Making the Change: TNK for Acute Ischemic Stroke

OSN Stroke Conference

DATE: October 16th, 2020 PRESENTED BY: Noah Jacobson RN, MN, CCRN-K, SCRN, Cerebrovascular Program Manager

Disclosures

- I have nothing to disclose

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Objectives

- Identify the pharmacological differences between Alteplase (tPA) and Tenecteplase (TNK)
- Understand the differences in symptomatic intracerebral hemorrhage rate
- Identify the two current indications for TNK use for the treatment of Acute Ischemic Stroke
- Learn how the change to TNK has affect outcomes for patients at Oregon Health & Science University

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Alteplase (ALT)

- Only FDA approved pharmacological treatment for Acute Ischemic Stroke (AIS) for patients who arrive within 3 hours of last know well

- Time frame extended to 4.5 hours after ECAS3 trail, though FDA has not approved the 3-4.5 hour time

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Tenecteplase (TNK)

- First-line IV thrombolytic drug for myocardial infarction

- Not FDA approved for Acute Ischemic Stroke

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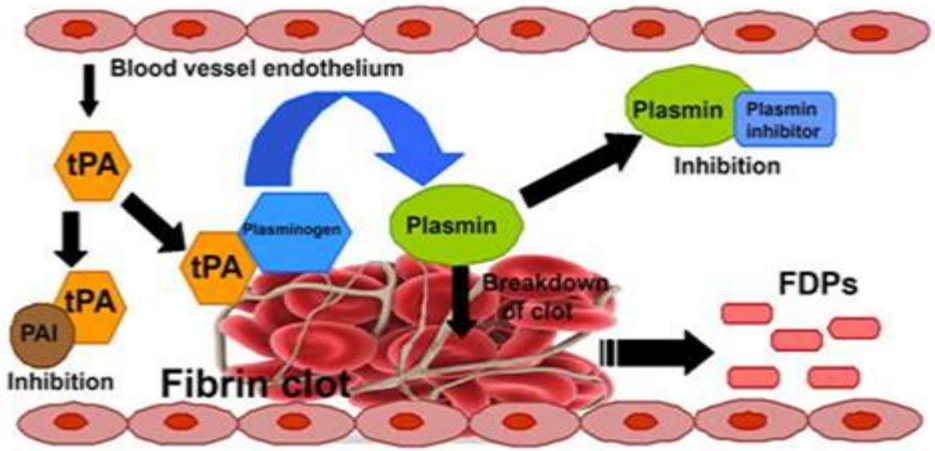
Plasminogen Activators

- Main role is to maintain patency of blood vessels



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Differences between ALT and TNK

- Tenecteplase is a genetically modified variant of alteplase
- TNK is a larger molecule with greater resistance to plasminogen activator inhibitor
- Increased fibrin specificity
- Half-life of TNK is 24 minutes ALT has a half-life of 5 min

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Symptomatic Intracerebral Hemorrhage Rates of TNK vs ALT

- ASSENT – 2 Trail for MI showed similar rates of intracranial hemorrhage
- Initial trials for ischemic stroke showed no SICH up to a dose of 0.5 mg/kg
- Later trails showed no difference in SICH rates

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Tenecteplase Implementation at OHSU

- Studies we reviewed to make the change
- How we made the change
- Our experience

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NOR-TEST

- Randomized control trail comparing ALT to TNK
- Dose 0.4 mg/kg TNK vs. 0.9 mg/kg ALT
- Primary end-point of this trail was to establish TNK as superior to ALT
- Trial showed TNK not superior nor inferior

Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial

Nicola Logallo [1], Vojtech Novotny [2], Jörg Assmus [3], Christopher E Kvistad [2], Lars Alteheld [4], Ole Morten Rønning [5], Bente Thommessen [6], Karl-Friedrich Amthor [7], Hege Ihle-Hansen [8], Martin Kurz [9], Håkon Tobro [10], Kamaljit Kaur [11], Magdalena Stankiewicz [12], Maria Carlsson [13], Åse Morsund [14], Titto Idicula [15], Anne Hege Aamodt [16], Christian Lund [16], Halvor Næss [17], Ulrike Waje-Andreassen [2], Lars Thomassen [2]

Affiliations + expand

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Abstract

Background: Tenecteplase is a newer thrombolytic agent with some pharmacological advantages over alteplase. Previous phase 2 trials of tenecteplase in acute ischaemic stroke have shown promising results. We aimed to investigate the safety and efficacy of tenecteplase versus alteplase in patients with acute stroke who were eligible for intravenous thrombolysis.

Methods: This phase 3, randomised, open-label, blinded endpoint, superiority trial was done in 13 stroke units in Norway. We enrolled adults with suspected acute ischaemic stroke who were eligible for thrombolysis and admitted within 4·5 h of symptom onset or within 4·5 h of awakening with symptoms, or who were eligible for bridging therapy before thrombectomy. Patients were randomly

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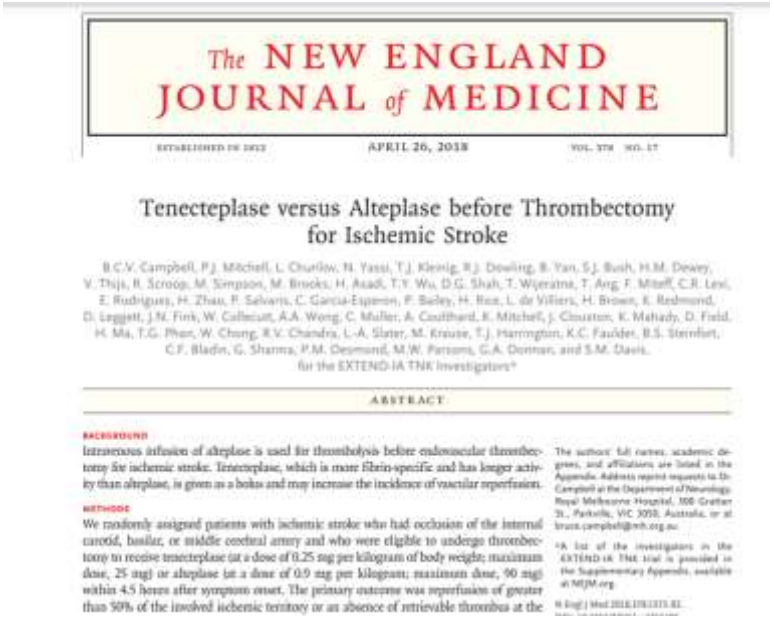
EXTEND-IA TNK

- Randomized trail comparing ALT to TNK for patients with a documented large vessel occlusion
- Dose of TNK 0.25 mg/kg vs 0.9 mg/kg ALT
- Recanalizaiton rates and median modified Rankin scores were both higher in the TNK arm



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Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Mitoff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia-Esperon, P. Bailey, H. Rice, L. de Villiers, H. Brown, E. Redmond, D. Leggett, J.N. Fink, W. Callecutt, A.A. Wong, C. Muller, A. Coulthard, K. Mitchell, J. Clouston, K. Mahady, D. Field, H. Ma, T.G. Phan, W. Chong, R.V. Chandra, L.-A. Slater, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Stenfort, C.F. Bladin, G. Sharma, P.M. Desmond, M.W. Parsons, G.A. Donnan, and S.M. Davis, for the EXTEND-IA TNK Investigators*

ABSTRACT

BACKGROUND

Intravenous infusion of alteplase is used for thrombolysis before endovascular thrombectomy for ischemic stroke. Tenecteplase, which is more fibrin-specific and has longer activity than alteplase, is given as a bolus and may increase the incidence of vascular reperfusion.

METHODS

We randomly assigned patients with ischemic stroke who had occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible to undergo thrombectomy to receive tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or alteplase (at a dose of 0.9 mg per kilogram; maximum dose, 90 mg) within 4.5 hours after symptom onset. The primary outcome was reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Campbell at the Department of Neurology, Royal Melbourne Hospital, 300 Grattan St., Parkville, VIC 3050, Australia, or at bruce.campbell@mh.org.au.

*A list of the investigators in the EXTEND-IA TNK trial is provided in the Supplementary Appendix, available at NEJM.org.

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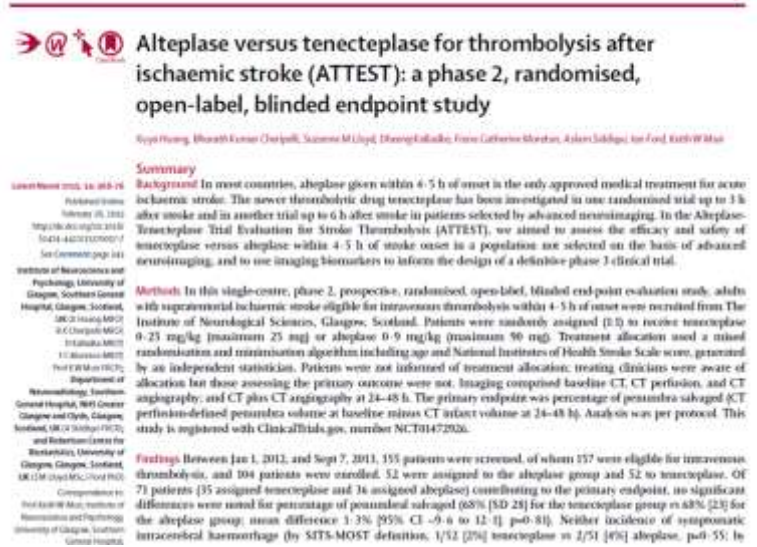
ATTEST - II

- Randomized control trail comparing ALT to TNK in the 4.5 hour time window
- Looked for difference in salvageable tissue using CTP at baseline



Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study

Summary

Background In most countries, alteplase given within 4·5 h of onset is the only approved medical treatment for acute ischaemic stroke. The newer thrombolytic drug tenecteplase has been investigated in one randomised trial up to 3 h after stroke and in another trial up to 6 h after stroke in patients selected by advanced neuroimaging. In the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST), we aimed to assess the efficacy and safety of tenecteplase versus alteplase within 4·5 h of stroke onset in a population not selected on the basis of advanced neuroimaging, and to use imaging biomarkers to inform the design of a definitive phase 3 clinical trial.

Methods In this single-centre, phase 2, prospective, randomised, open-label, blinded end-point evaluation study, adults with supratentorial ischaemic stroke eligible for intravenous thrombolysis within 4·5 h of onset were recruited from The Institute of Neurological Sciences, Glasgow, Scotland. Patients were randomly assigned (1:1) to receive tenecteplase 0·25 mg/kg (maximum 25 mg) or alteplase 0·9 mg/kg (maximum 90 mg). Treatment allocation used a mixed randomisation and minimisation algorithm including age and National Institutes of Health Stroke Scale score, generated by an independent statistician. Patients were not informed of treatment allocation; treating clinicians were aware of allocation but those assessing the primary outcome were not. Imaging comprised baseline CT, CT perfusion, and CT angiography, and CT plus CT angiography at 24–48 h. The primary endpoint was percentage of penumbra salvaged (CT perfusion-defined penumbra volume at baseline minus CT infarct volume at 24–48 h). Analysis was per protocol. This study is registered with ClinicalTrials.gov, number NCT01472926.

Findings Between Jan 1, 2012, and Sept 7, 2013, 155 patients were screened, of whom 157 were eligible for intravenous thrombolysis, and 104 patients were enrolled. 52 were assigned to the alteplase group and 52 to tenecteplase. Of 71 patients (35 assigned tenecteplase and 36 assigned alteplase) contributing to the primary endpoint, no significant differences were noted for percentage of penumbral salvaged (68% [SD 28] for the tenecteplase group vs 68% [23] for the alteplase group; mean difference 1·3% [95% CI −9·6 to 12·1]; p=0·81). Neither incidence of symptomatic intracerebral haemorrhage (by SITS-MOST definition, 1/52 [2%] tenecteplase vs 2/51 [4%] alteplase, p=0·55; by

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Making the Change

- Navigating Institutional Approval Boards

- Adding to formulary

Cost Difference?

- Assuming a 80kg patient TNK was less expensive than ALT

- Costs vary by insurance companies and region of the country

Education for Staff

	Alteplase (tPA)	Tenecteplase (TNK)
Dosing	0.9 mg/kg	0.25 mg/kg
Bolus	10% of overall dose pushed over 2 min	All of the dose pushed over 5 sec
IV infusion	Remaining 90% infused over 1 hour	NO INFUSION
BP guidelines	SBP less than 185 DBP less than 110	SBP less than 185 DBP less than 110
Monitoring before bolus	Full set of vital signs with in 15 min of IV Push	Full set of vital signs with in 15 min of IV Push
Monitoring after	Full set of vital signs and neuro exams Q15 min x 4 Q 30 min x 6 Q1 hr x 16	Full set of vital signs and neuro exams Q15 min x 4 Q 30 min x 6 Q1 hr x 16
mixing	Pharmacist to mix and draw up bolus: 100 mg vial. Use transfer set with accompanying diluent (100 mL vial of sterile water for injection); let stand undisturbed for several minutes to allow large bubbles to dissipate; mix by gentle swirling; do not shake. No vacuum is present in 100 mg vial. Final concentration 1 mg/mL. Bolus dose (10% of total dose) may be prepared by one of three methods: 1) Removal of the appropriate volume from reconstituted solution (1 mg/mL) 2) Removal of the appropriate volume from a port on the infusion line after priming 3) Programming an infusion pump to deliver the appropriate volume at the initiation of infusion	Pharmacist to mix and draw up bolus: Tenecteplase should be reconstituted using the supplied 10 mL syringe with TwinPak Dual Cannula Device and 10 mL sterile water for injection. Do not shake when reconstituting. Slight foaming is normal and will dissipate if left standing for several minutes. The reconstituted solution is 5 mg/mL. Any unused solution should be discarded.
Administration	Neurology Attending to be present at time of administration. Push by Attending/Fellow/Resident. Pharmacist to help with set up of infusion. Bedside RN to connect and start infusion.	Neurology Attending to be present at time of administration. Push by Attending/Fellow/Resident. There is no further infusion

- One of the easier changes we have made
- Change education done through OHSU huddle structure and unit level huddles

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Precautions with Change

- Pre-mixing
- ALT dosing vs. TNK dosing
- Dosing for MI, low NIH stroke, LVO

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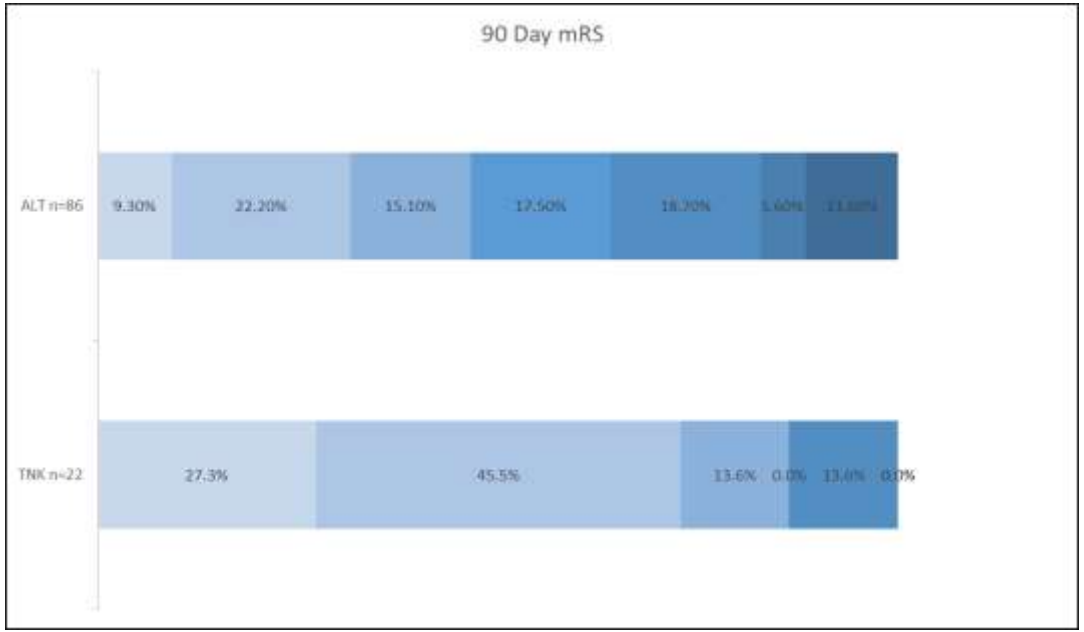
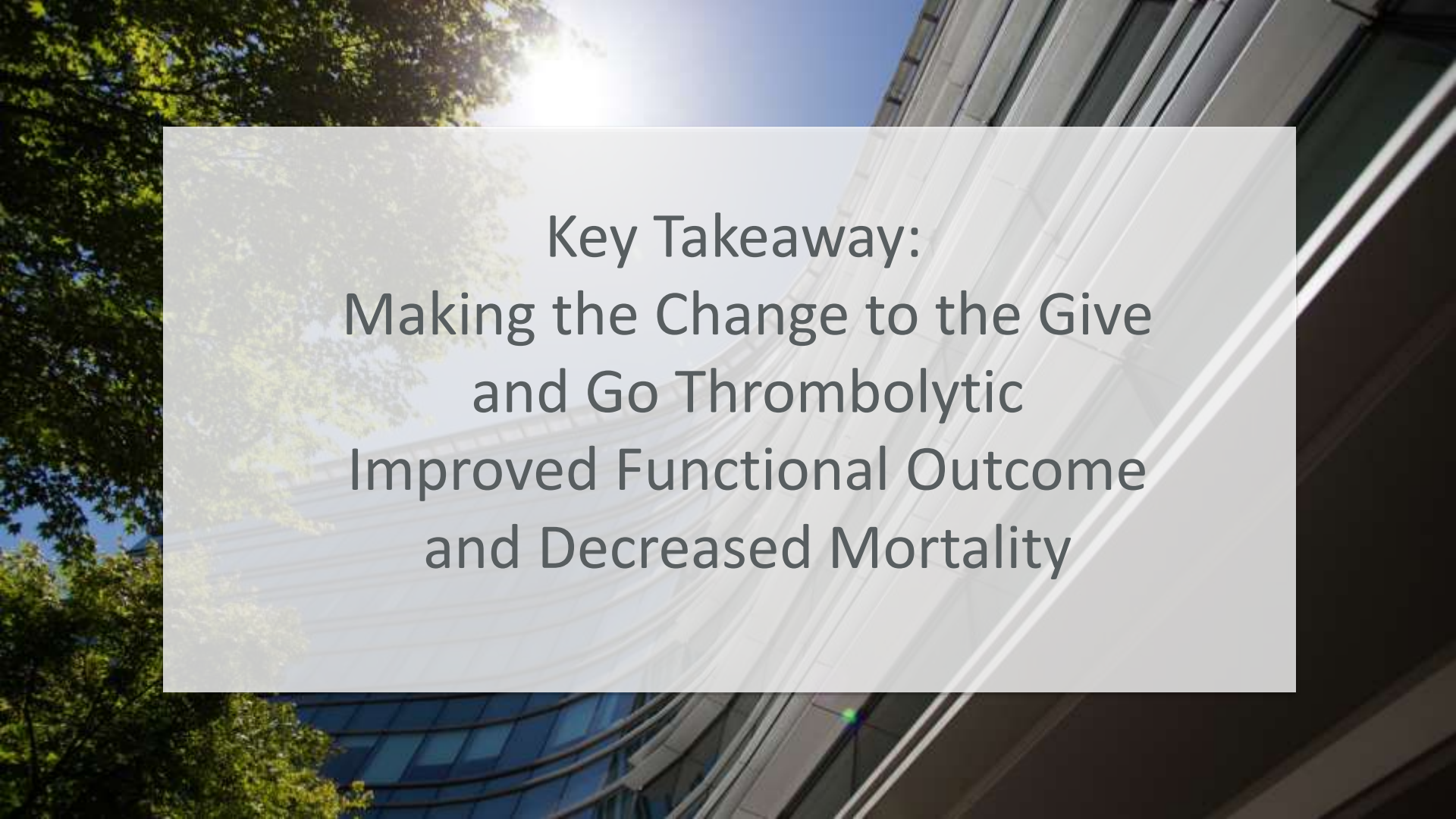
Outcomes of OHSU Patients




Key Takeaway:
Making the Change to the Give and Go Thrombolytic Improved Functional Outcome and Decreased Mortality

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Thank You