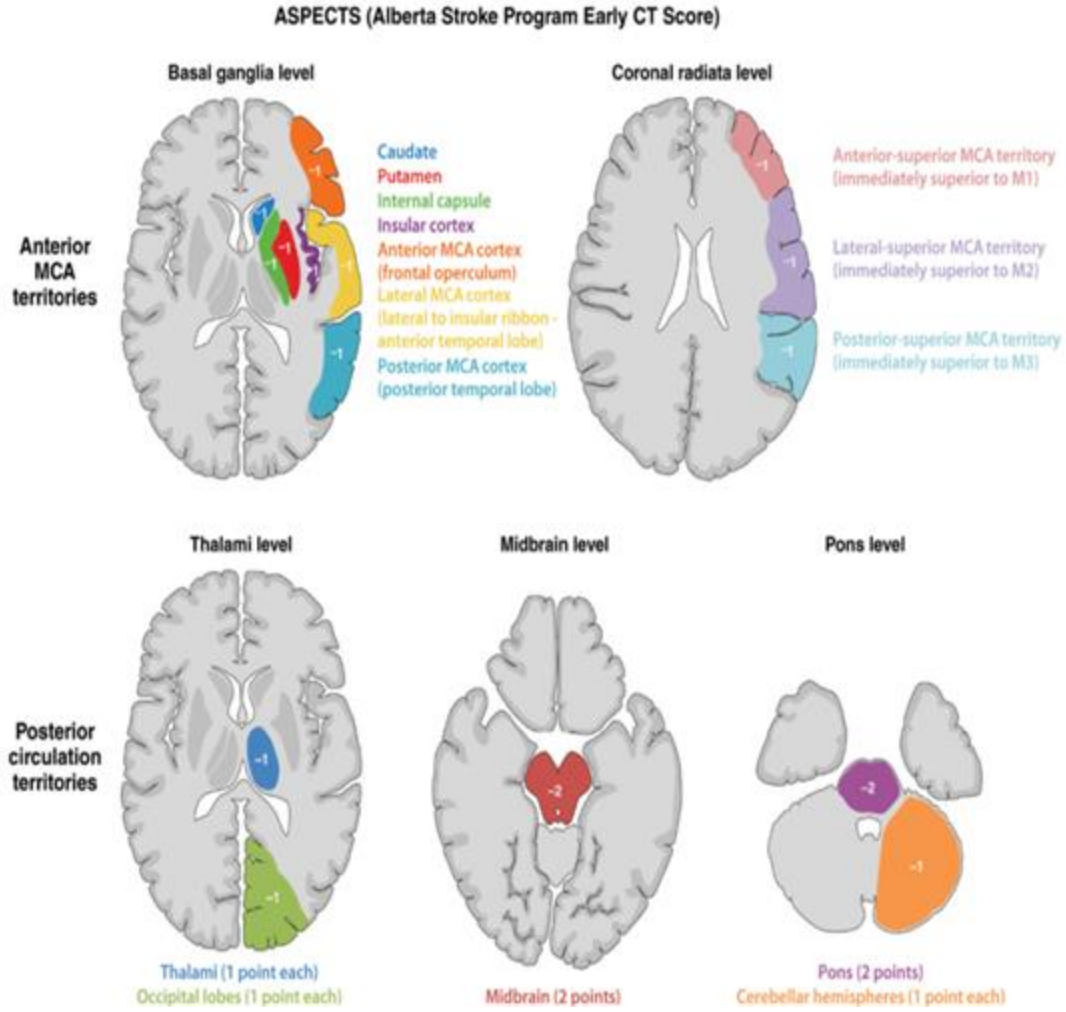
**Abbreviations:** ICH indicates intracerebral hemorrhage; and NIHSS, National Institutes of Health Stroke Scale.

Prabhakaran, S., et al. 2026 AHA/ASA Guideline for the Early Management of Patients with AIS. *Stroke.*

# ASPECTS: Alberta Stroke Program Early CT Score




**Abbreviations:** CT indicates computed tomography; and MC
artery.

Prabhakaran, S., et al. 2026 AHA/ASA Guideline for the Early Ma
Patients with AIS. *Stroke*.

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# Management

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# Antiplatelet Therapy

# Antiplatelet Treatment

| COR | RECOMMENDATIONS |
|---|---|
| 2a | In patients with minor (NIHSS score ≤5) noncardioembolic AIS or high-risk TIA (ABCD$^2$ score ≥4) within 24 to 72 hours from stroke onset, or NIHSS score of 4 to 5 within 24 hours from onset, who did not receive IVT, with presumed atherosclerotic cause (≥50% stenosis of intracranial or extracranial stenosis that was likely to have accounted for clinical presentation or acute new infarctions on imaging of presumed large artery atherosclerosis origin), DAPT (clopidogrel and aspirin) for 21 days followed by SAPT is reasonable to reduce the 90-day risk of recurrent stroke. |
| 3: No Benefit | In patients with AIS treated with IVT within 3 hours after symptom onset, adjunctive treatment with IV eptifibatide is not recommended to reduce disability at 3 months. |

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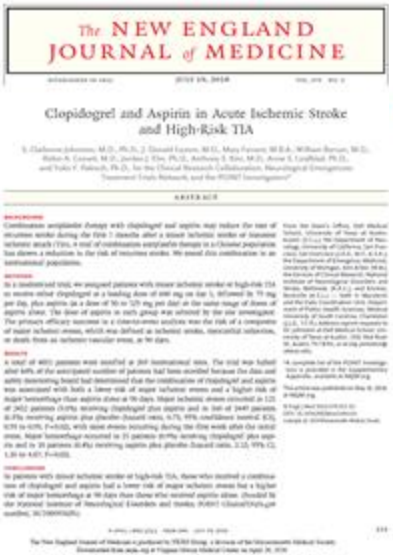
**Abbreviations:** AIS indicates acute ischemic stroke; DAPT, dual antiplatelet therapy; IVT, intravenous thrombolytics; NIHSS, National Institutes of Health Stroke Scale; SAPT, single antiplatelet therapy; and TIA, transient ischemic attack

Prabhakaran, S., et al. 2026 AHA/ASA Guideline for the Early Management of Patients with AIS. *Stroke*.

# DAPT for minor noncardioembolic AIS and TIA.

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack



The NEW ENGLAND JOURNAL of MEDICINE

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA

The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

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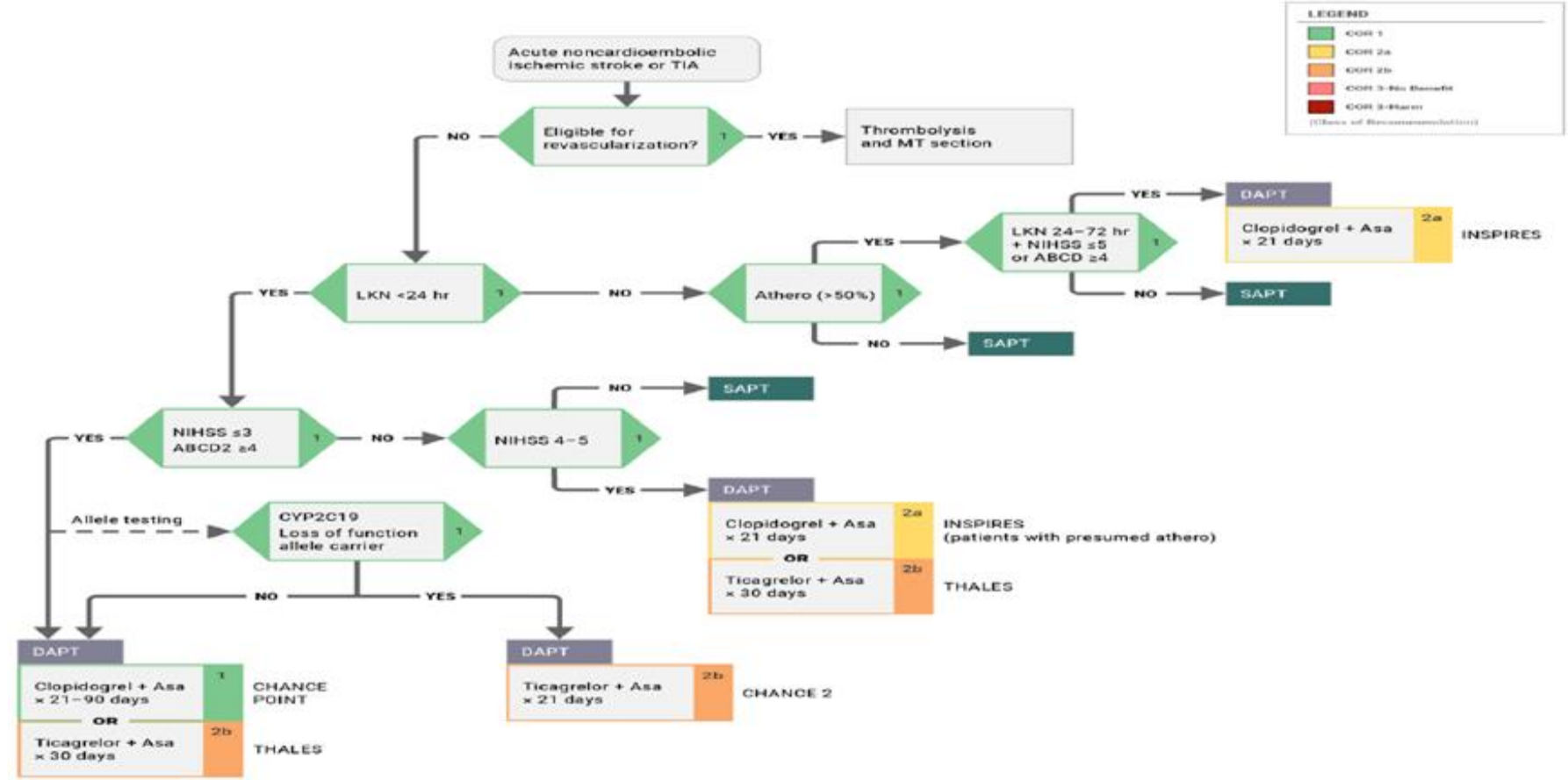


**Abbreviations:** ABCD2 indicates Age, Blood Pressure, Clinical Features, Duration, and Diabetes (TIA risk score); AIS, acute ischemic stroke; Asa, aspirin; Athero, atherosclerosis; CHANCE, Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events; CHANCE 2, Clopidogrel versus Ticagrelor in High-risk Patients with Acute Nondisabling Cerebrovascular Events; DAPT, Dual Antiplatelet Therapy; INSPIRES, Innovative Stroke Prevention and Intervention Research Study; LKN, last known normal; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; SAPT, Single Antiplatelet Therapy; THALES, Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death; and TIA, transient ischemic attack.

Prabhakaran, S., et al. 2026 AHA/ASA Guideline for the Early Management of Patients with AIS. *Stroke*.

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# Management of Intracranial Large Artery Atherosclerosis

| COR | RECOMMENDATIONS |
|---|---|
| | **Antithrombotic Therapy** |
| 1 | 1. In patients with a stroke or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg/d is recommended in preference to warfarin to reduce the risk of recurrent ischemic stroke and vascular death. |
| 2a | 2. In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for up to 90 days is reasonable to further reduce recurrent stroke risk. |
| 2b | 3. In patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery, the addition of ticagrelor 90 mg twice a day to aspirin for up to 30 days might be considered to further reduce recurrent stroke risk. |
| 2b | 4. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the addition of cilostazol 200 mg/day to aspirin or clopidogrel might be considered to reduce recurrent stroke risk. |
| 2b | 5. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, ticagrelor alone, or cilostazol alone for secondary stroke prevention is not well established. |

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**Abbreviations:** TIA indicates transient ischemic attack.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke.*

# Management of Extracranial Large Artery Atherosclerosis

| COR | RECOMMENDATIONS |
|---|---|
| 1 | 1. In patients with a TIA or nondisabling ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis, carotid endarterectomy (CEA) is recommended to reduce the risk of future stroke, provided that perioperative morbidity and mortality risk is estimated to be <6%. |
| 1 | 2. In patients with ischemic stroke or TIA and symptomatic extracranial carotid stenosis who are scheduled for carotid artery stenting (CAS) or CEA, procedures should be performed by operators with established periprocedural stroke and mortality rates of <6% to reduce the risk of surgical adverse events. |
| 1 | 3. In patients with carotid artery stenosis and a TIA or stroke, intensive medical therapy, with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension, is recommended to reduce stroke risk. |
| 1 | 4. In patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging, CEA is recommended to reduce the risk of future stroke, depending on patient-specific factors such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%. |
| 2a | 5. In patients ≥70 years of age with stroke or TIA in whom carotid revascularization is being considered, it is reasonable to select CEA over CAS to reduce the periprocedural stroke rate. |
| 2a | 6. In patients in whom revascularization is planned within 1 week of the index stroke, it is reasonable to choose CEA over CAS to reduce the periprocedural stroke rate. |

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**Abbreviations:** CAS indicates carotid artery stenting; CEA, carotid endarterectomy; and TIA, transient ischemic attack.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke.*

# Cont…Management of Extracranial Large Artery Atherosclerosis

| COR | RECOMMENDATIONS |
|---|---|
| 2a | 7. In patients with TIA or nondisabling stroke, when revascularization is indicated, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery to increase the likelihood of stroke free outcome. |
| 2a | 8. In patients with symptomatic severe stenosis (≥70%) in whom anatomic or medical conditions are present that increase the risk for surgery (such as radiation-induced stenosis or restenosis after CEA) it is reasonable to choose CAS to reduce the periprocedural complication rate. |
| 2b | 9. In symptomatic patients at average or low risk of complications associated with endovascular intervention, when the internal carotid artery stenosis is ≥70% by noninvasive imaging or >50% by catheter-based imaging and the anticipated rate of periprocedural stroke or death is >6 %, CAS may be considered as an alternative to CEA for stroke prevention, particularly in patients with significant cardiovascular comorbidities predisposing to cardiovascular complications with endarterectomy. |
| 2b | 10. In patients with a recent stroke or TIA (past 6 months), the usefulness of transcarotid artery revascularization (TCAR) for prevention of recurrent stroke and TIA is uncertain. |
| 3: No Benefit | 11. In patients with recent TIA or ischemic stroke and when the degree of stenosis is <50%, revascularization with CEA or CAS to reduce the risk of future stroke is not recommended. |
| 3: No Benefit | 12. In patients with a recent (within 120 days) TIA or ischemic stroke ipsilateral to atherosclerotic stenosis or occlusion of the middle cerebral or carotid artery, extracranial intracranial bypass surgery is not recommended. |

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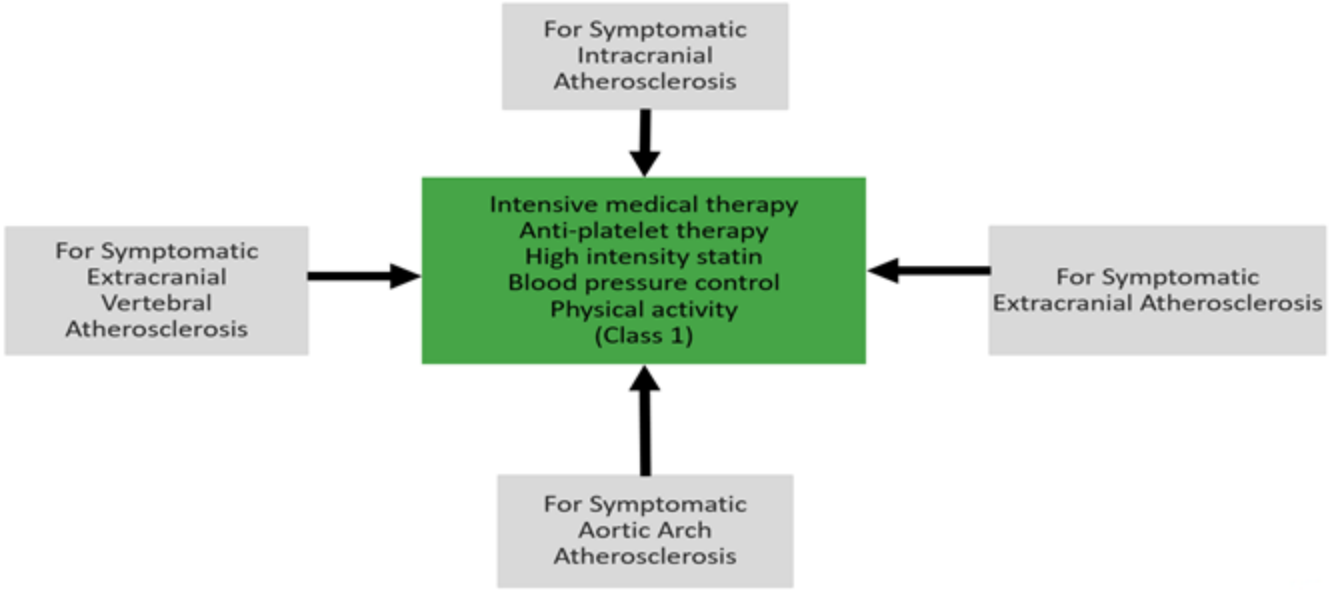
**Abbreviations:** CAS indicates carotid artery stenting; CEA, carotid endarterectomy; and TIA, transient ischemic attack.



Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Overall Stroke Risk Reduction Strategies

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Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Anticoagulation

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# Reasons for prolonged anticoagulation after acute ischemic stroke

- Deep venous thrombosis
- Pulmonary embolism
- Left ventricular thrombus/Atrial thrombus
- Dissection with free floating thrombus
- Atrial flutter
- **Atrial fibrillation**

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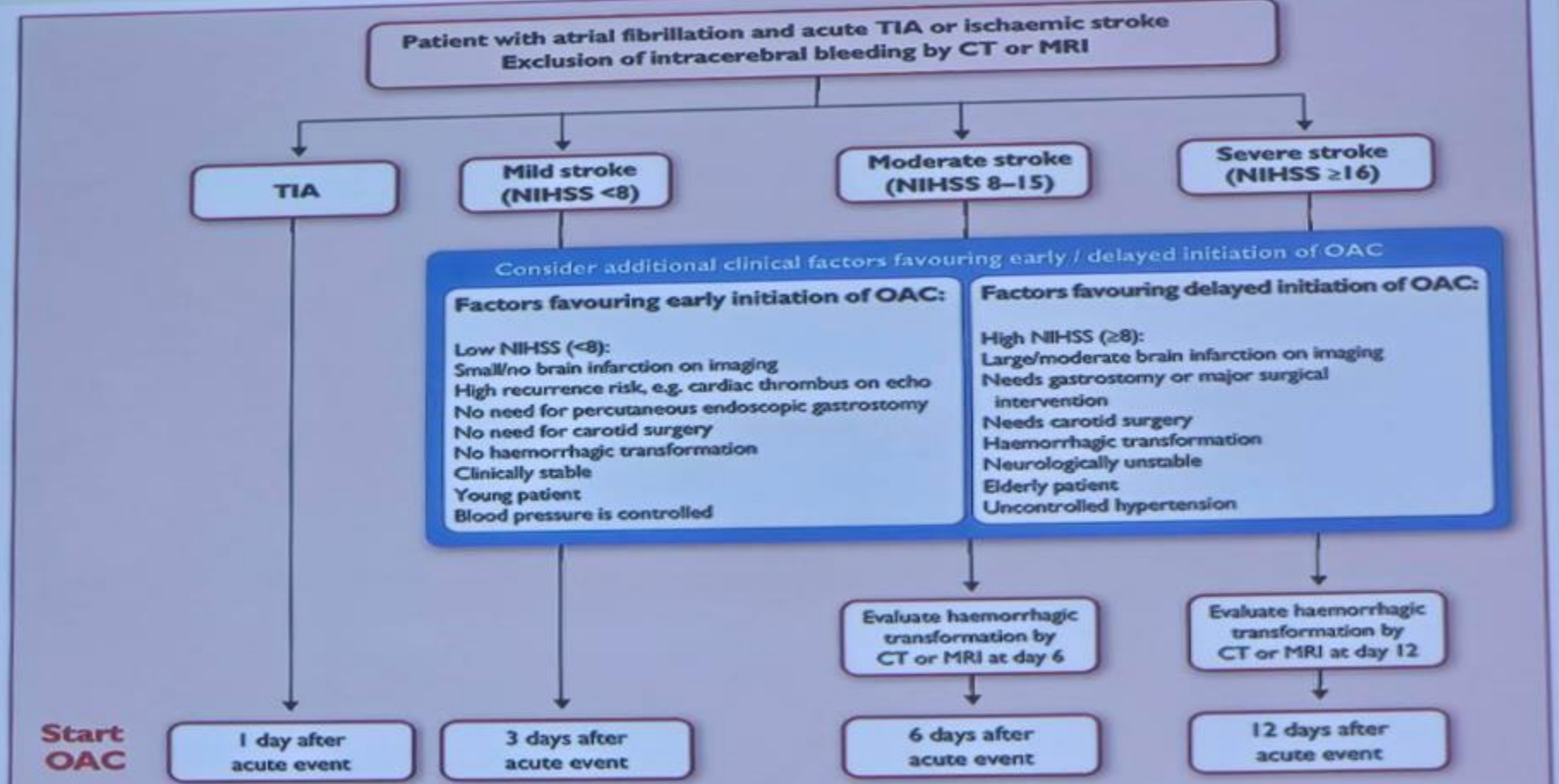
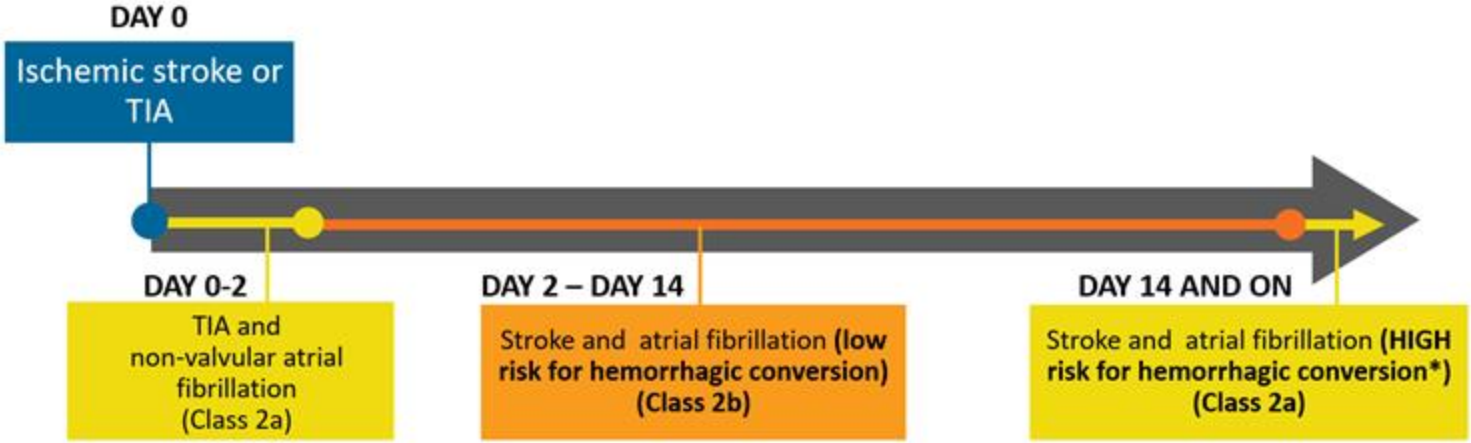



AF = atrial fibrillation; CT = computed tomography; NIHSS = National Institutes of Health stroke severity scale (available at http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf); OAC = oral anticoagulation; TIA = transient ischaemic attack

**Figure 9** Initiation or continuation of anticoagulation in atrial fibrillation patients after a stroke or transient ischaemic attack. This approach is based on consensus rather than prospective data.

# Timing of Anticoagulation after Stroke or TIA




*Large cerebral infarcts (NIHSS>15, lesions involving complete arterial territory or more than one arterial territory), evidence of hemorrhage on neuroimaging, or other features which place patient at increased risk of hemorrhagic conversion following acute stroke.

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**Abbreviation:** TIA indicates transient ischemic attack.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

**Recommendations for AF**

Referenced studies that support recommendations are summarized in online Data Supplement 32.

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with nonvalvular AF and stroke or TIA, oral anticoagulation (eg, apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) is recommended to reduce the risk of recurrent stroke.[419–426] |
| 1 | B-R | 2. In patients with AF and stroke or TIA, oral anticoagulation is indicated to reduce the risk of recurrent stroke regardless of whether the AF pattern is paroxysmal, persistent, or permanent.[427] |
| 1 | B-R | 3. In patients with stroke or TIA and AF who do not have moderate to severe mitral stenosis or a mechanical heart valve, apixaban, dabigatran, edoxaban, or rivaroxaban is recommended in preference to warfarin to reduce the risk of recurrent stroke.[419–426] |
| 1 | B-NR | 4. In patients with atrial flutter and stroke or TIA, anticoagulant therapy similar to that in AF is indicated to reduce the risk of recurrent stroke.[427] |
| 1 | C-EO | 5. In patients with AF and stroke or TIA, without moderate to severe mitral stenosis or a mechanical heart valve, who are unable to maintain a therapeutic INR level with warfarin, use of dabigatran, rivaroxaban, apixaban, or edoxaban is recommended to reduce the risk of recurrent stroke. |
| 2a | B-NR | 6. In patients with stroke at high risk of hemorrhagic conversion in the setting of AF, it is reasonable to delay initiation of oral anticoagulation beyond 14 days to reduce the risk of ICH.[428–431] |
| 2a | C-EO | 7. In patients with TIA in the setting of nonvalvular AF, it is reasonable to initiate anticoagulation immediately after the index event to reduce the risk of recurrent stroke. |
| 2b | B-R | 8. In patients with stroke or TIA in the setting of nonvalvular AF who have contraindications for lifelong anticoagulation but can tolerate at least 45 days, it may be reasonable to consider percutaneous closure of the left atrial appendage with the Watchman device to reduce the chance of recurrent stroke and bleeding.[432–436] |
| 2b | B-NR | 9. In patients with stroke at low risk for hemorrhagic conversion in the setting of AF, it may be reasonable to initiate anticoagulation 2 to 14 days after the index event to reduce the risk of recurrent stroke.[428,429,437] |
| 2b | B-NR | 10. In patients with AF and stroke or TIA who have end-stage renal disease or are on dialysis, it may be reasonable to use warfarin or apixaban (dose adjusted if indicated) for anticoagulation to reduce the chance of recurrent stroke.[438] |

# Where did these recommendations come from?

- Recurrent ischemic stroke risk is 0.5% per day to 1.3% per day in the first 14 days
- The rate of symptomatic hemorrhagic transformation after stroke ranges substantially
  - 6% to 21% of patients who receive acute thrombolysis
  - 1% to 7% who do not receive acute thrombolysis

ABSTRACT | Originally Published 1 September 1983 |

**Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study.**

R G Hart, B M Coull, and D Hart | AUTHOR INFO & AFFILIATIONS

Stroke • Volume 14, Number 5 • https://doi.org/10.1161/01.STR.14.5.688

RESEARCH ARTICLE | Originally Published 1 July 1999 |

**Hemorrhagic Transformation in Acute Ischemic Stroke : The MAST-E Study**

Assia Jaillard, Catherine Cornu, Anne Durieux, Thierry Moulin, Florent Boutitie, Kennedy R. Lees, Marc Hommel, and on behalf of the MAST-E Group | AUTHOR INFO & AFFILIATIONS

Stroke • Volume 30, Number 7 • https://doi.org/10.1161/01.STR.30.7.1326

| $CHA_2DS_2$-VASc score | | HAS-BLED score | |
|---|---|---|---|
| Category | Thromboembolic event rate/year | Category | Bleeding event rate/year |
| 0 | 0 | 0 | 0.59–1.13 |
| 1 | 0.6–1.3 | 1 | 1.02–1.51 |
| 2 | 1.6–2.2 | 2 | 1.88–3.20 |
| 3 | 3.2–3.9 | 3 | 3.74–19.51 |
| 4 | 1.9–4.0 | 4 | 8.70–21.43 |
| 5 | 3.2–6.7 | | |
| 6 | 3.6–9.8 | | |
| 7 | 8.0–9.6 | | |
| 8 | 6.7–11.1 | | |
| 9 | >15.2 | | |

"The optimal timing of initiating oral anticoagulation should be individualized for each patient's risk of hemorrhage versus recurrent embolism"


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Circulation

ORIGINAL RESEARCH ARTICLE

# Early Versus Delayed Non–Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study

Jonas Oldgren, MD, PhD*; Sigrid Åsberg, MD, PhD*; Ziad Hijazi, MD, PhD; Per Wester, MD, PhD; Maria Bertilsson, MSc; Bo Norrving, MD, PhD; for the National TIMING Collaborators

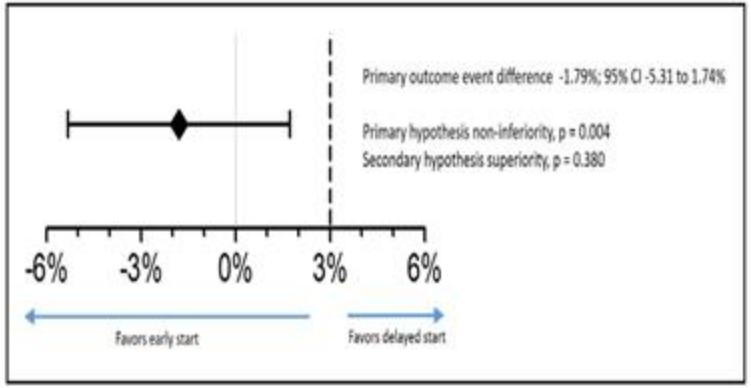



**Figure 2. Risk difference in the primary composite outcome for early vs delayed initiation of NOAC at 90 days.**
Primary outcome was a composite of ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality. Primary hypothesis testing for noninferiority at an absolute 3% margin, and secondary hypothesis testing for superiority. NOAC indicates non–vitamin K antagonist oral anticoagulant.

# Optimal timing of anticoagulation after acute ischaemic stroke with atrial fibrillation (OPTIMAS): a multicentre, blinded-endpoint, phase 4, randomised controlled trial

David J Werring, Hakim-Moulay Dehbi, Norin Ahmed, Liz Arram, Jonathan G Best, Maryam Balogun, Kate Bennett, Ekaterina Bordea, Emilia Caverly, Marisa Chau, Hannah Cohen, Mairead Cullen, Caroline J Doré, Stefan T Engelter, Robert Fenner, Gary A Ford, Aneet Gill, Rachael Hunter, Martin James, Archana Jayanthi, Gregory Y H Lip, Sue Massingham, Macey L Murray, Iwona Mazurczak, Philip S Nash, Amalia Ndoutoumou, Bo Norrving, Hannah Sims, Nikola Sprigg, Tishok Vanniyasingam, Nick Freemantle, on behalf of the OPTIMAS investigators*

Lancet 2024; 404: 1731-41

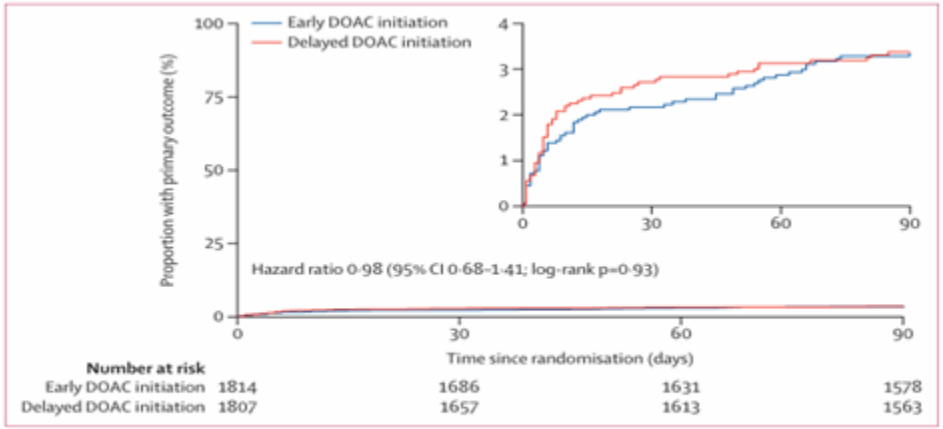
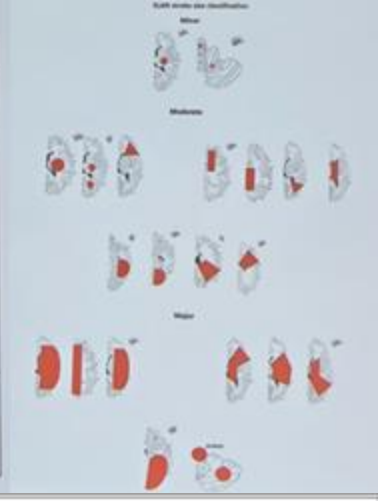



***Figure 2:*** **Time-to-event curves of the primary composite outcome of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days**
Hazard ratio adjusted for stroke severity (National Institutes of Health Stroke Scale score) at randomisation. DOAC=direct oral anticoagulant.

Table S13. Stroke Size Classification.

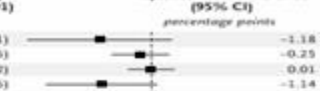
| Minor | Moderate | Major |
|---|---|---|
| Lesion is ≤ 1.5 cm in anterior or posterior circulation | Lesion is in a cortical superficial branch of the middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of the posterior cerebral artery, or in a cortical superficial branch of the anterior cerebral artery | Anterior: lesion involves the whole territory of the MCA, posterior cerebral artery, or anterior cerebral artery, in two cortical superficial branches of MCA, in a cortical superficial branch of the MCA associated with the MCA deep branch, or in > 1 artery territory (e.g., MCA associated with anterior cerebral artery territories)<br>Posterior: lesion is ≥ 1.5 cm in the brainstem or cerebellum |
| Caveat: multiple minor tiny spots (embolic shower) = minor stroke | Caveat: two minor lesions = moderate lesion (the sum of the lesions) | Caveat: two moderate lesions = large lesion |

Ischemic stroke size classification is based on recent guidelines.[9]



A

| Outcome within 30 Days | Early-Treatment Group (N=984) | Later-Treatment Group (N=991) | Adjusted Risk Difference (95% CI) |
|---|---|---|---|
| | no. of events (%) | | percentage points |
| Primary-outcome event | 29 (2.9) | 41 (4.1) | −1.18 (−2.84 to 0.47) |
| Major extracranial bleeding | 3 (0.3) | 5 (0.5) | −0.25 (−0.90 to 0.41) |
| Symptomatic intracranial hemorrhage | 2 (0.2) | 2 (0.2) | 0.01 (−0.52 to 0.53) |
| Recurrent ischemic stroke | 14 (1.4) | 25 (2.5) | −1.14 (−2.41 to 0.13) |
| Systemic embolism | 4 (0.4) | 9 (0.9) | −0.55 (−1.34 to 0.23) |
| Death from vascular cause | 11 (1.1) | 10 (1.0) | 0.13 (−0.84 to 1.09) |




B

| Outcome within 90 Days | Early-Treatment Group (N=968) | Later-Treatment Group (N=965) | Adjusted Risk Difference (95% CI) |
|---|---|---|---|
| | no. of events (%) | | percentage points |
| Primary-outcome event | 36 (3.7) | 54 (5.6) | −1.92 (−3.82 to −0.02) |
| Major extracranial bleeding | 3 (0.3) | 8 (0.8) | −0.61 (−1.37 to 0.14) |
| Symptomatic intracranial hemorrhage | 2 (0.2) | 2 (0.2) | 0.00 (−0.54 to 0.53) |
| Recurrent ischemic stroke | 18 (1.9) | 30 (3.1) | −1.29 (−2.72 to 0.13) |
| Systemic embolism | 4 (0.4) | 10 (1.0) | −0.70 (−1.53 to 0.13) |
| Death from vascular cause | 17 (1.8) | 16 (1.7) | 0.07 (−1.13 to 1.27) |


**Figure 2. The Primary Composite Outcome and Its Components at 30 and 90 Days.**
Shown are point estimates (squares) and two-sided 95% confidence intervals (horizontal bars) for the treatment effect, which was defined as a risk difference between the trial groups (early initiation of DOAC minus later initiation of DOAC). The absolute and relative numbers of events in each group are shown. The risk difference is derived from a penalized logistic regression adjusted for stratification factors. The widths of the confidence intervals were not adjusted for multiple comparisons, and the reported confidence intervals should not be used for hypothesis testing.


The NEW ENGLAND JOURNAL of MEDICINE

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# Early versus Later Anticoagulation for Stroke with Atrial Fibrillation


U. Fischer, M. Koga, D. Strbian, M. Branca, S. Abend, S. Trelle, M. Paciaroni, G. Thomalla, P. Michel, K. Nedeltchev, L.H. Bonati, G. Ntaios, T. Gattringer, E.-C. Sandset, P. Kelly, R. Lemmens, P.N. Sylaja, D. Aguiar de Sousa, N.M. Bornstein, Z. Gdovinova, T. Yoshimoto, M. Tiainen, H. Thomas, M. Krishnan, G.C. Shim, C. Gumbinger, J. Vehoff, L. Zhang, K. Matsuzono, E. Kristoffersen, P. Desfontaines, P. Vanacker, A. Alonso, Y. Yakushiji, C. Kulyk, D. Hemelsoet, S. Poli, A. Paiva Nunes, N. Caracciolo, P. Slade, J. Demeestere, A. Salerno, M. Kneihsl, T. Kahles, D. Giudici, K. Tanaka, S. Räty, R. Hidalgo, D.J. Werring, M. Göldlin, M. Arnold, C. Ferrari, S. Beyeler, C. Fung, B.J. Weder, T. Tatlisumak, S. Fenzl, B. Rezny-Kasprzak, A. Hakim, G. Salanti, C. Bassetti, J. Gralla, D.J. Seiffge, T. Horvath, and J. Dawson, for the ELAN Investigators*



## ABSTRACT

### BACKGROUND

The effect of early as compared with later initiation of direct oral anticoagulants (DOACs) in persons with atrial fibrillation who have had an acute ischemic stroke is unclear.

### METHODS

We performed an investigator-initiated, open-label trial at 103 sites in 15 countries. Participants were randomly assigned in a 1:1 ratio to early anticoagulation (within 48 hours after a minor or moderate stroke or on day 6 or 7 after a major stroke) or later anticoagulation (day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke). Assessors were unaware of the trial-group assignments. The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. Secondary outcomes included the components of the composite primary outcome at 30 and 90 days.

### RESULTS

Of 2013 participants (37% with minor stroke, 40% with moderate stroke, and 23% with major stroke), 1006 were assigned to early anticoagulation and 1007 to later anticoagulation. A primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group (risk difference, −1.18 percentage points; 95% confidence interval [CI], −2.84 to 0.47) by 30 days. Recurrent ischemic stroke occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group (odds ratio, 0.57; 95% CI, 0.29 to 1.07) by 30 days and in 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days (odds ratio, 0.60; 95% CI, 0.33 to 1.06). Symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups by 30 days.

### CONCLUSIONS

In this trial, the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days was estimated to range from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early than with later use of DOACs. (Funded by the Swiss National Science Foundation and others; ELAN ClinicalTrials.gov number, NCT03148457.)



The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Fischer can be contacted at urs.fischer@usb.ch or at the Department of Neurology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland.

*A list of the ELAN Investigators is provided in the Supplementary Appendix, available at NEJM.org.



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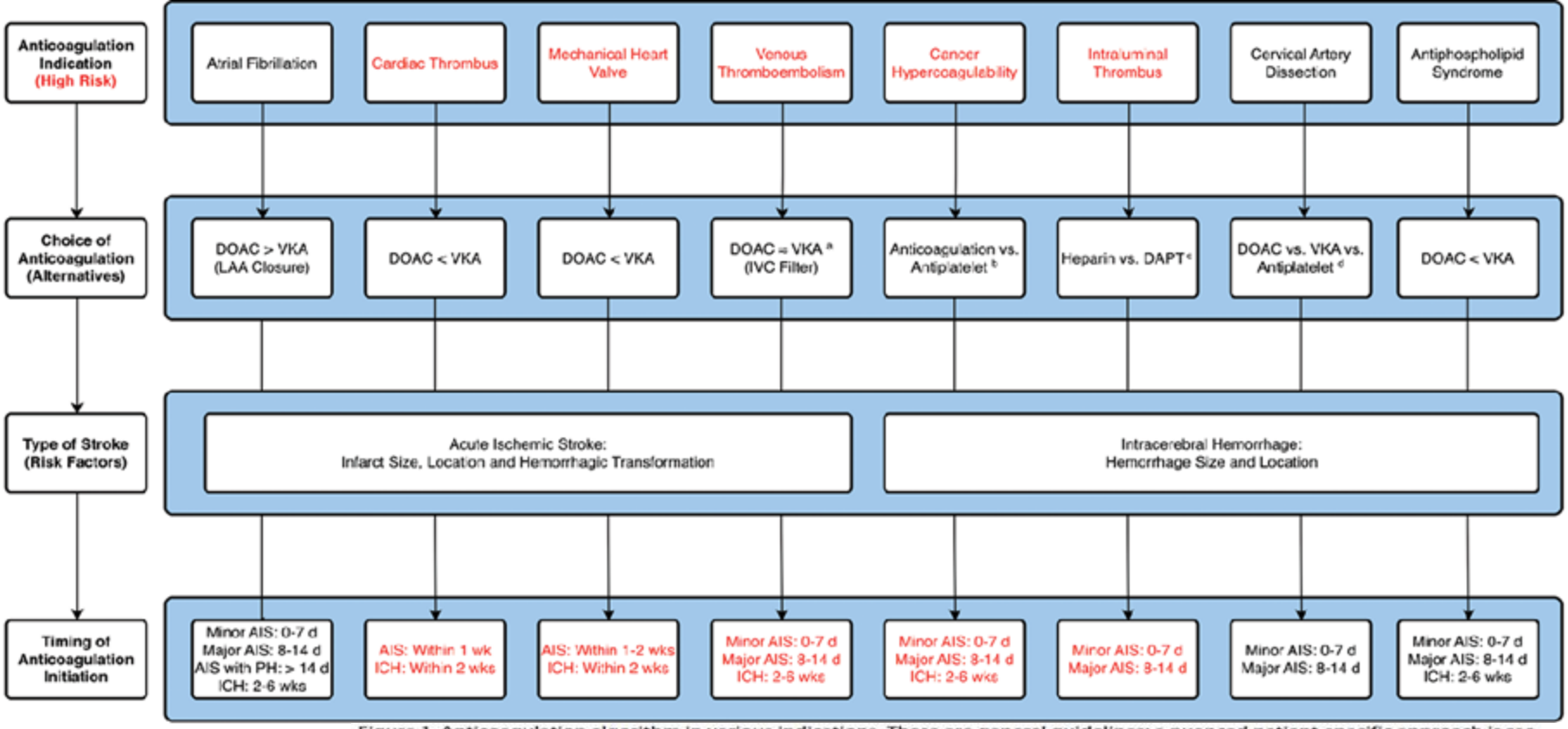


Figure 1. Anticoagulation algorithm in various indications. These are general guidelines; a nuanced patient-specific approach is recommended based on risk of hemorrhagic and early recurrence ischemic events. Abbreviations: AIS, acute ischemic stroke; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; ICH, intracranial hemorrhage; IVC, inferior vena cava; LAA, left atrial appendage; PH, parenchymal hemorrhage; VKA, vitamin K antagonist.

[a] DOACs are noninferior for recurrent venous thromboembolism and associated with a lower risk of major bleeding, including intracranial bleeding, compared to VKA.

[b] Clinical equipoise exists for whether DOAC, VKA, or antiplatelet are superior. There are ongoing clinical trials comparing antithrombotic regimens.

[c] Clinical equipoise exists for whether heparin, mono antiplatelet, or dual antiplatelet are superior.

[d] Clinical equipoise exists for whether DOAC, VKA or antiplatelet are superior. There are ongoing clinical trials comparing antithrombotic regimens.

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Liqi Shu, MD, Mu Ji Hwang, MD, Fransisca Indraswari, MD, and Shadi Yaghi, MD

# Summary

- These studies provided reassurance of starting anticoagulation within 4-6 days after moderate to severe ischemic stroke and as early as 48 hours in mild ischemic stroke in patients with nonvalvular atrial fibrillation without a significant risk of bleeding.
- We're not talking about the patients with HT and patients with high risk of bleeding from any other etiologies

# Anticoagulants

| COR | RECOMMENDATIONS |
|---|---|
| 2a | In carefully selected (eg, milder severity) patients with AIS with atrial fibrillation, a strategy of early oral anticoagulation poststroke is low risk and is reasonable compared with a strategy of delayed anticoagulation, although the efficacy of early anticoagulation for prevention of early recurrent stroke is not established. |
| 2b | In patients with an AIS and ipsilateral, high-grade ICA stenosis, the benefit of urgent anticoagulation is not well established |
| 2b | In patients with AIS with an ipsilateral, nonocclusive, extracranial intraluminal thrombus, the safety and efficacy of short-term anticoagulation are not well established. |
| 2b | In patients with AIS who experience HT, initiation or continuation of anticoagulation may be considered depending on the specific clinical scenario and underlying indication. |
| 3 No Benefit | In patients with AIS, the use of argatroban is not effective as an adjunctive therapy with IVT to improve long-term functional outcomes. |
| 3 No Benefit | In patients with AIS, early anticoagulation (within 48 hours of stroke onset) does not reduce the likelihood of early neurological worsening or increase the likelihood of a favorable functional outcome and is not recommended. |

**Abbreviations:** AIS indicates acute ischemic stroke; HT, hemorrhagic transformation; ICA, internal carotid artery; and IVT, intravenous thrombolytics.



Prabhakaran, S., et al. 2026 AHA/ASA Guideline for the Early Management of Patients with AIS. *Stroke*.

# Other considerations:

## Extracranial Carotid Artery Dissection

## Cardiac etiologies

## Hypercoagulable State

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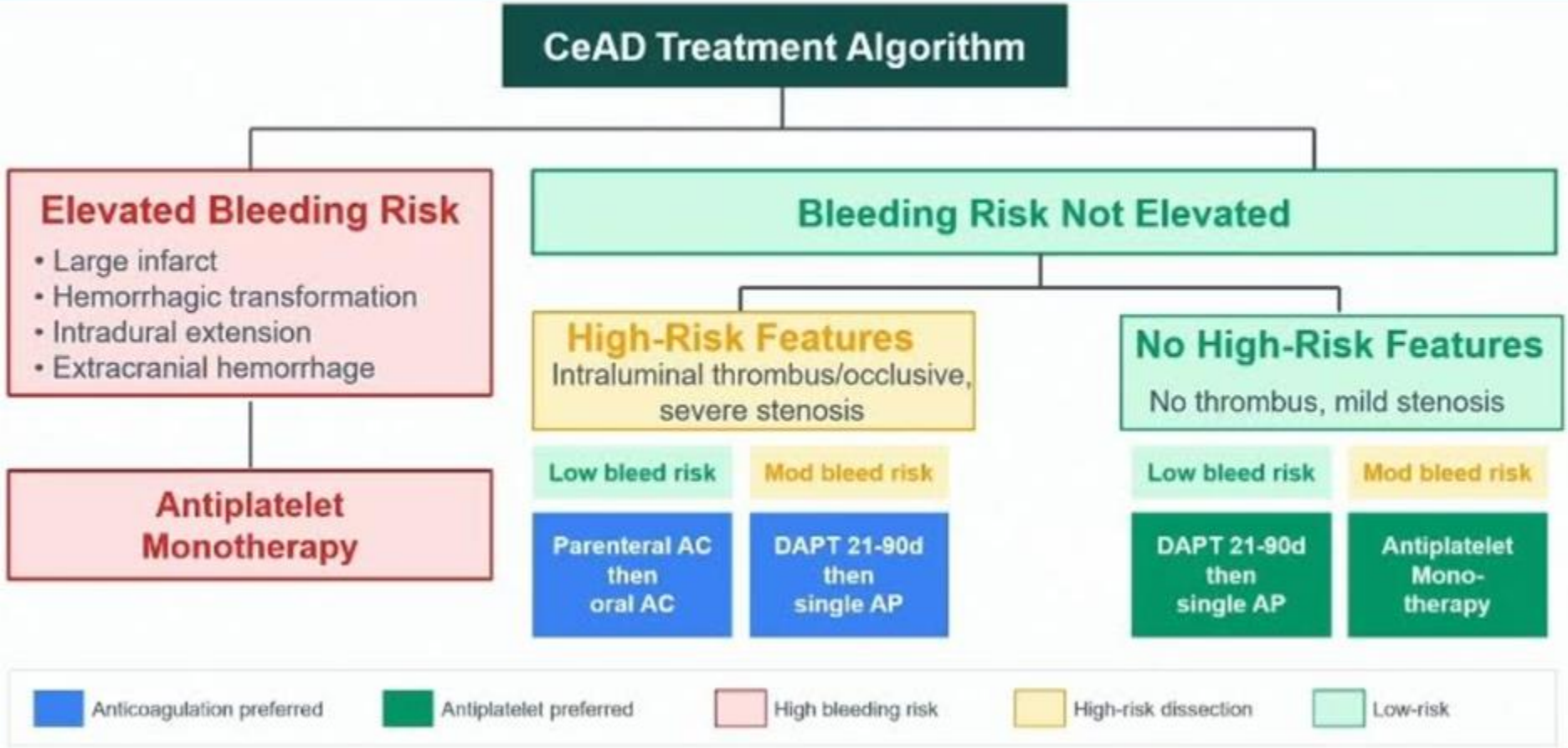
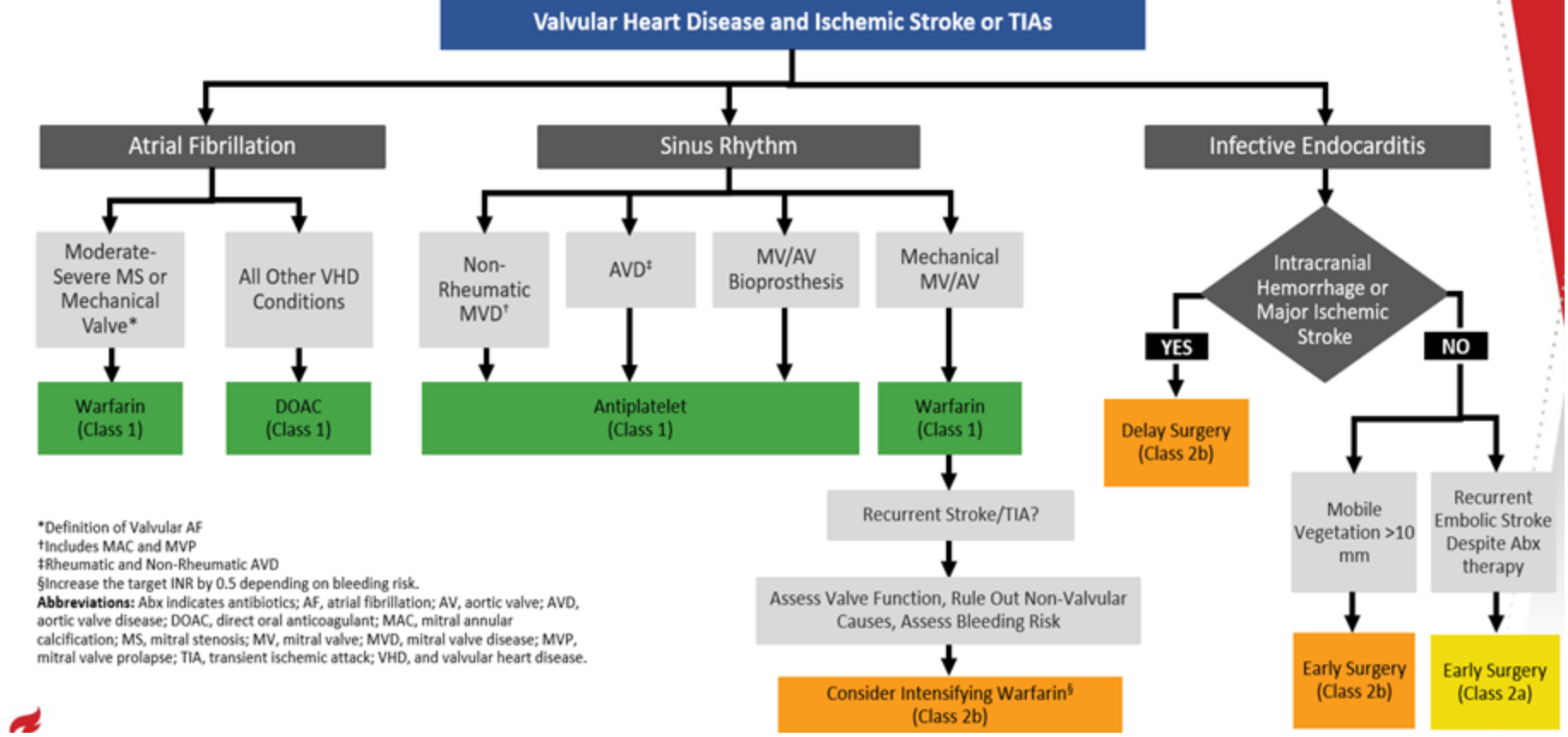
# Practical Guide: Selecting Antithrombotics in CeAD




APT = Dual Antiplatelet Therapy | AC = Anticoagulation | AP = Antiplatelet | Mod = Moderate

Yaghi S, Engelter S, Del Brutto VJ et al. Stroke. 2024 PMID: 38299330




*Definition of Valvular AF
†Includes MAC and MVP
‡Rheumatic and Non-Rheumatic AVD
§Increase the target INR by 0.5 depending on bleeding risk.
**Abbreviations:** Abx indicates antibiotics; AF, atrial fibrillation; AV, aortic valve; AVD, aortic valve disease; DOAC, direct oral anticoagulant; MAC, mitral annular calcification; MS, mitral stenosis; MV, mitral valve; MVD, mitral valve disease; MVP, mitral valve prolapse; TIA, transient ischemic attack; VHD, and valvular heart disease.

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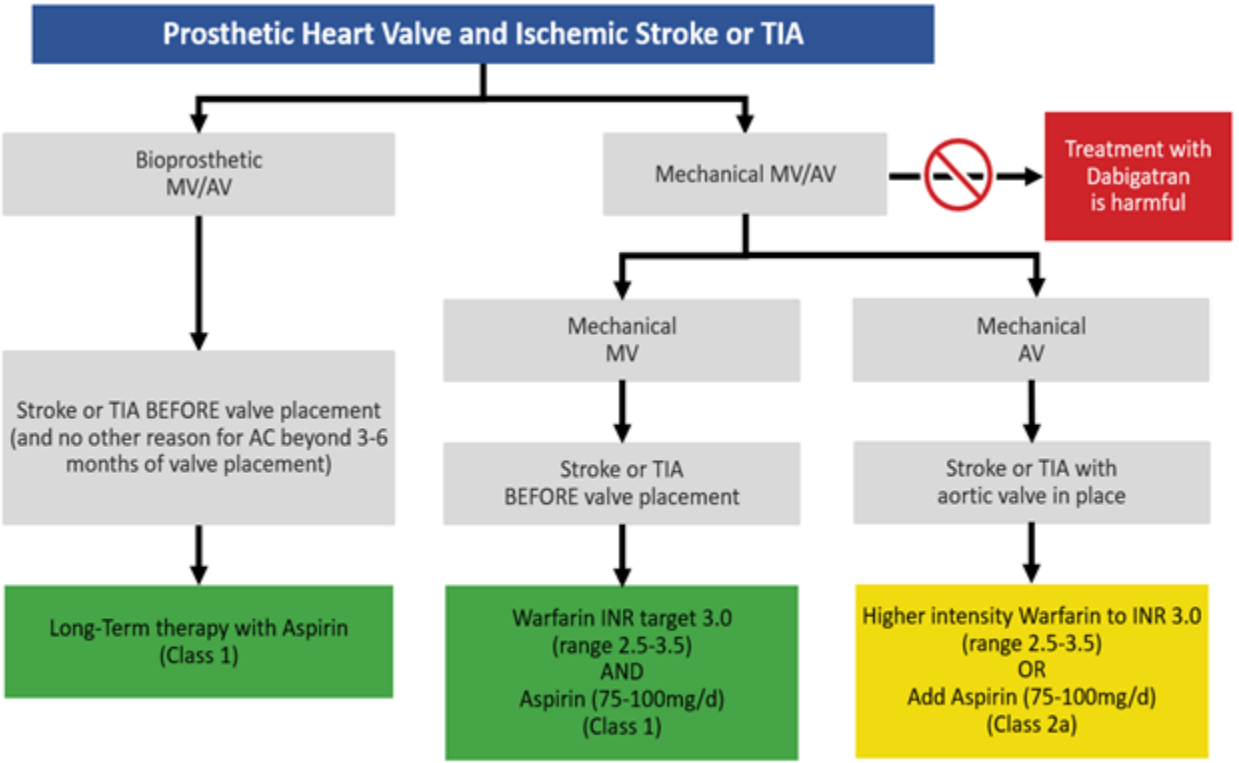
Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Secondary Stroke Prevention with Prosthetic Heart Valves

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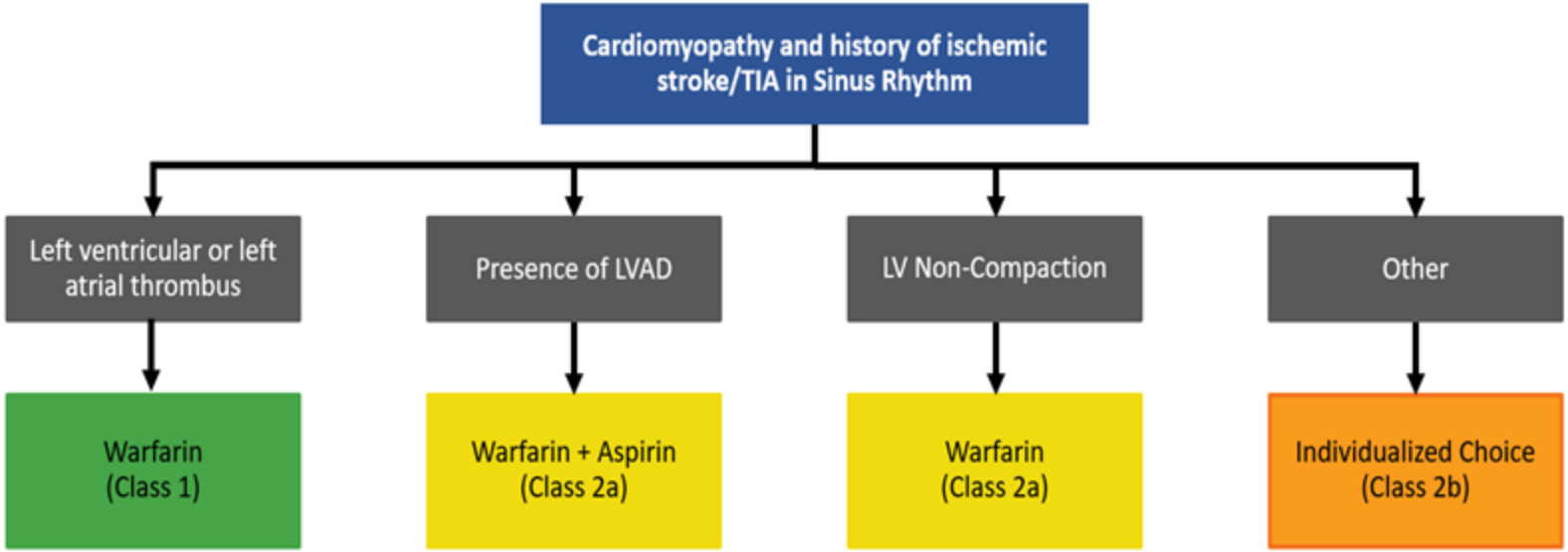
**Abbreviations:** AC indicates anticoagulation; AV, aortic valve; INR, international normalized ratio; MV, mitral valve; and TIA, transient ischemic attack.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Secondary Stroke Prevention in cardiomyopathy and intra-cardiac thrombus

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**Abbreviations:** LV indicates left ventricle; LVAD, left ventricular assist device; and TIA, transient ischemic attack.



Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Hypercoagulable State

| COR | RECOMMENDATIONS |
|---|---|
| 2a | In patients with ischemic stroke or TIA of unknown source despite thorough diagnostic evaluation and no other thrombotic history who are found to have prothrombin 20210A mutation, activated protein C resistance, elevated factor VIII levels, or deficiencies of protein C, protein S, or antithrombin III, antiplatelet therapy is reasonable to reduce the risk of recurrent stroke or TIA. |

**Abbreviations:** TIA indicates transient ischemic attack.

Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Hypercoagulable States: Antiphospholipid Syndrome

| COR | LOE | RECOMMENDATIONS |
|---|---|---|
| 1 | B-NR | 1. In patients with ischemic stroke or transient ischemic attack who have an isolated antiphospholipid antibody but do not fulfill the criteria for antiphospholipid syndrome, antiplatelet therapy alone is recommended to reduce the risk of recurrent stroke. |
| 2a | B-R | 2. In patients with ischemic stroke or transient ischemic attack with confirmed antiphospholipid syndrome, treated with warfarin, it is reasonable to choose a target international normalized ratio between 2-3 over a target international normalized ratio > 3 to effectively balance the risk of excessive bleeding against the risk of thrombosis. |
| 2a | C-LD | 3. In patients with ischemic stroke or transient ischemic attack who meet the criteria for the antiphospholipid syndrome, it is reasonable to anticoagulate with warfarin to reduce the risk of recurrent stroke or transient ischemic attack. |
| 3 HARM | B-R | 4. In patients with ischemic stroke or transient ischemic attack, antiphospholipid syndrome with history of thrombosis and triple positive aPL antibodies (i.e., lupus anticoagulant, anticardiolipin and anti-beta2-glycoprotein I), rivaroxaban is not recommended because it is associated with excess thrombotic events compared to warfarin. |



**Abbreviations:** aPL indicates antiphospholipid.



Kleindorfer, D. O., et al. (2021). 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. *Stroke*.

# Shared Decision-Making & Adherence

## Shared Decision Making

- Key component of patient-centered care
- Process in which clinicians describe options, risks, benefits and assists patients in evaluating options
- Collaboratively develop care plans with patients, incorporating patients' wishes, goals, and concerns

## Assessing Barriers to Adherence

- Assess and address barriers to adherence to medications and lifestyle
- In recurrent stroke, vital to assess whether taking prescribed medications
- Explore and, if possible, address factors that contributed to non-adherence, prior to assuming medications were ineffective

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# Take Home message

- ❑ Antiplatelets: TIA/Minor ischemic stroke within 72 hours, for 21-30 days, atherosclerotic disease (large artery aspirin 325 mg); DAPT Not greater than 90 days; ESUS
- ❑ Warfarin: Valvular Afib, mechanical heart valve, congenital heart disease, triple positive APLA, LV/LA thrombus
- ❑ DOAC: non-valvular Afib even after LAA exclusion or ablation
- ❑ Factor XI inhibitors: New class to AC (Asundexian, Milvexian) to prevent stroke (Afib related and non-cardioembolic) with lower bleeding risks than current DOACs. Potentially safer, not more effective at least in Afib
- ❑ Pregnancy: Aspirin and LMWH
- ❑ Dissections: risk stratification and either SAPT, DAPT or DOAC

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**The American Heart Association requests this electronic slide deck be cited as follows:** Abumoawad, A., Kole, A., Pathangey, G., Sajja, S., Williams, S., Reyna, G.G., & Antman, E. M. (2026). AHA Clinical Slides [PowerPoint slides]; Adapted from the 2026 AHA/ASA Guideline for the Early Management of Patients with AIS. *Stroke.* Guideline Essentials: AHA Clinical Slide Series - Professional Heart Daily | American Heart Association

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# Questions?

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# Thank you

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# Frequently asked questions if none from the audience

- Repeat HCT prior AC?
- Stroke w/mass effect
- Definition of HT when deciding on AC
- HT and starting AC
- HT+ Big PE and starting AC
- Cerebellar infarct > 3 cm w/HT

# *Stroke Care Beyond the Acute Event*: Blood Pressure Targets & Hypertension Management After Stroke

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# Disclosures

- Nothing to disclose

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# Objectives

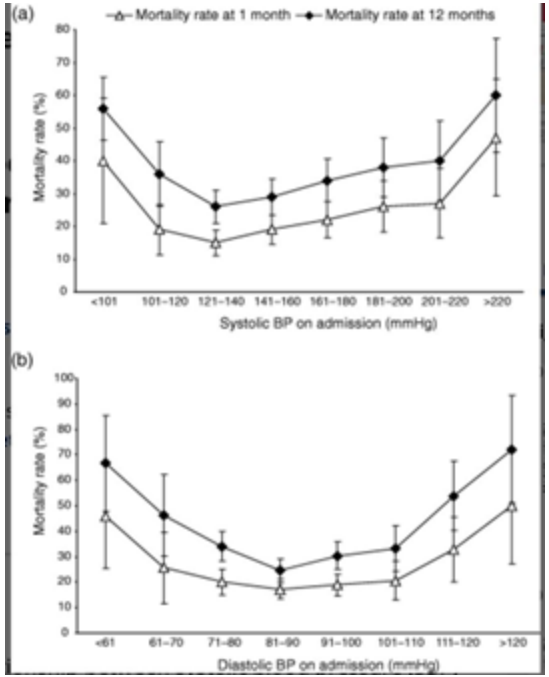
- Review ideal blood pressure goals in adults per updated American Heart Association / American Stroke Association guidelines.
- Identify blood pressure goals following acute ischemic strokes with and without stroke interventions.
- Identify blood pressure targets following hemorrhagic strokes (both intraparenchymal and subarachnoid).
- Review IV and oral anti-hypertensives for use in the acute stroke setting and for secondary stroke prevention.

# Blood Pressure Categories

- Updated 2025 AHA/ASA Guidelines for management of high blood pressure define 4 categories for blood pressure:
  - (1) Normal, (2) Elevated, (3) Stage 1 HTN, (4) Stage 2 HTN

| | SBP | | DBP |
|---|---|---|---|
| **BP Category** | | | |
| **Normal** | <120 mm Hg | and | <80 mm Hg |
| **Elevated** | 120 to 129 mm Hg | and | <80 mm Hg |
| **Hypertension** | | | |
| **Stage 1** | 130 to 139 mm Hg | or | 80 to 89 mm Hg |
| **Stage 2** | ≥140 mm Hg | or | ≥90 mm Hg |

# Hypertension & Stroke




- Approx 80% of acute stroke patients will present with hypertension
- Blood pressure targets / goals are dependent on type of stroke:
  - **ischemic** vs **hemorrhagic** (including intraparenchymal & subarachnoid)
  - Both have a U-shaped relationship - early, aggressive BP reduction and late-stage uncontrolled HTN resulting in increased mortality in stroke patients
- **ISCHEMIC** stroke → cerebral autoregulation in the ischemic penumbra is abnormal and perfusion pressure is necessary for adequate blood & oxygen
  - Goal: enhance cerebral perfusion while minimizing edema & risk for hemorrhagic transformation (hence permissive HTN)
  - Rapid reduction of BP can thus be detrimental ("starving the penumbra"), *BUT may be indicated in those with comorbid conditions (e.g. ACS, acute HF, aortic dissection, pre-eclampsia/eclampsia)*

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# Acute ISCHEMIC Strokes

- Acute phase (initial 48-72 hrs), **NO** interventions
  - **BP >220/110** → treatment "unclear" (2b) but tend to treat
    - 2025 HTN guidelines state it is "reasonable" (2b) to **lower by 15%** in initial 24hrs
  - **BP <220/110** → no benefit to treating (3)
    - **spontaneous BP lowering will occur w/ 75% of patients w/in 2-3 days*

| | | |
|---|---|---|
| 2b | C-EO | 3. In patients with BP ≥220/120 mm Hg who did not receive IVT or EVT and have no comorbid conditions requiring urgent antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. |
| 3: No Benefit | A | 4. In patients with BP <220/120 mm Hg who did not receive IVT or EVT and do not have a comorbid condition requiring urgent antihypertensive treatment, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an AIS is not effective to prevent death or dependency.[4] |

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# Acute ISCHEMIC Strokes

- Acute phase (initial **24hrs**) & candidate for **IV thrombolytic** (tPA / alteplase or TNK / tenecteplase)
  - PRE-treatment**: BP <185/110**
  - POST-treatment: **maintain BP <180/105** (*ideal **SBP 140 – 180**)*
    - *No benefit found from intensive BP lowering (BP <140)*

| | | |
|---|---|---|
| Before reperfusion treatment | | |
| 1 | B-NR | 5. Patients with AIS who have elevated BP and are otherwise eligible for treatment with IVT should have their SBP lowered to <185 mm Hg and diastolic blood pressure (DBP) <110 mm Hg before IVT therapy is initiated to reduce hemorrhagic complications.[5–9] |
| 2a | B-NR | 6. In patients for whom EVT is planned and who have not received IVT therapy, it is reasonable to maintain BP ≤185/110 mm Hg before the procedure to avoid complications and improve patient outcomes.[10] |
| After IVT | | |
| 1 | B-R | 7. BP should be maintained at <180/105 mm Hg for at least the first 24 hours after IVT treatment.[11–13] |

# Acute ISCHEMIC Strokes

- Acute phase (initial **24hrs**) & candidate for **endovascular thrombectomy (EVT)**
  - PRE-treatment**: BP <185/110** (2a)
  - ***POST-treatment: **maintain BP <180/105** (*ideal **SBP 140 – 180**)*
    - *recent RCTs demonstrated **worsened** clinical outcomes for those with SBP targets <140 (especially <120) within 24-72 of treatment*

| After endovascular thrombectomy | | |
|---|---|---|
| 2a | B-NR | 9. In patients who undergo EVT, it is reasonable to maintain BP at a level ≤180/105 mm Hg during and for 24 hours after the procedure.[14–17] |
| 3: Harm | A | 10. In patients with AIS with LVO of the anterior circulation who have been successfully recanalized by endovascular therapy (mTICI 2b, 2c, or 3) and without other indication for blood pressure management target, intensive SBP reduction target of <140 mm Hg for the first 72 hours is harmful and not recommended.[18–21] |

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# Acute HEMORRHAGIC Strokes

- Elevated BP is prevalent in pts with acute ICH / IPH & SAH
  - uncontrolled HTN → hematoma / hemorrhage expansion → neurologic worsening and potentially death or increased dependency
- current recommendations based on data from 3 largest trials (INTERACT2 & 3 + ATACH-2)
- **SUBARACHNOID HEMORRHAGE (SAH)**:
  - 2023 guidelines do NOT give a specific BP target
  - if initial SBP >180, then generally aim for **SBP goal <160 mm Hg** initially (*meta-analyses showed early re-bleeding when SBP >160 but not with SBP <140*)
    - post intervention (clipping vs coiling), higher SBP goals may be allowed in order to help prevent vasospasm & delayed cerebral ischemia (DCI)
  - avoid hypotension (mean arterial pressure, MAP <65 mm Hg)

# Acute HEMORRHAGIC Strokes

| Recommendations for Acute Intracerebral Hemorrhage | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **2a** | **A** | 1. For adult patients with acute spontaneous intracerebral hemorrhage (ICH) who present with SBP between 150 and 220 mm Hg, it can be beneficial to immediately lower SBP to 130 to <140 mm Hg for at least 7 days after ICH to improve functional outcomes but stop antihypertensive medications if SBP <130 mm Hg.[1-3] |
| **2a** | **B-NR** | 2. In adults with acute spontaneous ICH requiring acute BP lowering, careful titration to ensure smooth, nonlabile, and sustained control of BP, avoiding peaks and large variability in SBP, can be beneficial for improving functional outcomes.[3,4] |
| **3: Harm** | **B-NR** | 3. For adult patients with acute spontaneous ICH who present with SBP >220 mm Hg, SBP should not be lowered below 130 mm Hg to reduce adverse events.[5-7] |

- **INTRACEREBRAL / INTRAPARENCHYMAL HEMORRHAGES (ICH & IPH)**
- if initial SBP 150 - 220, then aim for target range: **SBP 130 – 150 *(hence the <140 goal)***
- if initial SBP >220, reasonable to aim for target **SBP <160** *(guidelines say consider SBP goal 160 - 180)*
  - AVOID lowering SBP <130 (associated with cerebral HYPOperfusion & worsened outcomes)

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# Acute Medical Management

- In acute setting (within initial 24 - 72 hours) for ALL stroke types (AIS, ICH / IPH, & SAH) when rapid BP control indicated, advise use of **IV infusions initially over PRN IV pushes or oral meds**
  - IV infusion → **nicardipine** or clevidipine (calcium channel blockers)
  - supplement with IV PRNs such as: labetalol (alpha & beta blocker) +/- hydralazine (vasodilator)
- ISCHEMIC STROKE: permissive HTN period = 24 - 72 hrs
  - following this period, tend to recommend restarting or initiating oral anti-hypertensives
- HEMORRHAGIC STROKES: concern for H.E. in initial 24 hrs
  - if hemorrhage remains stable, tend to recommend restarting or initiating oral anti-hypertensives

# Secondary Stroke Prevention

**Recommendations for Secondary Stroke Prevention**
**References that support recommendations are summarized in the Evidence Table.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with hypertension who have experienced an ischemic stroke, transient ischemic attack (TIA), or ICH, treatment with a thiazide-type diuretic, ACEi, or ARB is recommended for lowering BP and reducing recurrent stroke and ICH risk.[1-3] |
| 1 | B-R | 2. In patients with hypertension who have experienced an ischemic stroke, TIA, or ICH, an office SBP/DBP goal of <130/80 mm Hg is recommended to reduce the risk of recurrent stroke, ICH, and other vascular events.[1,3-5] |
| 2a | B-R | 3. In patients with no history of hypertension who have experienced an ischemic stroke, TIA, or ICH and have an average office SBP/DBP of ≥130/80 mm Hg, antihypertensive medication treatment can be beneficial to reduce the risk of recurrent stroke, ICH, and other vascular events.[5-7] |

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- Post stroke (AIS or ICH), BP goal:
  - **<130 / 80 mm Hg**
  - *optimal timing per 2025 HTN guidelines are unclear*
- Recommended anti-hypertensives:
  - thiazide-type diuretic (e.g. HCTZ)
  - Angiotensin-converting enzyme inhibitors (ACEi) (e.g. lisinopril)
  - Angiotensin II receptor blockers (ARB) (e.g. losartan)
  - ***Pregnant pts**: labetalol or ER nifedipine
  - ***limited data on calcium channel blockers (CCBs) and their efficacy for secondary stroke prevention*

# Secondary Stroke Prevention

- Other considerations when treating HTN in post stroke patients:
  - Obstructive sleep apnea (OSA)
    - treatment with CPAP shown to reduce BP in pts w/ mod-severe OSA & resistant HTN
  - Modifiable risk factors, including:
    - Weight
    - Diet / Nutrition
    - Physical activity
    - Substance use / abuse (including tobacco & alcohol use)

**Recommendations for OSA**
**Referenced studies that support the recommendations are summarized in the Evidence Table.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-R | 1. In adults with hypertension and OSA who are overweight or obese, weight loss interventions when combined with continuous positive airway pressure (CPAP) treatment can be effective in reducing SBP.[1] |
| 2a | B-R | 2. In adults with resistant hypertension and moderate-to-severe OSA, CPAP treatment can be useful in reducing BP.[2,3] |

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# Secondary Stroke Prevention

Table 4. Dietary Details of Typical Mediterranean-Type Diets

| Mediterranean diet (summarized) | DASH diet (summarized) |
|---|---|
| High monounsaturated/saturated fat ratio (use of olive oil as main cooking ingredient and/or consumption of other traditional foods high in monounsaturated fats such as tree nuts) | Limited saturated fat and cholesterol and emphasized nut consumption |
| High intake of plant-based foods, including fruits, vegetables, and legumes | Emphasizes fruit, vegetables, and legumes consumption |
| High consumption of whole grains and cereals | Emphasizes whole grains |
| Increased consumption of fish | |
| Low consumption of meat and meat products Discourages red and processed meats | Limits red and processed meats |
| Low to moderate red wine consumption | |
| Moderate consumption of milk and dairy products | Emphasizes fat-free/low-fat dairy |
| Discourages soda drinks, pastries, sweets, commercial bakery products, and spread fats | Limits sweets, added sugars, salt, and sugar-sweetened beverages. |

- OBESITY: 5-10% weight loss recommended (class 1)
- NUTRITION: Mediterranean-type diet & reduce sodium intake by 1g/day (class 2a)
- PHYSICAL ACTIVITY:
  - moderate (e.g. brisk walking) 10 min x 4 days/week or
  - vigorous (e.g. jogging) 20 min x 2 days/week
- SUBSTANCE USE:
  - Smoking cessation & avoidance of environmental tobacco smoke (passive smoking) (class 1)
  - Alcohol (no more than >2/day for men & >1/day for women) (class 1)
  - Stimulant cessation (e.g. cocaine, methamphetamines)

# Blood Pressure Cheat Sheet

- Acute **ISCHEMIC** Stroke – no interventions:
  - Treat **BP >220/110 mm Hg** (lower by approx 15%)
  - Permissive HTN: 24 - 72 hrs & then GRADUAL goal BP <130/80
- Acute **ISCHEMIC** Stroke - IV thrombolytic candidate (tPA or TNK):
  - Pre: Attain **BP <185/110** & Post: Maintain **BP <180/105**
- Acute **ISCHEMIC** Stroke – endovascular thrombectomy:
  - Pre: ideal **<185/110** & Post (*new*): **<180/105** (typically **SBP 140 – 180**)
- Acute **HEMORRHAGIC** stroke (ICH / IPH or SAH):
  - Subarachnoid: generally **SBP goal <160** (aim for 140), MAP >65
  - ICH/IPH: **SBP 130 – 150** (if initial 150 - 220) or **SBP <160** (if initial >220)


# Questions?

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# References


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# Thank you for your time and attention!


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# Stroke Related Fatigue and Depression

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5/9/2026

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# Disclosures

- I have no relevant disclosures

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# Objectives

- Differentiate between Post-Stroke Fatigue (PSF) vs sleepiness in stroke
- Review screening tools and treatment modalities for PSF and sleepiness post stroke
- Discuss poststroke depression (PSD) and current recommendations for screening and treatment

# Post-Stroke Fatigue

- Persistent feeling of tiredness, lack of energy, low motivation, and difficulty concentrating that is disproportionate to exertion and not relieved by rest/sleep
- One of the most common and debilitating sequelae of stroke
- Largely impacts rehabilitation engagement, quality of life

**Epidemiology**

- Affects ~30-75% of individuals with stroke
- Stroke severity and location not directly correlated to degree of PSF
- Can persist for months to years

**Clinical features**

- Sense of exhaustion distinct from weakness or sadness
- Lack of energy interfering with daily activities of living
- Mental fatigability
- Worse with cognitive load
- May not be relieved by rest and can fluctuate throughout the day

**Pathophysiology**

- Poorly understood: Likely combination of neuroinflammation, disturbances in cortical excitability, and alteration in neurotransmitters
- Medical contributors: pain, medications,deconditioning

# Sleepiness in stroke

- Often referred to as excessive daytime sleepiness
- Increased physiologic drive to fall asleep

Etiologies

- Sleep-disordered breathing (~60%)
- Medication side effects
  - Sedatives, spasticity treatment, antiepileptics
- Thalamic/brainstem involvement
- Circadian disruption
- Mood disorders

Clinical features

- Falling asleep during the day
- Unable to stay awake during tasks such as sitting, reading, watching television
- Associated with a drive for sleep
- Rest can be restorative

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# Screening tools

Post-Stroke Fatigue

- Fatigue Severity Scale (FSS)
- Fatigue Impact Scale
- Multidimensional Fatigue Inventory

| *During the past week, I have found that:* | Disagree ◄——► Agree |
|---|---|
| 1. My motivation is lower when I am fatigued | 1 2 3 4 5 6 7 |
| 2. Exercise brings on my fatigue | 1 2 3 4 5 6 7 |
| 3. I am Easily fatigued | 1 2 3 4 5 6 7 |
| 4. Fatigue interferes with my physical functioning | 1 2 3 4 5 6 7 |
| 5. Fatigue causes frequent problems for me | 1 2 3 4 5 6 7 |
| 6. My fatigue prevents sustained physical functioning | 1 2 3 4 5 6 7 |
| 7. Fatigue interferes with carrying out certain duties and responsibilities | 1 2 3 4 5 6 7 |
| 8. Fatigue is among my three most disabling symptoms | 1 2 3 4 5 6 7 |
| 9. Fatigue interferes with my work, family or social life | 1 2 3 4 5 6 7 |

**Total Score:** _____

Sleepiness

- Epworth Sleepiness Scale
- STOP-BANG score
- Sleep study
- Evaluate contributors: Medications, mood, other comorbidities

| Item | Question |
|---|---|
| 1. **S**noring | Do you snore loudly (louder than talking or loud enough to be heard through closed doors)? |
| 2. **T**ired | Do you often feel tired, fatigued or sleepy during the daytime? |
| 3. **O**bserved | Has anyone observed you stop breathing during your sleep? |
| 4. Blood **P**ressure | Are you being, or have been, treated for high blood pressure? |
| 5. **B**ody mass index | Is your body mass index > 35 kg/m²? |
| 6. **A**ge | Are you > 50 years old? |
| 7. **N**eck circumference | Is your neck circumference > 40 cm? |
| 8. **G**ender | Are you male? |

**EPWORTH SLEEPINESS SCALE**

How likely are you to doze off or fall asleep during the following situations?

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

| | Score |
|---|---|
| 1. Sitting and reading | 0 1 2 3 |
| 2. Watching TV | 0 1 2 3 |
| 3. Sitting, inactive in a public place | 0 1 2 3 |
| 4. As a passenger in a car for an hour without a break | 0 1 2 3 |
| 5. Lying down to rest in the afternoon when circumstances permit | 0 1 2 3 |
| 6. Sitting and talking to someone | 0 1 2 3 |
| 7. Sitting quietly after a lunch without alcohol | 0 1 2 3 |
| 8. In a car, while stopped for a few minutes in the traffic | 0 1 2 3 |
| | Total _____ |

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# Treatment of PSF

**Non-pharmacologic**

- Physical activity
  - Aerobic (3-5 days per week, 20-60 min sessions, 40-60% VO2 reserve)
  - Muscular strength/endurance
  - Flexibility/balance
- Cognitive behavioral therapy (CBT)
  - Randomized control trial showed that CBT and graded activity training over 12 weeks improved PSF over CBT alone (Zedlitz et al.,Stroke,2012)
- Conservation of Energy
  - Scheduling rest periods through the week, pace/plan/prioritize, utilize technology

**Pharmacologic**

- Modafinil 200 mg/day (MIDAS Trial, Bivard et al., Stroke, 2017)
- Methylphenidate 5-15 mg twice daily (Grade et al., Arch Phys Med Rehabil, 1998)
- Current literature has not supported antidepressants for treatment of PSF
- Timing? Duration of treatment?

# Treatment of Sleepiness

- Treatment of obstructive sleep apnea

| Study / Source | Design | Population | Intervention | Key Findings | Clinical Relevance |
|---|---|---|---|---|---|
| Brill et al., *Neurology* (2018) | Meta-analysis of RCTs | Stroke/TIA + sleep-disordered breathing (n=564) | CPAP vs usual care/sham | CPAP feasible; avg use ~4.5 hrs/night | Supports CPAP use post-stroke; adherence is critical |
| Fu et al., *J Clin Sleep Med* (2023) | Meta-analysis (14 studies) | Stroke + OSA (n=1065) | CPAP | Improved neurological function (SMD 0.28) | Suggests CPAP may improve recovery outcomes |
| Povitz et al., Meta-analysis (2014) | Meta-analysis of 19 RCTs | OSA patients | CPAP or mandibular device | Improved depressive symptoms (greater effect if baseline depression present) | Relevant to post-stroke depression management |
| Campos-Rodriguez et al., RCT (2016) | Multicenter RCT (n=307) | Moderate–severe OSA (women) | CPAP vs usual care | Improved quality of life, mood, and daytime symptoms | Reinforces CPAP benefits beyond AHI reduction |
| TOROS Trial (BMC Neurology) | Randomized controlled trial | Stroke + OSA | CPAP vs usual care | Evaluates fatigue, cognition, mood outcomes | Direct relevance to post-stroke fatigue & recovery |

- Pharmacologic therapies vs avoiding polypharmacy
- Delirium precautions (during hospitalization)
- Treatment of other contributing sleep disorders

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# Poststroke Depression

DSM-5:“Mood disorder due to a general medical condition (i.e. stroke)” with the specifiers of depressive features, major depressive-like episodes, manic features, or mixed features”.

- Symptoms lasting at least 2 weeks

**Epidemiology**

- Common mood disorder after stroke affecting one third of stroke survivors
- Cumulative incidence of 55%
- Can develop:
  - Within weeks
  - Months to years later (frequency is highest in first year)

**Pathophysiology**

- Poorly understood; evidence suggests biological component and not just psychological response to new disability
  - Late onset depression associated with white matter disease and small silent infarcts
  - Increased depression after transient ischemic attack and minor stroke

# Poststroke Depression

**Clinical significance**

- Associated with:
  - Increased mortality
  - Poor functional recovery
  - Reduced medication adherence

**Risk factors for PSD**

- Prior history of depression
- Stroke severity and disability
- Cognitive impairment
- Social isolation
- Female sex (in some studies)

**Clinical Pearl:**

- Fatigue and depression frequently coexist but require **separate evaluation**

# Screening for PSD

**Recommended in all stroke survivors**

**Gold Standard:**

- Structured psychiatric interview, meeting DSM criteria

**Primary tool:**

- PHQ-9
  - High diagnostic accuracy first 2 months post stroke

**Alternative tools:**

- Hospital Anxiety and Depression scale (HADS)
- Geriatric Depression Scale (GDS)
- Hamilton Depression Scale (HDS)

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**PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)**

| Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✔" to indicate your answer) | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| 9. Thoughts that you would be better off dead or of hurting yourself in some way | 0 | 1 | 2 | 3 |

**Recommendations for Depression**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients with AIS, administration of a structured depression inventory is recommended to routinely screen for poststroke depression (PSD), although the optimal timing of screening is uncertain.[1-4] |
| 1 | B-R | 2. In patients diagnosed with PSD, treatment with antidepressants and/or nonpharmacological interventions (ie, psychotherapy, noninvasive brain stimulation, acupuncture) is recommended to improve depressive symptoms.[5-17] |

# Treatment of PSD

**Pharmacologic**

- Selective serotonin reuptake inhibitors (SSRIs)
- Tricyclic antidepressants

**Non-pharmacologic**

- Repeated transcranial magnetic stimulation (rTMS)
  - 2017 meta-analysis by Shen et al demonstrated benefit from rTMS
- Psychotherapy:
  - Cognitive behavioral therapy
- Acupuncture
  - Meta-analysis of 13 RTCs:The combined therapy of acupuncture with antidepressants led to a significant reduction in the HDS score when compared with antidepressant therapy alone (Zhang et al.,Medicine (Baltim),2021)
- Music therapy
- Exercise
- Support groups

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# Summary

**Post-Stroke Fatigue (PSF)**

- Affects nearly 3 in 4 stroke survivors and is **frequently underrecognized**
- Characterized by **persistent exhaustion not relieved by rest**
- No single effective therapy →
  - Pharmacologic strategies
  - Functional strategies (exercise, energy conservation)

**Sleepiness in stroke**

- Characterized by excessive daytime fatigue and physiologic drive to fall asleep
- Recognizing/treating OSA and other sleep disorders is paramount

**Post-Stroke Depression (PSD)**

- Affects ~30% of patients
- Associated with:
  - Worse recovery
  - Increased mortality
- **Routine screening with PHQ-9 or other tool is recommended**

**What to Do in Practice**

- Screen **all stroke patients** for:
  - Fatigue (clinical assessment ± FSS) and OSA
  - Depression (PHQ-9)
- Treat contributing conditions and initiate therapy early
- Reassess regularly—symptoms evolve over time

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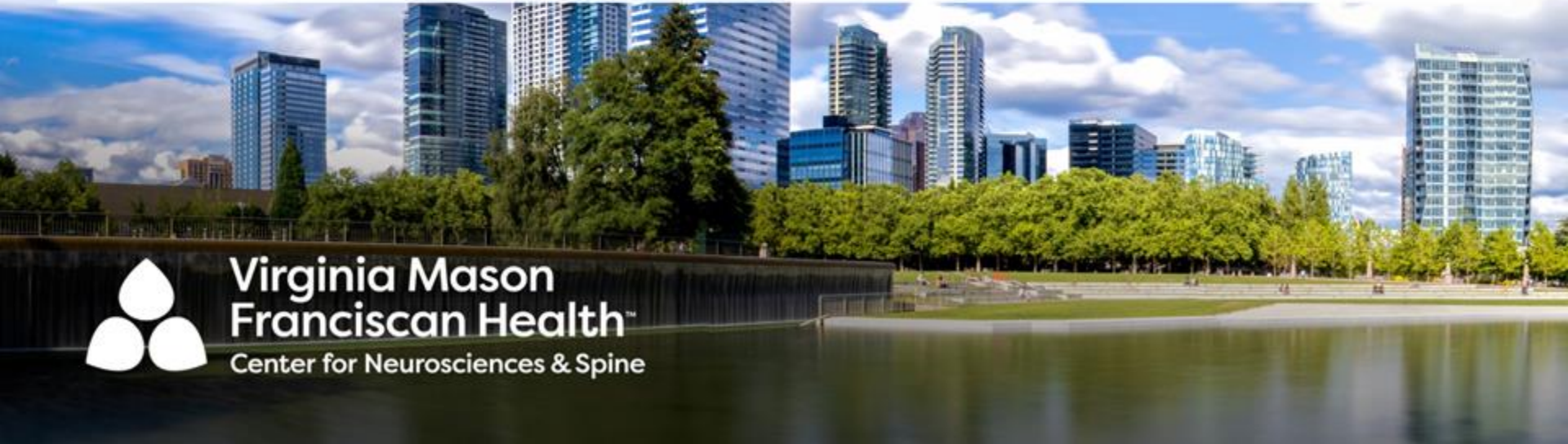
# Question & Answer

Audience - please raise hand for roaming mic

Virtual Attendees - please click on Q&A button



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