Ischemic Stroke: Understanding, Timely Care, Rehabilitation & Prevention

Updates on Evidence and Guidelines

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The landscape

- ~87% of all strokes are ischemic (AHA 2023).
- Incidence ~ 700,000/year
- Prevalence ~ 3,000,000 *
- Burden
- per CDC - combined cost of **$56.2 billion** for 2019-2020.
- per AHA – costs will increase to **$184.13 billion by 2030**.

The regional landscape

- Estimated population of SD + surrounding parts of MN+IA+NE
  925,000+90,000+50,000+30,000 = 1,095,000
- Using national incidence rates – 2300 ischemic strokes/yr
- **IVT – 10-15% - 230-345/year**
- **30% of Ischemic stroke – LVO – 690 LVOs/year**
- How many are we doing?

The problem - IVT

- Overall rate of IV thrombolysis administration - **7% to 11%**
- Get With The Guidelines-Stroke 2018 - **75% of eligible acute ischemic stroke patients received intravenous tissue plasminogen activator (tPA) within 60 minutes of arrival**.
- Large disparities exist –
- **Comprehensive Stroke Centers (CSCs):** 91%
- **Primary Stroke Centers (PSCs):** 85%
- **Non-certified facilities:** 52%

The problem - IAT

- About 25% of ischemic strokes have LVOs
- Only 48% of eligible patients initially arrived at a thrombectomy capable center
- Only 30% of eligible patients receive treatment

What shall we do?

Fear not! Your humble neighborhood Neurointerventionist to the rescue!!

Spectrum of stroke management

- Prevention
- Out of hospital recognition
- Emergency medical services
- Transport
- Care in ER
- IVT/IAT/DAPT/STAT/ETC/ASAP/WHAA
- Care in ICU/Step down/Floor
- Rehabilitation
- Secondary prevention

EMS Assessment — LVO Scales

- Selected Comparative Performance:
- • RACE: sensitivity ~0.85, specificity ~0.68 for anterior circulation LVO.
- • FAST-ED: AUROC ~0.86; strong negative predictive value.
- • LAMS: simple motor scale, slightly lower predictive power for M2 occlusions.

Neuroprotection

- Optimize Cerebral Perfusion: BP targets per guidelines
- Neuroprotective Interventions:
- Remote Ischemic Conditioning (ongoing RESIST trial)
- Nerinetide - ESCAPE-NA1 - neutral
- glibenclamide, uric acid, 3K3A-APC - investigational.
- Metabolic & Supportive Care: Normoglycemia, treat fever >38°C, maintain normoxia
- Systems of Care: Rapid recognition & transport to EVT/IVT centers; Mobile Stroke Units; Telestroke; streamlined prehospital triage.

Mobile Stroke Units — Evidence

- NEJM 2021: Multicenter trial — MSU patients had **better 90-day utility-weighted mRS vs usual care**.
- JAMA 2021 Berlin study: MSU dispatch linked with lower disability at 3 months (common OR 0.71).
- Stroke 2022 BEST-MSU subanalysis: Onset-to-tPA 36 min shorter; 33% vs 3% treated in first hour.
- Observational 2022: **MSU thrombolysis ≤60 min (31.9% vs 12.2%); better outcomes trend;** mortality similar.
- SVIN 2023 (LVO): **MSU improved outcomes via faster IVT;** EVT times unchanged.
- Systematic reviews: MSUs reduce onset-to-needle 20–41 min; ↑ golden-hour IVT; cost-effectiveness uncertain.

Telestroke Metrics (JAMA Net Open, 2025)

- Design: Retrospective cohort (42 hospitals, 2022–2023); telestroke vs non-telestroke in IVT-eligible AIS
- Primary: Thrombolysis use; DTN; DIDO
- Result: Higher IVT use with telestroke; longer DTN & DIDO; lower odds of DTN ≤60 min
- Link: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2839374

Transfers

- Comprehensive (CSC) and Thrombectomy-capable Stroke Centers (TSC) consistently outperform Primary Stroke Centers (PSC) on timeliness (DTN/DTP), reperfusion use (IVT/EVT), and in-hospital outcomes
- Certification expansion – more certified hospitals – better care
- Interhospital transfers: **Door-in-door-out (DIDO) frequently exceeds 90–120 min; longer DIDO correlates with lower functional independence**
- Mothership vs Drip-and-Ship: Mothership shortens onset-to-puncture and often increases EVT rates
- **Bottom line: Prefer direct transport to EVT-capable centers when prehospital LVO suspicion is high; where DS is necessary, minimize DIDO with predefined transfer pathways and real-time coordination.**

IVT/IAT/DAPT/STAT/ETC/ASAP/WHAA

- IVT ≤4.5h (alteplase, TNK).
- IVT 4.5-24h – evidence outlined
- EVT ≤24h in select patients (DAWN, DEFUSE 3, SELECT2, ANGEL-ASPECT, RESCUE-Japan LIMIT).
- Door-to-needle and door-to-groin strongly linked to outcomes.
- Telestroke increases IVT use but can delay DTN/DIDO (JAMA Net Open 2025).

Late-Window IVT: Perfusion-Selected (4.5–24 h) — Key Trials

- HOPE (JAMA 2025): Alteplase 0.9 mg/kg vs standard care in patients with salvageable tissue on CTP/MRP; no initial plan for MT.
- Primary: Functional independence (mRS 0–1) at 90 d.
- Result: 40% (tPA) vs 26% (control) achieved mRS 0–1; sICH 3.8% vs 0.5%; mortality 11% both arms.
- TIMELESS (NEJM 2024): Tenecteplase 0.25 mg/kg vs placebo, 4.5–24 h; perfusion-selected; majority underwent EVT.
- Primary: 90-day mRS (shift). Result: Neutral; sICH similar. Link:

Minor Non-Disabling Stroke (Low NIHSS): DAPT with Loading

- ARAMIS (JAMA 2023): NIHSS ≤5, nondisabling; ≤4.5 h.
- Intervention: Clopidogrel 300 mg load day 1 → 75 mg/d + Aspirin 100 mg/d for 12 (±2) days; then guideline antiplatelet.
- Primary: mRS 0–1 at 90 d. Result: **DAPT non-inferior to IV alteplase; less bleeding.**
- INSPIRES (NEJM 2023): Mild stroke/high-risk TIA (atherosclerotic); start ≤72 h.
- Primary: New stroke at 90 d. Result: **DAPT ↓ recurrent stroke vs aspirin**; modest ↑ moderate-severe bleeding.

Mechanical thrombectomy

- How long after onset?
- How severe is too severe? Not severe enough?
- How small a vessel?
- How large an established infarct?
- Anterior circulation same as posterior?
- What is “acceptable outcome?
- Choice of device, does it matter?

EVT Benefit Up to 24 Hours

- **AHA/ASA 2019 Guidelines - EVT recommended within 16 h and reasonable up to 24 h in selected LVO with imaging selection per DAWN/DEFUSE 3 criteria.**

- DAWN (NEJM 2018): EVT 6–24 h or wake-up/unknown onset with clinical-core mismatch; improved functional independence vs medical therapy.

- DEFUSE 3 (NEJM 2018): EVT 6–16 h with perfusion-core mismatch on CTP/MRP; superior 90-day outcomes vs medical therapy.

- SELECT2 (NEJM 2023): Large ischemic core (low ASPECTS or large core by imaging) ≤24 h; EVT improved disability outcomes vs medical care.

- ANGEL-ASPECT (NEJM 2023): Large core anterior-circulation LVO ≤24 h; EVT improved functional outcomes; more ICH with EVT.

EVT in Posterior Circulation Stroke

- **TL;DR: Benefit dependent on severity, location, access, time since onset. No clear guidelines yet**

- BASICS (NEJM 2021): RCT, BAO ≤6h. Neutral overall; subgroup signal of EVT benefit in NIHSS ≥10.
- BEST (Lancet Neurol 2020): RCT, BAO ≤8h. Early stopped, high crossover; no significant difference primary outcome, per-protocol favored EVT
- ATTENTION (NEJM 2022): RCT, BAO ≤12h, NIHSS ≥10. EVT improved independence (46% vs 23%) and reduced mortality (37% vs 55%).
- BAOCHE (NEJM 2022): RCT, BAO 6–24h, NIHSS ≥6, pc-ASPECTS ≥6. EVT better outcomes (mRS 0–3: 46% vs 24%); mortality 31% vs 42%.
- Meta-analyses (2022–23): Pooled BASICS, BEST, ATTENTION, BAOCHE — EVT doubles odds of independence (OR ~1.9–2.0), lowers mortality, ↑ sICH.

EVT in Large Core Infarcts

- **TL;DR: EVT is effective and should be considered in selected large core infarcts, expanding eligibility beyond traditional criteria.**

- Multiple RCTs (RESCUE-Japan LIMIT, SELECT2, ANGEL-ASPECT) demonstrate EVT benefit in large core infarcts.
- Meta-analyses (2023–24): **EVT nearly doubles odds of functional independence even with ASPECTS 3–5 or core ≥50 mL.**
- **Consistent benefit across subgroups** (age, onset-to-treatment, imaging modality).
- Increased risk of symptomatic ICH, but no excess mortality.

EVT in Distal & Medium Vessel Occlusions (DMVOs)

- **TL;DR: Routine EVT for DMVOs not supported; selective use reasonable in disabling presentations at experienced centers.**

- DMVOs (M2, M3, A2, P2) cause significant disability but were excluded from most EVT RCTs.
- Pooled data: EVT yields higher reperfusion but inconsistent functional outcome benefit; ↑ sICH risk.
- **Potential signals of benefit in proximal M2 or high NIHSS patients.**

- ESCAPE-MeVO (NEJM 2025
- DISTAL (NEJM 2025.
- DISCOUNT (ESOC 2023, France

Secondary Prevention

- Non-cardioembolic: ASA, clopidogrel, or DAPT short-term (CHANCE, POINT, INSPIRES, ARAMIS).
- Cardioembolic (AF): DOACs preferred; Warfarin if mechanical valves.

Secondary prevention

- Hypertension
- Diabetes
- Smoking
- Sleep apnea
- Hyperlipidemia
- Diet and Exercise
- Healthy body weight

Rehabilitation

- Multidisciplinary: PT/OT, speech, psychology.
- Early mobilization safe; intensity tailored (AVERT, Lancet 2015).
- Telerehab effective adjunct (Stroke 2023 review).

Take-Home Points

- Stroke common, disabling, more treatable now.
- Fast reperfusion saves brain — up to 24h with imaging.
- Telestroke and systems of care vital.
- Rehab + secondary prevention (antiplatelets, anticoagulants, risk factor control) reduce recurrence.
- Both advanced technology and meticulous prevention matter.

Acute Ischemic Stroke: Major Trials, Guidelines & Treatment Updates

For the perfectionists amongst us,
not satisfied with TL;DR

RESCUE-Japan LIMIT (NEJM, 2022)

- Design: Randomized; large core (ASPECTS 3–5); EVT + medical care vs medical care
- Primary: 90-day mRS (shift)
- Result: EVT improved functional outcomes; any ICH increased
- Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2118191

ANGEL-ASPECT (NEJM, 2023)

- Design: Randomized; large core anterior LVO ≤24 h; EVT + medical care vs medical care
- Primary: 90-day mRS (shift)
- Result: EVT improved functional outcomes; more ICH with EVT
- Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2213379

SELECT2 (NEJM, 2023)

- Design: Randomized; large core by imaging/low ASPECTS; EVT vs medical care
- Primary: 90-day mRS (shift)
- Result: EVT improved functional outcomes; vascular complications higher with EVT; ICH infrequent
- Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2214403

ESCAPE-MeVO (NEJM, 2025)

- Design: Multicenter randomized PROBE; MeVO ≤12 h; EVT + usual care vs usual care
- Primary: 90-day mRS (shift)
- Result: EVT did not improve 90-day outcomes vs best medical care
- Link: https://pubmed.ncbi.nlm.nih.gov/39908448/

DISTAL (NEJM, 2025)

- Design: Randomized, assessor-blinded; medium/distal vessel occlusion within 24h; EVT+BMT vs BMT.
- Primary outcome: 90-day mRS (shift).
- Result: No improvement in disability/death with EVT; neutral trial.
- Link: https://pubmed.ncbi.nlm.nih.gov/39908430/

ESCAPE-MeVO Subgroup Findings

Device / Occlusion Site	Result
M2	No EVT benefit vs medical care
M3, ACA, PCA	Neutral
Stent retriever vs aspiration	No difference

DISTAL Subgroup Findings

Device / Occlusion Site	Result
M2	No significant effect
ACA/PCA	Neutral
Stent retriever vs aspiration	No difference

TIMELESS (NEJM, 2024)

- Design: Multicenter, double-blind RCT; tenecteplase 0.25 mg/kg vs placebo; 4.5–24 h; perfusion-selected.
- Primary outcome: 90-day mRS (shift).
- Result: No significant difference in functional outcome vs placebo.
- Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2310392

TEMPO-2 (Lancet, 2024)

- Design: Randomized, open-label, phase 3; minor, non-disabling stroke with proven occlusion; TNK 0.25 mg/kg vs non-thrombolytic SOC.
- Primary outcome: Return to baseline function at 90 days.
- Result: No benefit; signal of possible harm.
- Link: https://pubmed.ncbi.nlm.nih.gov/38768626/

Reteplase vs Alteplase (NEJM, 2024)

- Design: Randomized; AIS ≤4.5 h; reteplase vs alteplase
- Primary outcome: Excellent functional outcome at 90 days (mRS 0–1).
- Result: Reteplase superior for excellent outcome; sICH/death similar; any ICH higher with reteplase
- Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2400314

Prehospital BP Reduction in Suspected Stroke (NEJM, 2024)

- Design: Randomized trial; intensive ambulance-delivered BP reduction vs usual care in suspected stroke.
- Primary outcome: 90-day functional outcome.
- Result: No improvement in functional outcomes with prehospital BP reduction.
- Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2314741

Post-EVT Blood Pressure Targets (JAMA Net Open, 2024)

- Design: Systematic review/meta-analysis of BP targets post-EVT.
- Outcome: Functional outcomes and safety with intensive vs standard targets.
- Result: Intensive BP reduction post-EVT showed no benefit and potential risk; conservative targets favored until more data.
- Link: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2815387

AcT (Lancet, 2022)

- Design: Randomized, pragmatic; TNK 0.25 mg/kg vs alteplase ≤4.5 h
- Primary: mRS 0–1 at 90 days (non-inferiority)
- Result: TNK non-inferior to alteplase; comparable safety
- Link: https://www.thelancet.com/article/S0140-6736(22)01054-6/fulltext

TRACE-2 (Lancet, 2023)

- Design: Randomized; TNK 0.25 mg/kg vs alteplase ≤4.5 h (EVT-ineligible)
- Primary: mRS 0–1 at 90 days (non-inferiority)
- Result: TNK non-inferior to alteplase
- Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02600-9/fulltext

ATTEST-2 (Lancet Neurol, 2024)

- Design: Randomized; TNK 0.25 mg/kg vs alteplase ≤4.5 h
- Primary: mRS 0–1 at 90 days (non-inferiority)
- Result: TNK non-inferior across prespecified subgroups
- Link: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(24)00377-6/fulltext

DIRECT-SAFE (Lancet, 2022)

- Design: Non-inferiority RCT; direct EVT vs IV alteplase + EVT (bridging) ≤4.5 h
- Primary: Functional independence (mRS 0–2) at 90 days
- Result: Non-inferiority of direct EVT not shown; safety similar
- Link: https://pubmed.ncbi.nlm.nih.gov/35810757/

ENCHANTED2/MT (Lancet, 2022)

- Design: Randomized; post-EVT SBP target <120 vs 140–180 mmHg for 72 h
- Primary: 90-day mRS (shift)
- Result: Intensive target worsened outcomes; avoid very low targets post-EVT
- Link: https://pubmed.ncbi.nlm.nih.gov/36341753/

Practice Implications (Author Conclusions)

Trial	Authors' Conclusion (verbatim/condensed)
Telestroke Cohort (JAMA 2025)	Higher IVT use but longer DTN/DIDO with telestroke.
ESCAPE-MeVO (NEJM 2025)	EVT did not improve outcomes vs medical care in MeVO.
DISTAL (NEJM 2025)	EVT not superior to best medical therapy for distal occlusions.
TIMELESS (NEJM 2024)	Tenecteplase did not improve functional outcomes in 4.5-24 hr at 90 days.
TEMPO-2 (Lancet 2024)	No benefit of TNK in minor non-disabling stroke; possible harm.
Reteplase vs Alteplase (NEJM 2024)	Reteplase yielded higher excellent outcomes vs alteplase.
Prehospital BP (NEJM 2024)	No functional benefit from intensive prehospital BP lowering.
Post-EVT BP (JAMA Net Open 2024)	No benefit to intensive BP targets

Late-Window IVT (4.5–24 h): Trial Comparison

Feature	HOPE (JAMA 2025)	TIMELESS (NEJM 2024)
Design	Open-label RCT; China; 26 centers	Double-blind RCT; multinational
Imaging Selection	CTP/MR-perfusion salvageable tissue	CTP/MR-perfusion; LVO required
EVT Plan at Baseline	Excluded (no initial EVT plan)	Many went on to EVT
Drug & Dose	Alteplase 0.9 mg/kg	Tenecteplase 0.25 mg/kg
Primary Outcome	mRS 0–1 at 90 d	mRS shift at 90 d
Main Result	40% vs 26% mRS 0–1; sICH 3.8% vs 0.5%; mortality 11% vs 11%	Neutral vs placebo; sICH similar
Links	PubMed: https://pubmed.ncbi.nlm.nih.gov/40773205/	PubMed: https://pubmed.ncbi.nlm.nih.gov/38329148/

Tenecteplase Trials (2022–2024)

Trial	Population	Intervention	Comparator	Primary Outcome	Result	Link
AcT (Lancet 2022)	AIS ≤4.5 h, pragmatic Canadian trial	TNK 0.25 mg/kg IV	Alteplase 0.9 mg/kg IV	mRS 0–1 at 90 d (non-inferiority)	TNK non-inferior; safety comparable	https://www.thelancet.com/article/S0140-6736(22)01054-6/fulltext
TRACE-2 (Lancet 2023)	AIS ≤4.5 h, EVT-ineligible	TNK 0.25 mg/kg IV	Alteplase 0.9 mg/kg IV	mRS 0–1 at 90 d (non-inferiority)	TNK non-inferior to alteplase	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02600-

DAPT Trials: Inclusion, Regimen, Outcomes

Trial	Population	Timing	Regimen	Primary Outcome	Result	Link
ARAMIS (JAMA 2023)	Minor, nondisabling AIS; NIHSS ≤5	≤4.5 h	Clopidogrel 300 mg load + ASA 100 mg/d; then 12±2 d DAPT	mRS 0–1 at 90 d	Non-inferior to IV alteplase; less bleeding	https://pubmed.ncbi.nlm.nih.gov/37367978/
INSPIRES (NEJM 2023)	Mild stroke/high-risk TIA of atherosclerosis	≤72 h	Clopidogrel + aspirin	New stroke at 90 d	Reduced recurrence; modest ↑ moderate-severe bleeding	https://www.nejm.org/doi/full/10.1056/NEJMoa2309137

DOAC vs Warfarin — 2024–2025 Data

- FinACAF registry 2024: Poor TTR → worse outcomes; best-TTR warfarin ≈ DOACs.
- Meta-analysis 2025 (reduced-dose DOACs): excellent-TTR warfarin had lowest bleeding/mortality; DOACs remain effective.
- Earlier meta-analysis (2021): DOACs lowered SSE even at TTR>66%; bleeding risk similar.
- Cost-effectiveness 2024–25: Apixaban remains cost-effective vs warfarin in US analyses.

Anticoagulation After Ischemic Stroke/TIA: DOAC vs Warfarin

- FinACAF nationwide cohort (2024): Warfarin stratified by individual TTR quartiles (median TTR 72%).
- Finding: Poor TTR → higher IS/ICH/mortality; **high-TTR warfarin ≈ standard-dose DOACs** (differences absent/modest).
- Luojus et al. (EHJ Open 2025) meta-analysis: Reduced-dose DOACs effective/safe vs warfarin of sufficient TTR; **excellent-TTR warfarin** associated with **lowest bleeding & mortality** in that comparison.
- Context: Earlier TTR-stratified meta-analysis (Am J Cardiol 2021) showed DOACs reduced SSE even at TTR >66% (HR ~0.78), ICH lower; major bleeding similar.

DOAC vs Warfarin: Key 2024–2025 Evidence

Study	Design	Warfarin TTR Definition	Comparators	Primary/Key Outcomes	Main Finding	Link
FinACAF 2024	Nationwide cohort (AF)	Individual TTR quartiles; median 72%	Standard-dose DOACs	IS, ICH, mortality	Poor TTR worse; high-TTR ≈ DOACs (differences absent/modest)	https://pubmed.ncbi.nlm.nih.gov/38873855/
Luojus 2025 (EHJ Open)	Meta-analysis	Sufficient/excellent TTR subgroup analyses	Reduced-dose DOACs	Effectiveness & safety endpoints	Reduced-dose DOACs effective/safe; excellent-	https://academic.oup.com/ehjopen/article/5/3/oeaf046/8118063

Guidelines in Window

- AHA/ASA: No new early-management AIS guideline published 2022–2025; current U.S. guideline remains the 2019 update (Stroke).
- Link: https://pubmed.ncbi.nlm.nih.gov/31662037/
- ESO: 2023 expedited recommendation favors TNK 0.25 mg/kg over alteplase for IVT in eligible AIS within 4.5 h.
- Link: https://pubmed.ncbi.nlm.nih.gov/37021186/

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- Luojus 2025 (EHJ Open): https://academic.oup.com/ehjopen/article/5/3/oeaf046/8118063
- Am J Cardiol 2021 meta-analysis: https://pubmed.ncbi.nlm.nih.gov/33189659/