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ST ELEVATION MYOCARDIAL INFARCTION

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ACS/STEMI 2016

ACUTE CORONARY SYNDROMES PATHOPHYSIOLOGY

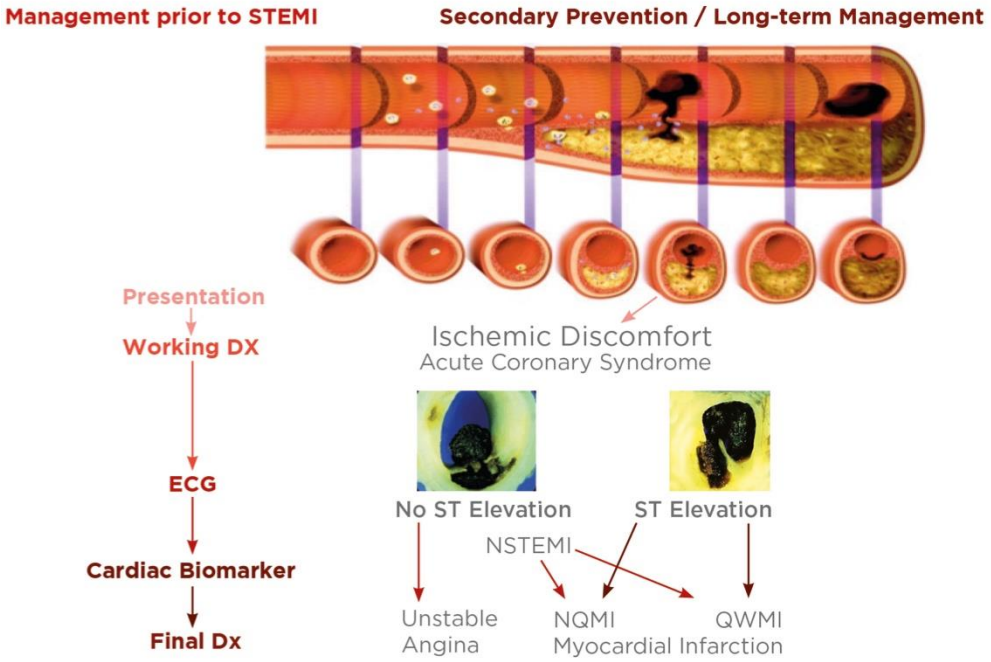
CORONARY ARTERY PLAQUE RUPTURE[1]:

- **Intraluminal thrombus**
- **Obstruction to coronary flow**
- **ACS**

Severity of **CORONARY VESSEL OBSTRUCTION** & extent of myocardium involved **DETERMINES CHARACTERISTICS** of clinical presentation

ONSET OF STEMI:
- Pre-hospital
- Initial recognition and management in the Emergency Department
-

HOSPITAL MANAGEMENT:
- Medications
- Arrhythmias
- Complications
- Preparations for discharge



1. Davies M. CORONARY DISEASE: The pathophysiology of acute coronary syndromes [Internet]. 2019 [cited 5 February 2019]. Available from: https://heart.bmj.com/content/83/3/361.full
2. Antman E, Bassand J, Klein W, Ohman M, Lopez Sendon J, RydŽn L et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. Journal of the American College of Cardiology. 2000;36(3):959-969.

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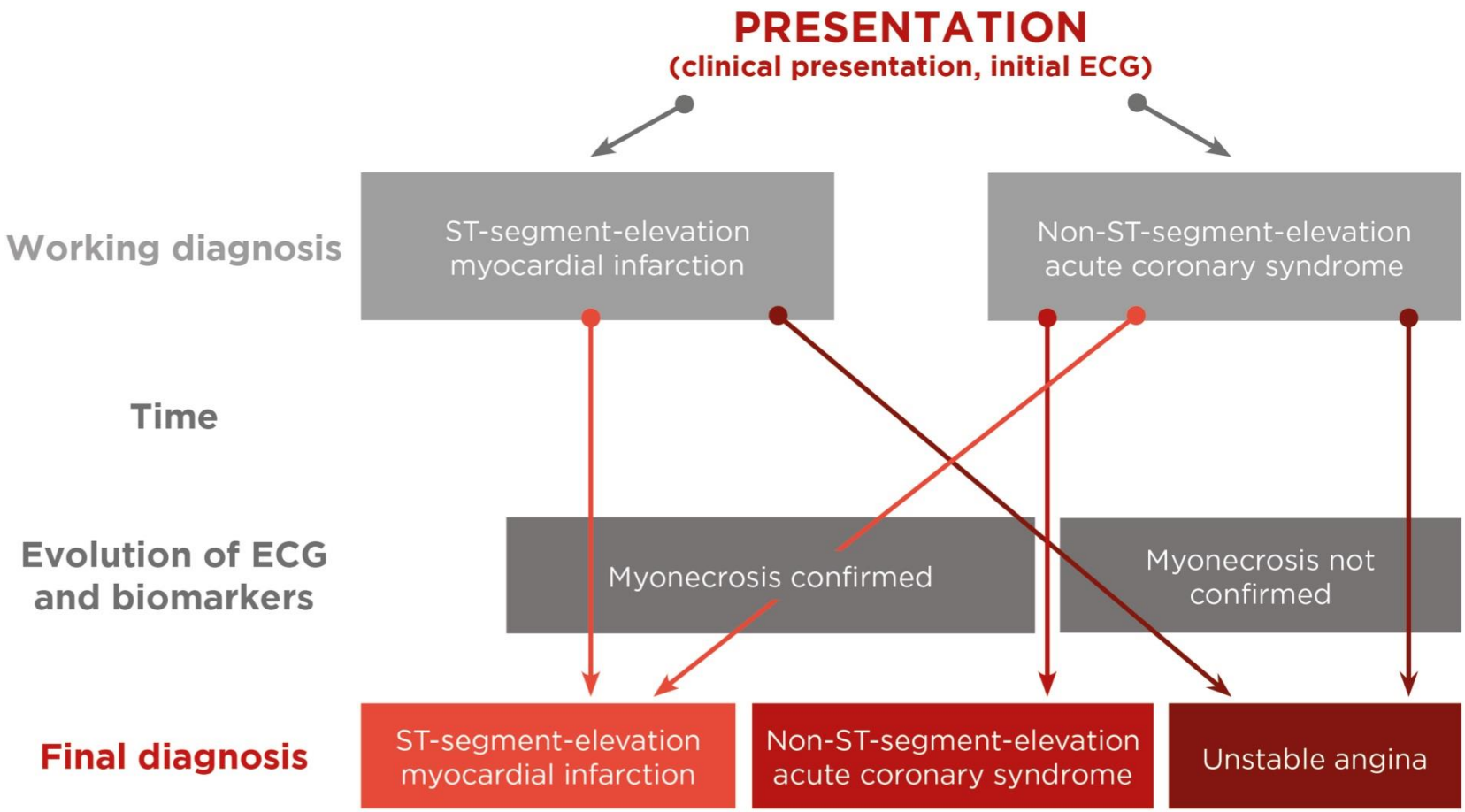
ACUTE CORONARY SYNDROMES



ECG Interpretation: [Internet]. Intranet.tdmu.edu.ua. 2019 [cited 5 February 2019]. Available from: http://intranet.tdmu.edu.ua/data/kafedra/internal/vnutrmed2/classes_stud/en/med/lik/ptn/Internal%20medicine/5%20course/03.%20Acute%20coronary%20syndrome.%20Acute%20myocardial%20infarction.htm

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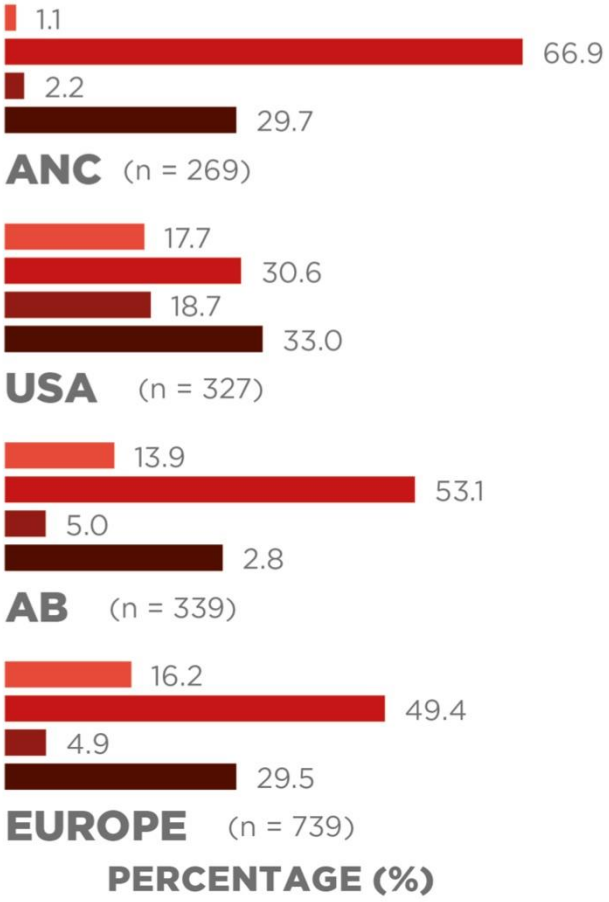
REAL WORLD DATA



REPERFUSION THERAPY BY GEOGRAPHIC REGION IN THE GRACE STUDY

Up to 1/3 of STEMI patients did not receive reperfusion Rx

ANC: Australia, New Zealand, Canada; AB: Argentina, Brazil

Eagle K, Goodman S, Avezum ç, Budaj A, Sullivan C, L—pez-Send—n J. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). The Lancet. 2002;359(9304):373-377.

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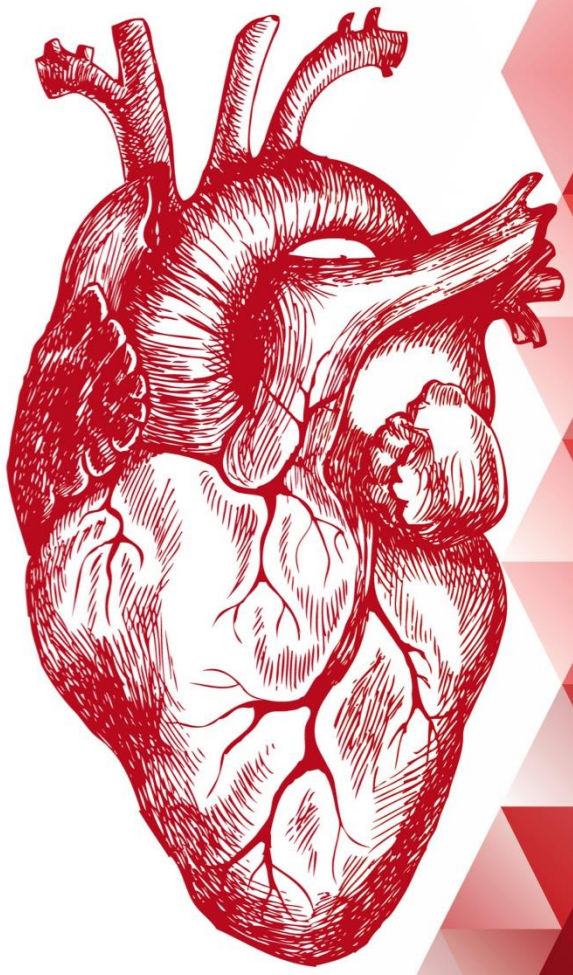
REAL WORLD DATA IN SA

LIMITED INFORMATION:

- ONE PUBLISHED STUDY – STATE SECTOR
- PILOT STUDY IN PRIVATE SECTOR (PRETORIA REGION)

SO WHAT DO WE KNOW?



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REAL WORLD

DNT for **FIBRINOLYTICS** in Acute MI:

- **Retrospective study** of patient who received thrombolytics for AMI
- **State sector** (3 hospitals in Cape Town) – Jan 2008 to July 2010

Time intervals	Median time (range) (min)
Door to Triage	6 (0 – 157)
Triage to ECG	2 (0 – 245)
Door to ECG	13 (1 – 402)
ECG to fibrinolytic	38 (4 – 262)
Door to needle time	54 (13 – 553)

Range from 13min to 9hrs!

Maharaj R, Geduld H, Wallis L. Door-to-needle time for administration of fibrinolytics in acute myocardial infarction in Cape Town. South African Medical Journal. 2012;102(4):241-244.

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DELAYS

Reasons for delay in fibrinolytic initiation	%
Attending GP seeking advice from senior Dr before starting fibrinolysis	28.6%
Difficulty in interpreting ECG	18.6%
Pt with atypical symptoms – delays diagnosis of AMI	12.9%
Pt in cardiac arrest before thrombolysis can be started	11.4%
Pt with hypertension	7.1%
Change of shift – Dr/Nurses could not attend timeously	7.1%
Delay in chest X-ray	4.3%
Not stock of agent in Casualty – fetch from pharmacy	4.3%
Waiting: Workups, intensive care beds, equipment	5.7%

EDUCATION OF MEDICAL OFFICER CONTRIBUTED TO 60% OF DELAY IN INITIATION OF LYTIC THERAPY

Maharaj R, Geduld H, Wallis L. Door-to-needle time for administration of fibrinolytics in acute myocardial infarction in Cape Town. South African Medical Journal. 2012;102(4):241-244.

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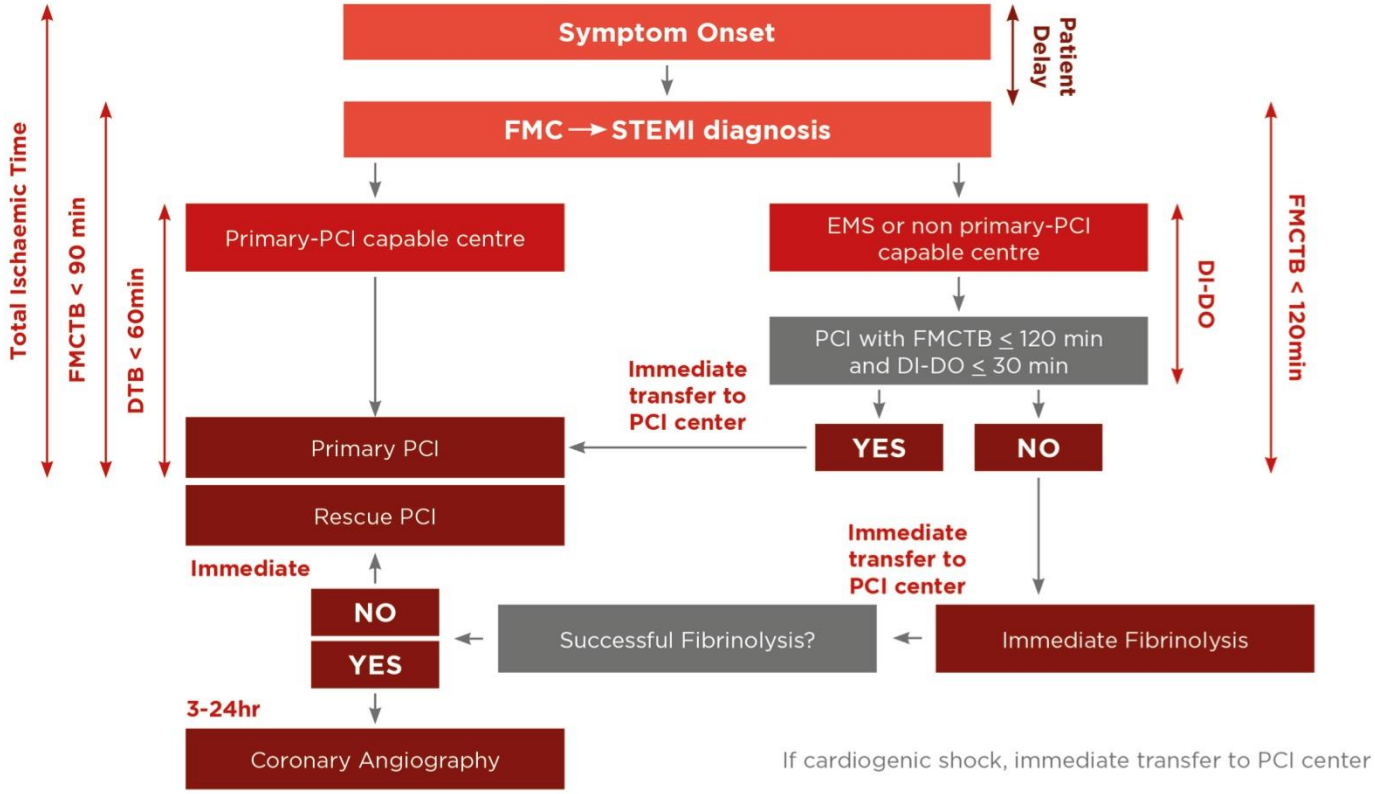
REPERFUSION STRATEGY: ESC 2014



DI-DO = door-in to door-out time; DTB = door-to-balloon time; EMS = emergency medical service; FMC = first medical contact; FMCTB = first-medical-contact-to-ballon-time; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

2014 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2014;35(37):2541-2619.

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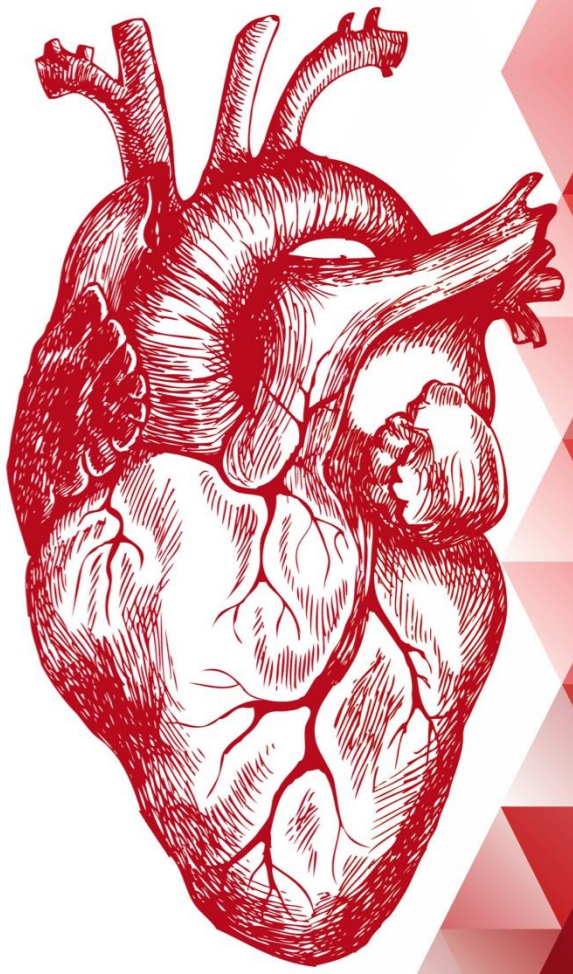
FIBRINOLYSIS

Therefore fibrinolysis becomes an
IMPORTANT REPERFUSION STRATEGY

Available fibrinolytics in SSA:

- Alteplase – Actilyse®
- Tenecteplase (TNK) - Metalyse®
- Streptokinase (STK) - Streptase®



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Steg P, James S, Atar D, Badano L, Lundqvist C, Borger M et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2012;33(20):2569-2619.

PHARMACOLOGICAL DIFFERENCES BETWEEN AVAILABLE FIBRINOLYTICS

	Streptokinase	Alteplase	Tenecteplase
Fibrin specificity	-	++	+++
Plasminogen activation	Indirect	Direct	Direct
Half life	23-29 min	4-8 min	20 min
Dose	1.5 MIU over 60 min	100 mg over 90 min	0.5 mg/kg single bolus
Antigenicity	+	-	-

Adapted from:
Adapted from Kunadian V, Gibson C. Thrombolytics and Myocardial Infarction. Cardiovascular Therapeutics. 2010;30(2):e81-e88.

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CLINICAL ADVANTAGES OF TENECTEPLASE VS OTHER FIBRINOLYTICS

LONGER HALF LIFE:

- Allows for single bolus injection – improved time and resource management

MORE FIBRIN SELECTIVE:

- Less systemic side effects
- Increased lytic potency

NO ANTIGENICITY:

- Can be administered to patients who have been exposed to STK ≤ 1 year.

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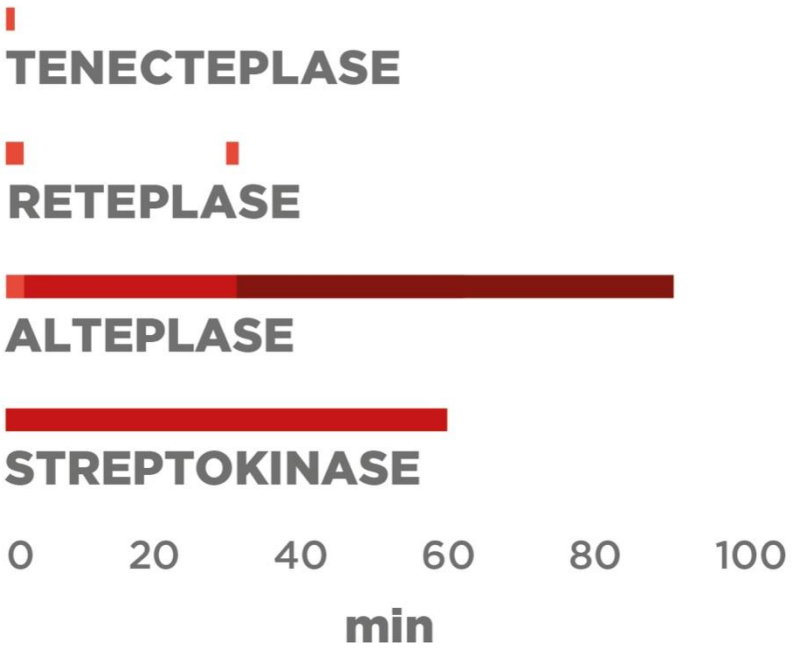
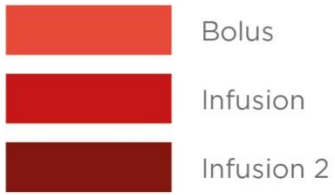
Kunadian V, Gibson C. Thrombolytics and Myocardial Infarction. Cardiovascular Therapeutics. 2010;30(2):e81-e88.

SINGLE BOLUS: CONVENIENCE



First thrombolytic agent that can be administered over **5-10 SECONDS IN A SINGLE DOSE**



Llevadot J. Bolus Fibrinolytic Therapy in Acute Myocardial Infarction. JAMA. 2001;286(4):442.

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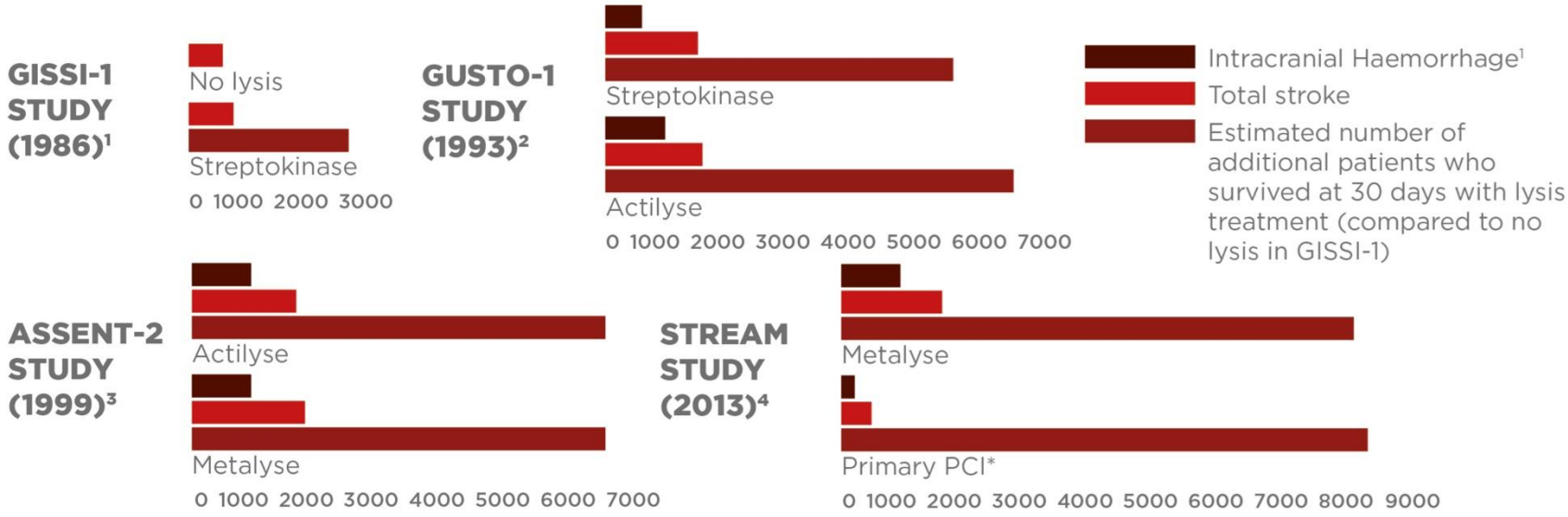
WEALTH OF EVIDENCE TO SUPPORT TNK EFFICACY

Note that this slides compares patient numbers to show the breadth of evidence. thus for linking purposes, use each trial population sizes on outcomes mentioned. Trials found in reference pack



ESTIMATED NUMBER OF EVENTS PER 100,000 PATIENT YEARS IN PATIENTS SUFFERING FROM ACUTE HEART ATTACK**

Since approval, Metalyse has treated 1.25 million patients and provided a 30 day survival benefit to an estimated 102,500 more patients than treatment with no lysis.

* Primary Percutaneous Coronary Intervention **treated within 6 hours after onset of symptoms

1. Rovelli F, De Vita C, Feruglio G, Lotto A, Selvini A, Tognoni G. EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION. The Lancet. 1986;327(8478):397-402.
2. Califf R, White H, Van de Werf F, Sadowski Z, Armstrong P, Vahanian A et al. One-Year Results From the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial. Circulation. 1996;94(6):1233-1238.
3. TNKase¨ ASSENT-2 Clinical Trial Design and Methodology [Internet]. Tnkase.com. 2019 [cited 20 January 2019]. Available from: https://www.tnkase.com/ami-treatment-clinical-trial-data/assent-2-clinical-trial.html
4. Armstrong P, Gershlick A, Goldstein P, Wilcox R, Danays T, Lambert Y et al. Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction. New England Journal of Medicine. 2013;368(15):1379-1387.

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CLINICAL TRIAL OVERVIEW

GUSTO:
Alteplase superior to STK

ASSENT-2:
TNK as effective as Alteplase

TNK ≥ ALTEPLASE > STK

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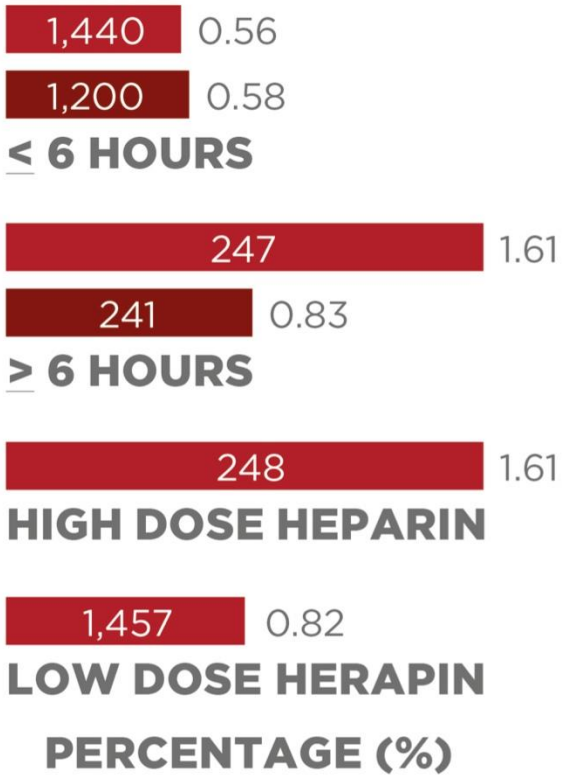
ASSENT I



LOWER ICH IF PT TREATED WITHIN 6HR + LOWER HEPARIN DOSE

ASSENT I (Assessment of the Safety and Efficacy of a New Thrombolytic). **Phase II randomised, open label, multicentre trial of TNK in AMI = 3 235 pt**

AIM:

to identify an appropriate dose of TNK in ST elevation MI Patients with clinical outcomes at 30 days

OUTCOMES:

- High survival rate if patients treated ‹ 6hr
- Lower ICH if pt treated within 6hr + lower heparin dose
- 50mg dose stopped early and replaced with 40mg

30mg TNK, n = 1 705

40mg TNK, n = 1 457

Van de Werf F, Cannon C, Luyten A, Houbracken K, McCabe C, Berioli S et al. Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: The ASSENT-1 trial. American Heart Journal. 1999;137(5):786-791.

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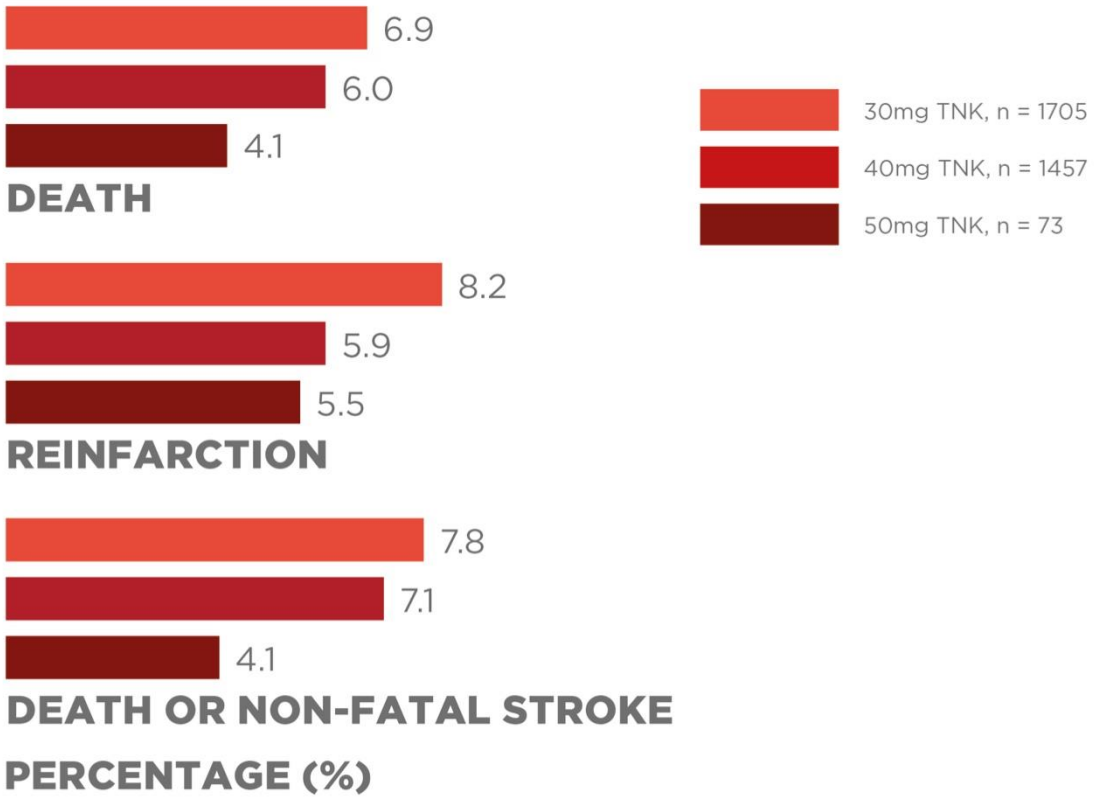
ASSENT-1:
MAJOR CLINICAL OUTCOMES AT 30 DAYS



Van de Werf F, Cannon C, Luyten A, Houbracken K, McCabe C, Berioli S et al. Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: The ASSENT-1 trial. American Heart Journal. 1999;137(5):786-791.

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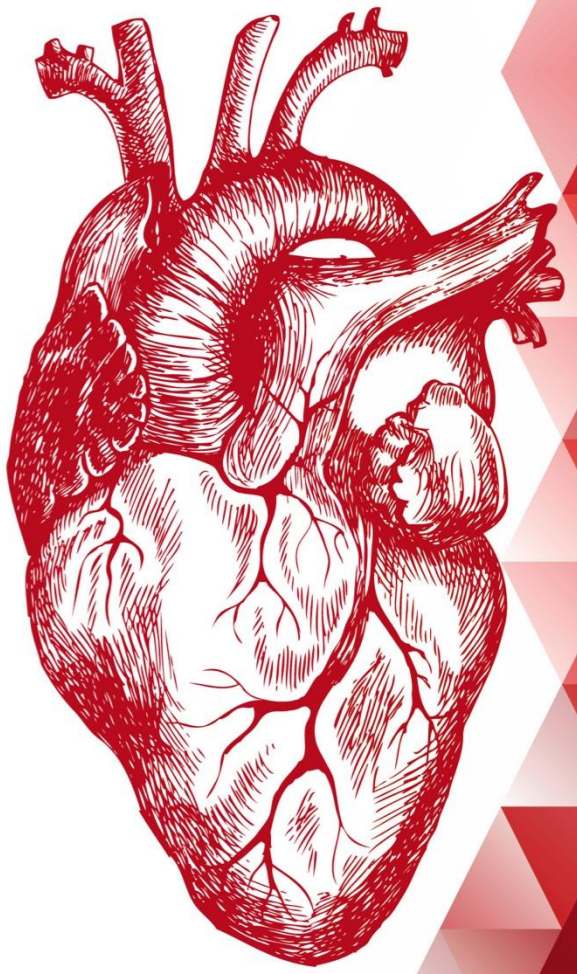
ASSENT II

ASSENT II (Assessment of the Safety and Efficacy of a New Thrombolytic)
Phase III randomised, open label, multicentre trial of TNK in AMI = 16 494 pts

AIM:
Comparing a single-bolus TNK compared with rt-PA in acute myocardial infarction Dose of TNK = 0.53mg/kg (ASSENT I)

Outcomes:

- **30-DAY MORTALITY CONFIRMS EQUIVALENCE BETWEEN TNK AND RT-PA – PERSISTED AT 1-YEAR FOLLOWUP**
- **SIGNIFICANTLY FEWEr** MB in TNK vs rt-PA
- **COMPARABLE RATES** of stroke



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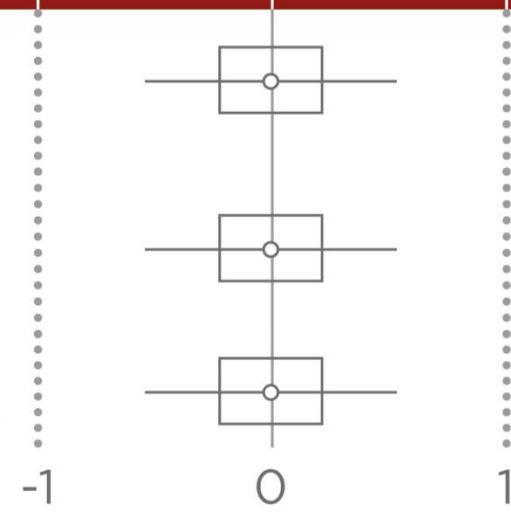
Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

Abstract in reference pack provides info for this slide

ASSENT II

ASSENT-2: 30-DAY MORTALITY CONFIRMS EQUIVALENCE OF TNK AND RT-PA

	TNK-t-PA (%)	rt-PA (%)	Absolute difference (90% CI)	p value for equivalence
Primary analysis (adjusted rate)	6.179	6.151	0.028 (-0.55, 0.60)	0.0059
Secondary analysis (unadjusted rate)	6.160	6.176	-0.016 (-0.62, 0.59)	0.0060
Logistic regression	6.089	6.140	-0.051 (-0.62, 0.52)	0.0025



Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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ASSENT I TRIAL

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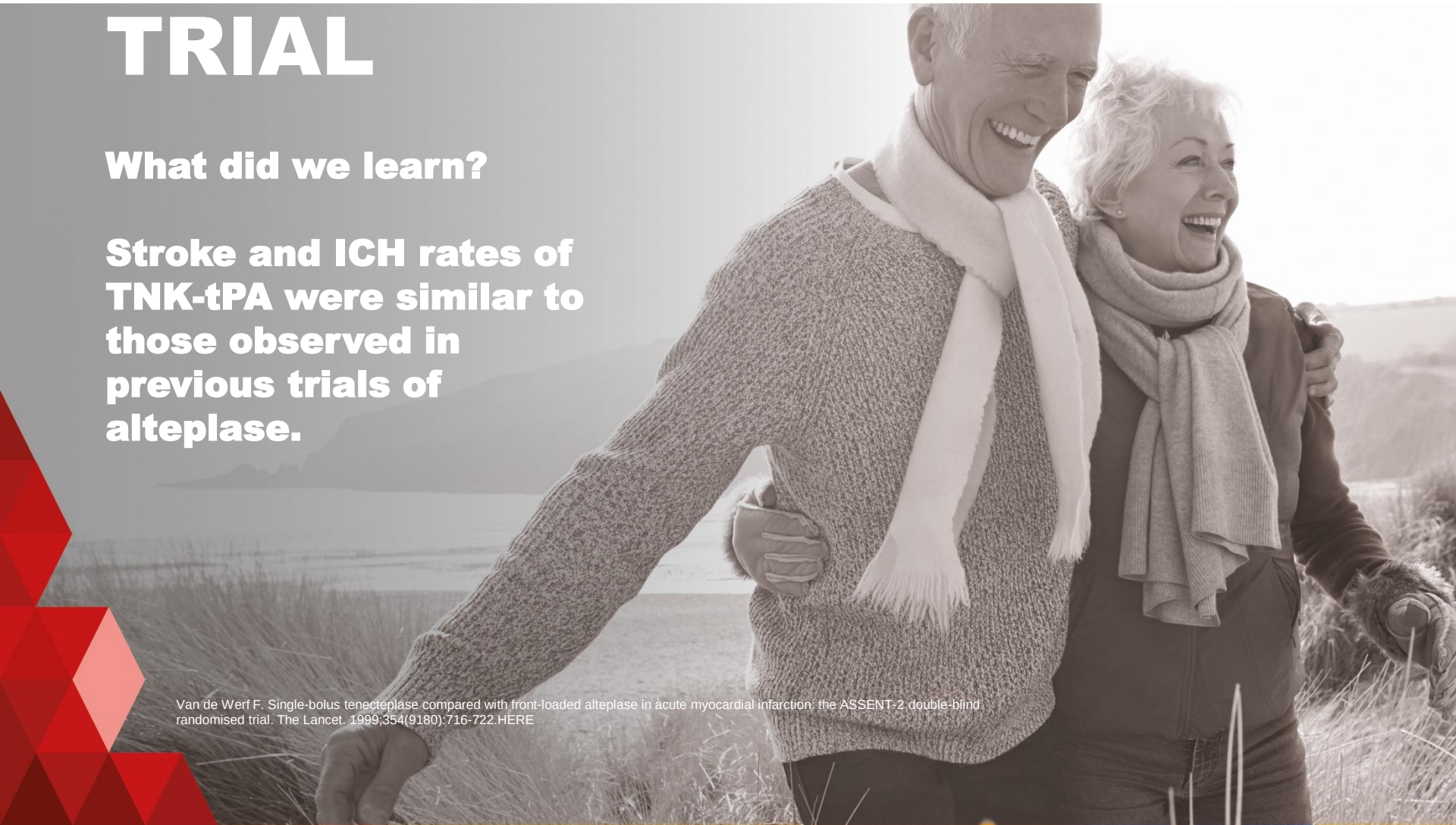
What did we learn?

Stroke and ICH rates of TNK-tPA were similar to those observed in previous trials of alteplase.

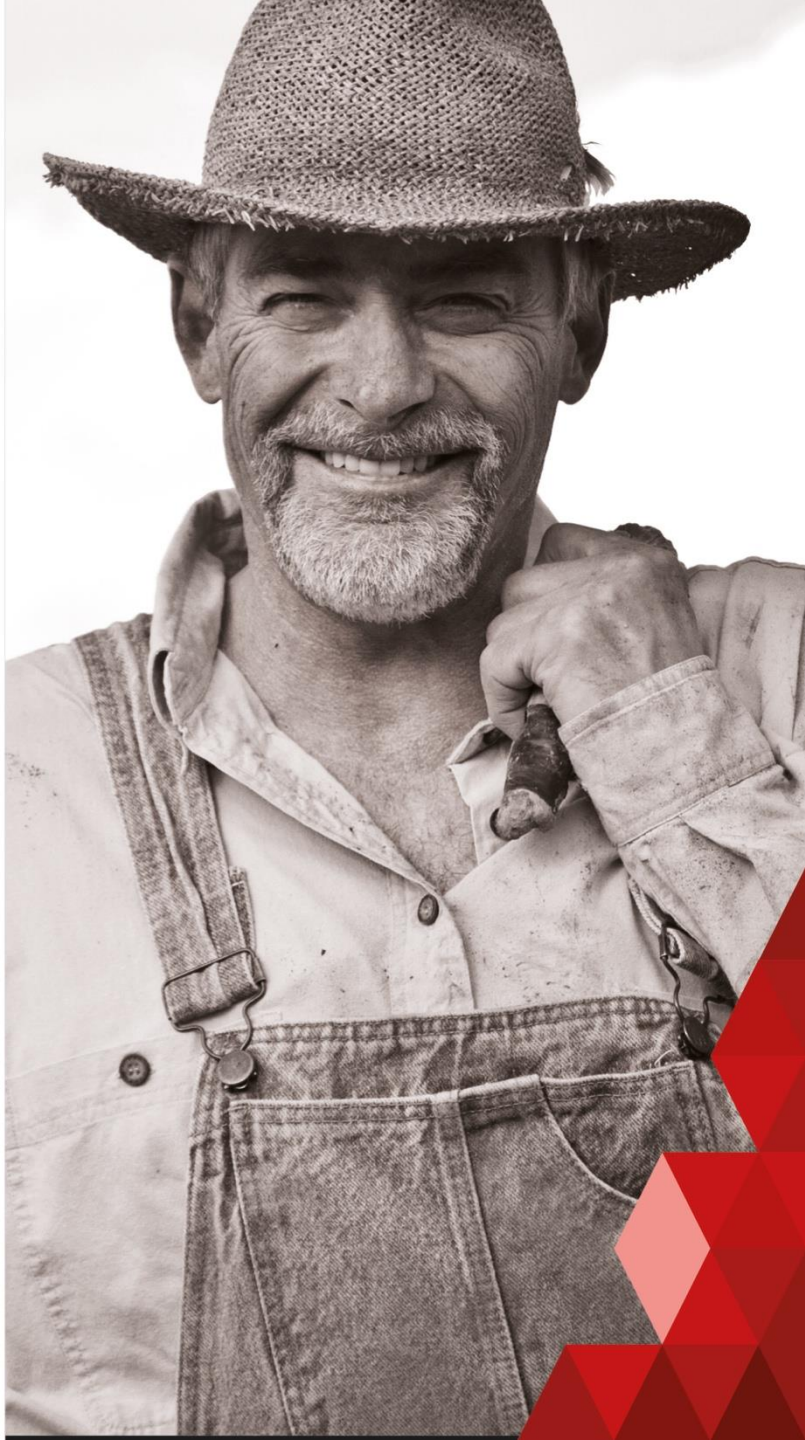


Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.HERE

ASSENT II TRIAL

WHAT DID WE LEARN?

The trial achieved its primary objective and found TNK-tPA & alteplase to be significantly equivalent



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Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

ASSENT 3 TRIAL
TENECTEPLASE + ENOXAPARIN - THE WINNING REGIMEN

WHAT DID WE LEARN?

The reductions in ischaemic complications in the full dose TNK plus enoxaparin group **WERE MORE CONSISTENT.**

These reductions were found to be **PRESENT EARLY** after the start of treatment.

Because of its ease of administration, TNK-tPA plus enoxaparin seems to be an **ATTRACTIVE ALTERNATIVE RE-PERFUSION REGIMEN.**

The full-dose TNK-tPA/enoxaparin arm is **THE CLEAR WINNER** since its **EFFICACY, SAFETY AND EASE OF ADMINISTRATION** make it the preferred strategy in acute myocardial infarction.

Armstrong P. Efficacy and safety of unfractionated heparin versus enoxaparin: a pooled analysis of ASSENT-3 and -3 PLUS data. Canadian Medical Association Journal. 2006;174(10):1421-1426.

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ACTILYSE CT SUMMARY

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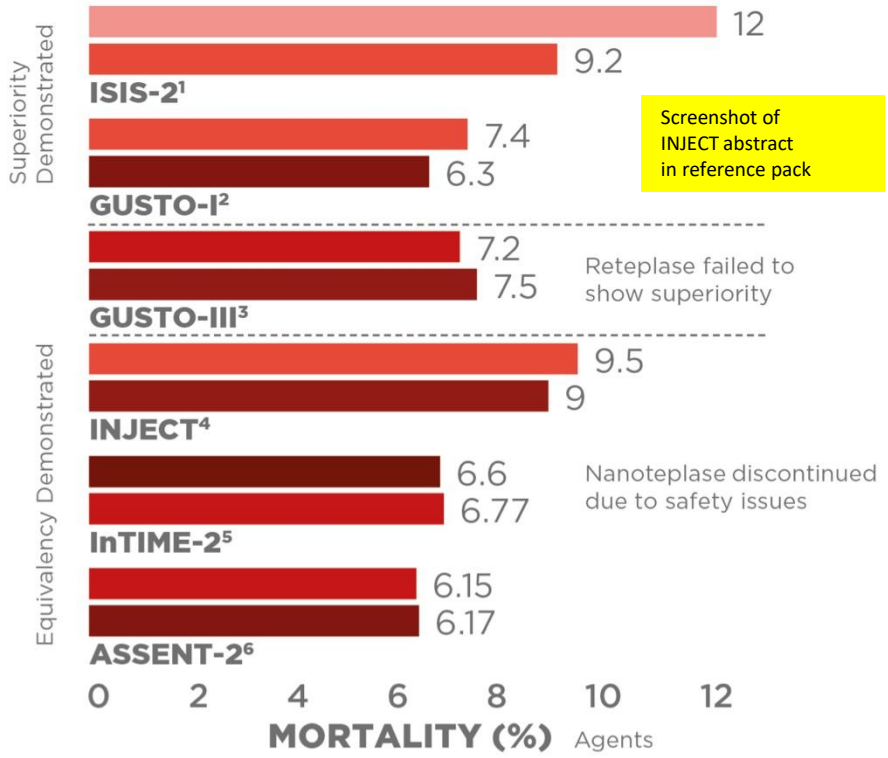
MAJOR TRIALS COMPARING 30- OR 35-DAY MORTALITY AMONG FIBRINOLYTICS



Screenshot of INJECT abstract in reference pack

	Superiority	Equivalency
ISIS-2	2P<0.00001	P=NS
GUSTO-I	P=0.001	P=NS
GUSTO-III	P=NS	P=NS
INJECT	P=NS	P=0.0003
InTIME-2	P=NS	P=0.047
ASSENT-2	P=NS	P=0.006

Placebo
Streptokinase
Alteplase
Reteplase
Nanoteplase*
Tenecteplase

* *Higher ICH, rate for n-PA, (0.62% vs 1.13%; P=0.003). * Lower major bleeds for TNK-tPA (4.7% vs 5.9%; P=0.0002).

1. Randomised Trial of Intravenous Streptokinase, Oral Aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. The Lancet. 1988;332(8607):349-360.
2. Adapted from Califf R, White H, Van de Werf F, Sadowski Z, Armstrong P, Vahanian A et al. One-Year Results From the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial. Circulation. 1996;94(6):1233-1238.
3. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.
4. Wilcox R. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. The Lancet. 1995;346(8971):329-336.
5. Intravenous NPA for the treatment of infarcting myocardium early. InTIME-II, a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. European Heart Journal. 2000;21(24):2005-2013.
6. Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 doubleblind randomised trial. The Lancet. 1999;354(9180):716-722.

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FIBRINOLYTIC AGENT

Fibrinolytic Agent	Dose[1]	Fibrin Specificity[1]	Fibrinogen Depletion[2]	Antigenic[1]	Patency Rate (90-min TIMI 2 or 3 flow)
FIBRIN SPECIFIC					
Tenecteplase (TNK)	Single IV weight based Bolus±	++++	Minimal	No	75%[2]
Reteplase (r-PA)	10 units + 10-unit IV boluses given 30 min apart	++	Moderate	No	75%[2]
Alteplase (t-PA)	90-min weightbased infusion	++	Mild	No	75%[2]
NON-FIBRIN SPECIFIC					
Streptokinase	1.5 million units IV given over 30-60 min	No	Marked	Yes	50%[2]

1. Adapted from Kunadian V, Gibson C. Thrombolytics and Myocardial Infarction. Cardiovascular Therapeutics. 2010;30(2):e81-e88.
2. Wander G, Chabra S. Critical Analysis of Various Drugs Used for Thrombolytic Therapy in Acute Myocardial Infarction [Internet]. Citeseerx.ist.psu.edu. 2019 [cited 9 February 2019]. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.672.6208&rep=rep1&type=pdf

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TABLE 6: FIBRINOLYTIC AGENT

FIBRINOLYTIC AGENTS AVAILABLE FOR TREATMENT OF ACUTE STEMI IN LMICS

Characteristic	Streptokinase	Alteplase	Reteplase	Tenecteplase
Dose / Administration	1.5 MU infusion over 60 min	15mg bolus + 90 min infusion up to 85mg	10 + 10 units double bolus, each given over 2 min, 30 min apart	If weight of patient is: <60kg then 30mg IV bolus 60-69kg then 35mg IV bolus 70-79kg then 40mg IV bolus 80-89kg then 45mg IV bolus >90kg then 50mg IV bolus
Allergic reactions	Yes	No	No	No
Plasminogen activation	Indirect	Direct	Direct	Direct
Plasma half-life	18	5	18	20
Fibrin specificity	Poor	Good	Moderate	Excellent
Activity on plateletrich clot	Poor	Good	Moderate	Excellent
90-minute patency	Good	Excellent	Excellent	Excellent
TIMI Grade 3 flow (%)	32	54	60	63
Resistance to PAI-I	No	No	No	Yes
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal

Wander G, Chabra S. Critical Analysis of Various Drugs Used for Thrombolytic Therapy in Acute Myocardial Infarction [Internet]. Citeseerx.ist.psu.edu. 2019 [cited 9 February 2019]. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.672.6208&rep=rep1&type=pdf

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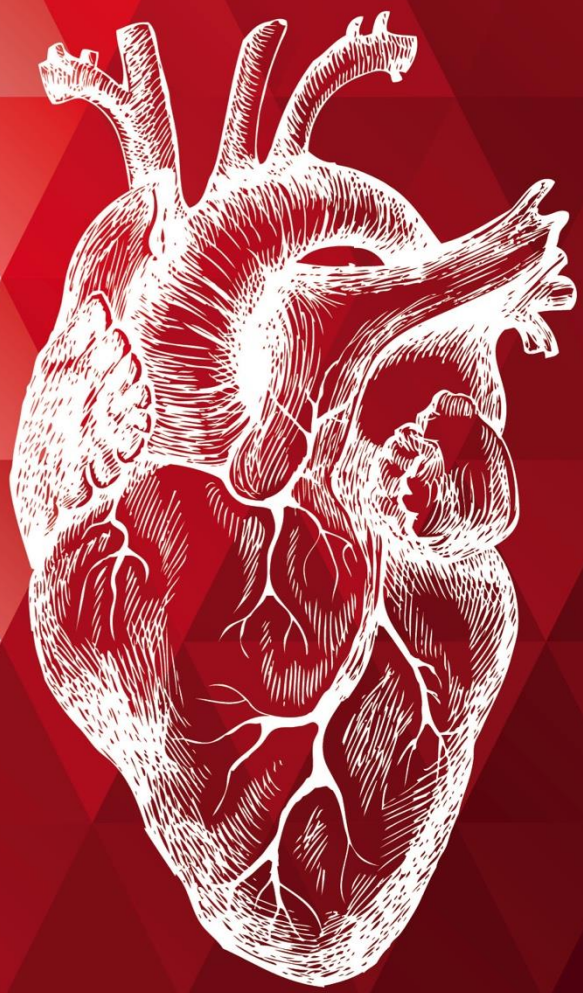
FIBRINOLYTIC AGENTS

HOW DO I CHOOSE AN AGENT?

THE EVIDENCE



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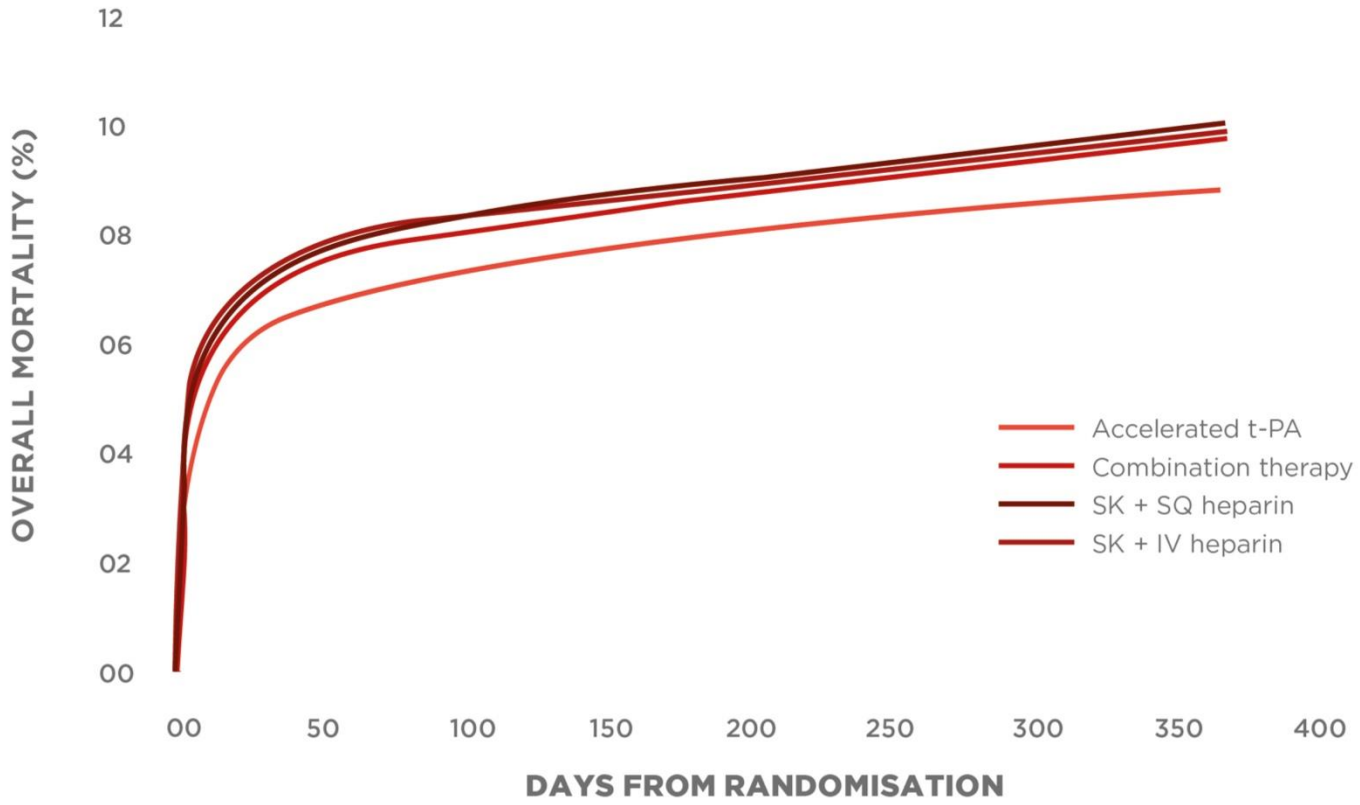
GUSTO 1

GUSTO-1 STUDY

STEMI DIAGNOSIS



Global use of strategies to open occluded coronary arteries I

Adapted from:

Califf R, White H, Van de Werf F, Sadowski Z, Armstrong P, Vahanian A et al. One-Year Results From the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial. Circulation. 1996;94(6):1233-1238.

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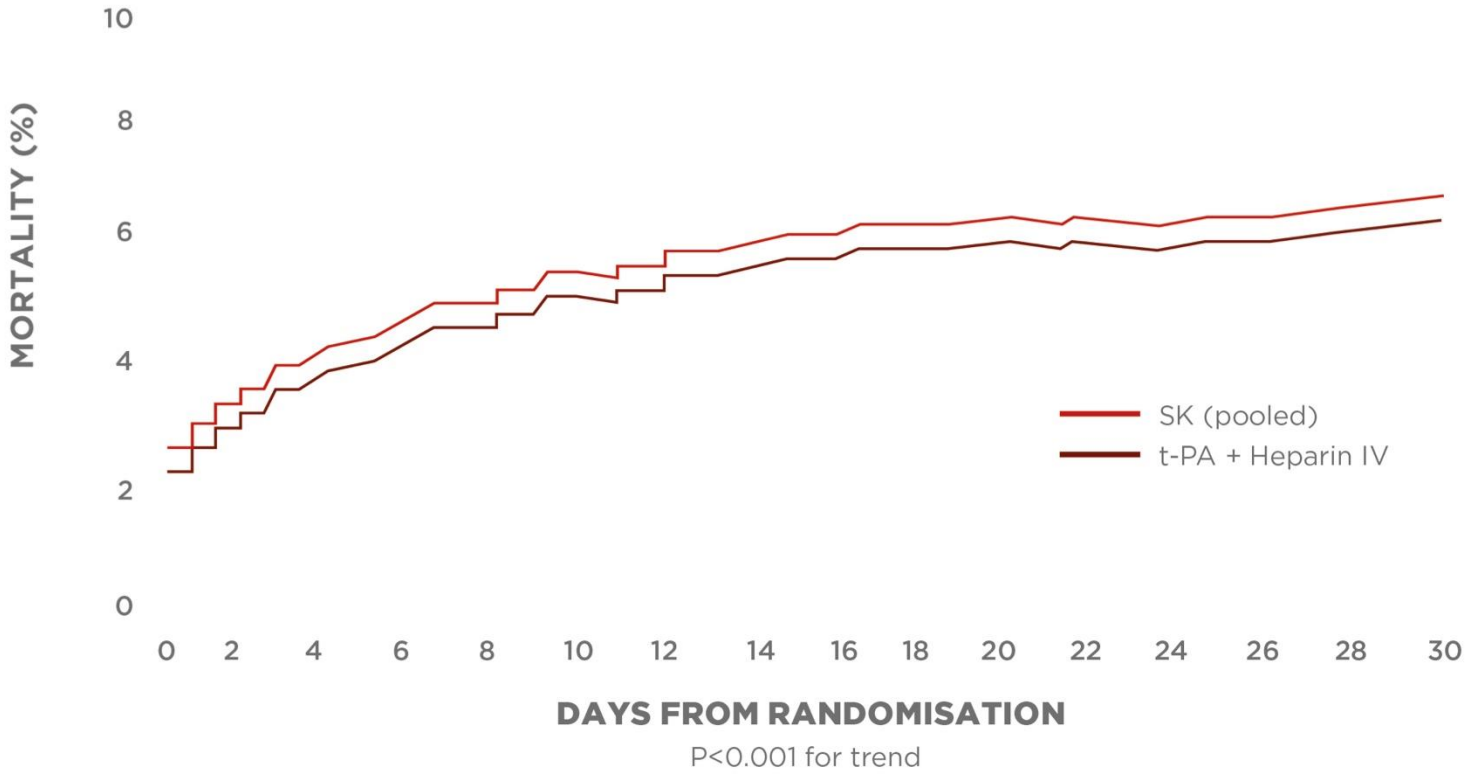
GUSTO-1 STUDY

30-DAY MORTALITY STREPTOKINASE (POOLED) VS ACCELERATED t-PA



1. Rathore S, Curtis J, Chen J, Wang Y, Nallamothu B, Epstein A et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ. 2009;338(may19 1):b1807-b1807.
Link to for this reference found in the discussion of the article
2. Antman E. ST-segment elevation myocardial infarction: Management. In: Bonow RO, Mann DL, Zipes P, et al, eds. Braunwald's Heart Disease. 9th ed. Philadelphia, PA: Elsevier Saunders; 2011a:1087-1110.

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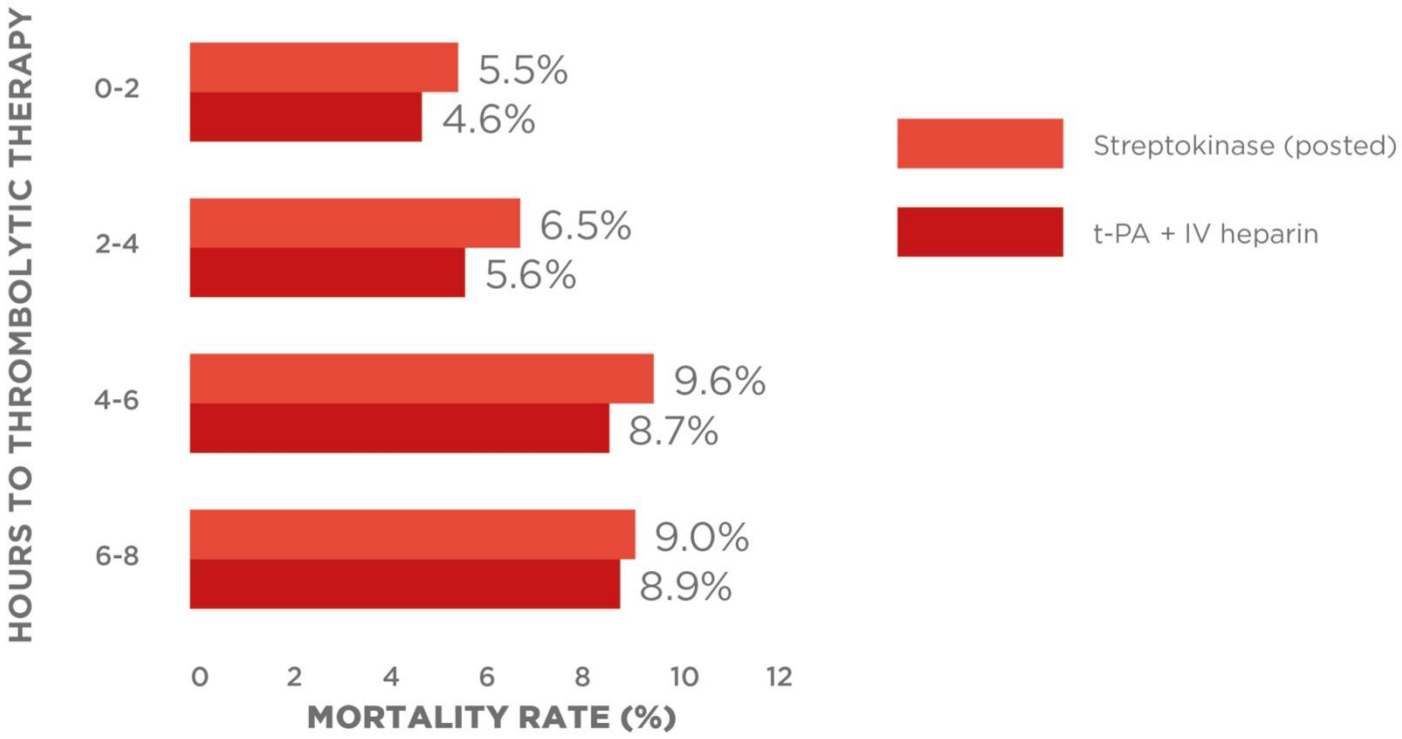
GUSTO-1 STUDY

30-DAY MORTALITY BY TIME TO THROMBOLYTIC THERAPY



1. Topol E, Califf R, Lee K. More on the GUSTO Trial. New England Journal of Medicine. 1994;331(4):277-278.
2. More on the GUSTO Trial. New England Journal of Medicine. 1994;331(10):687-687.

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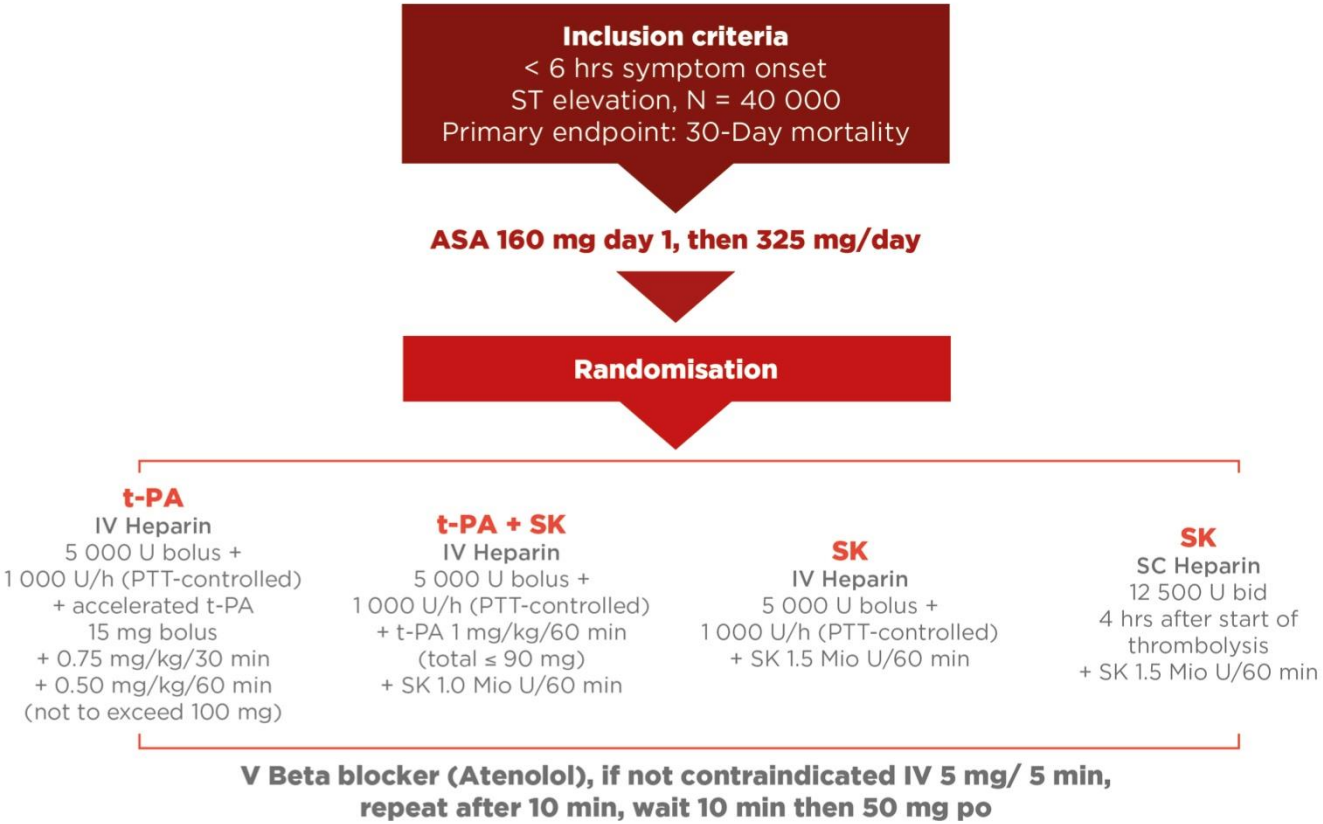
GUSTO-1 STUDY DESIGN



An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.

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GUSTO-1 STUDY CLINICAL EVENTS

	Streptokinase and Subcutaneous heparin	Streptokinase and Intravenous Heparin	Accelerated t-PA and Intravenous heparin	Both Thrombolytic agents and Intravenous heparin
Patient Numbers	8,669	9,260	9,235	9,139
Reinfarction	3.4%	4.0%	4.0%	4.0%
Cardiodiogenic shock	6.9%	6.3%	5.1%	6.1%
Congestive heart failure	17.5%	16.8%	15.2%	16.8%
Recurrent Ischeamia	19.9%	19.6%	19.0%	18.8%

An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.

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GUSTO-1 STUDY NET CLINICAL BENEFIT

30-DAY MORTALITY OR NON-FATAL STROKE

	Streptokinase + SC heparin	Streptokinase + IV heparin	Acc t-PA + IV heparin	t-PA/SK + IV heparin
Patients (N)	9,796	10,377	10,344	10,328
Death or non-fatal stroke	7.9%	8.2%	7.2%	7.9%
Death or non-fatal disabling stroke	7.7%	7.9%	6.9%	7.6%

An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.

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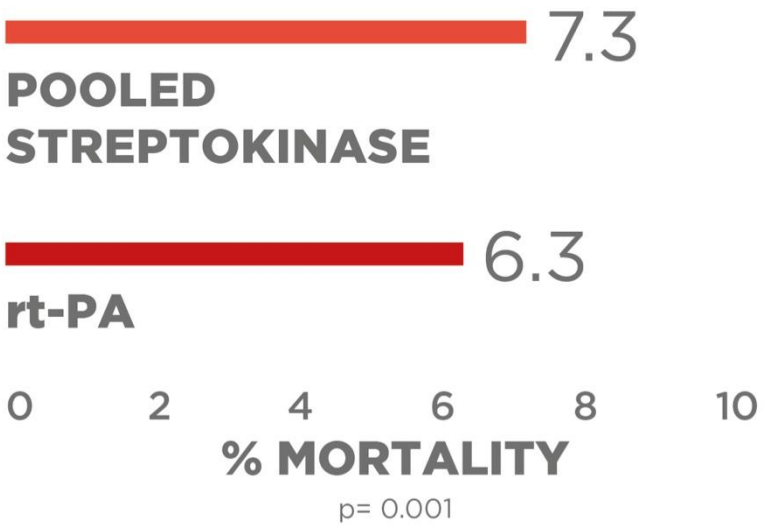
GUSTO-1 MORTALITY STUDY - IMPROVED SURVIVAL WITH rt-PA

GUSTO-1: 30 DAY MORTALITY



Accelerated rt-PA was significantly better at **REDUCING 30-DAY MORTALITY** than streptokinase regimens.

Accelerated rt-PA achieved the pre-defined objective for superiority of a **1% ABSOLUTE REDUCTION IN MORTALITY** over streptokinase.

Following acute MI, patients have a **BETTER CHANCE OF SURVIVAL** following accelerated rt-PA than with streptokinase.

1. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.
2. STEMI Clinical Evidence Update 21 Nov 2017.

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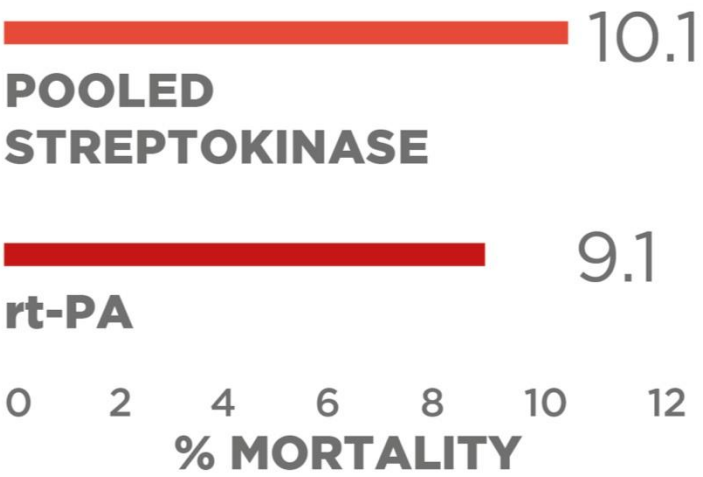
LONG TERM FOLLOW-UP OF MORTALITY STUDY - IMPROVED SURVIVAL WITH rt-PA

GUSTO-1: 1 YEAR MORTALITY



The mortality benefit for rt-PA over streptokinase **WAS MAINTAINED** at 1-year follow-up

Califf R, White H, Van de Werf F, Sadowski Z, Armstrong P, Vahanian A et al. One-Year Results From the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial. Circulation. 1996;94(6):1233-1238.

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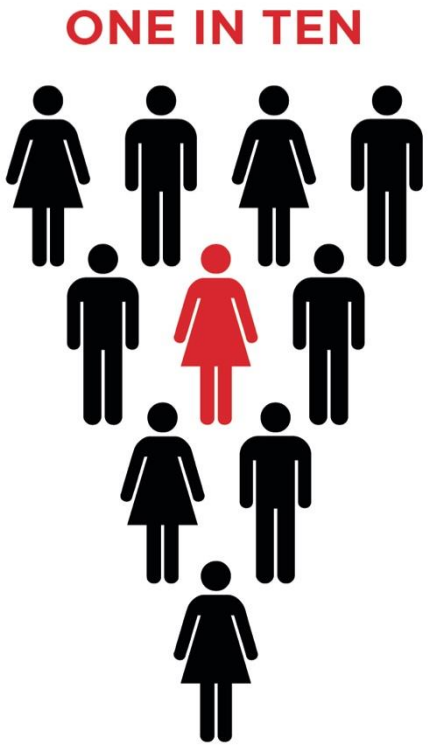
A CLINICALLY RELEVANT SURVIVAL BENEFIT OVER STREPTOKINASE



The **SURVIVAL BENEFIT** for rt-PA over streptokinase in GUSTO-1.

"...translated into **10 LIVES SAVED PER 1,000 PATIENTS TREATED**, or the **PREVENTION OF ONE OUT OF TEN DEATHS** that would be expected with standard thrombolytic therapy."[1]

Holmes D, Califf R, Topol E. Lessons we have learned from the GUSTO trial. Journal of the American College of Cardiology. 1995;25(7):S10-S17.

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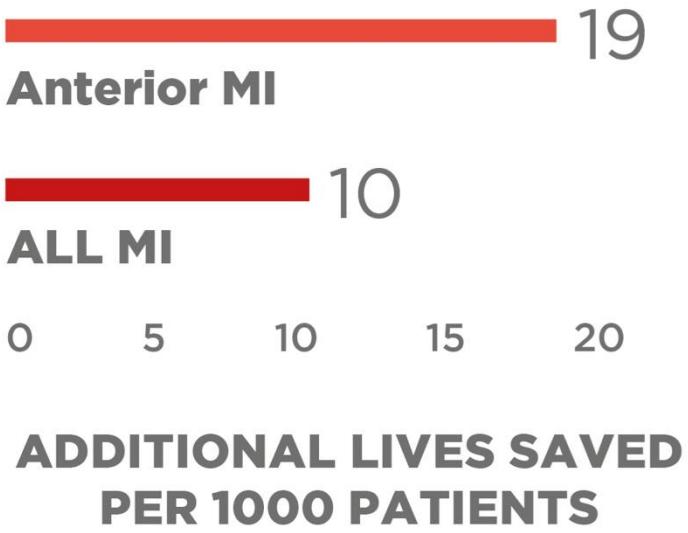
HIGH RISK PATIENTS - rt-PA INCREASED BENEFITS

THE 30-DAY SURVIVAL BENEFIT OF rt-PA STREPTOKINASE IN LIVES SAVED PER 1000 PATIENTS TREATED[2]



The survival benefit for rt-PA over streptokinase **INCREASES** with the **SEVERITY OF UNDERLYING RISK FACTORS**[1,3]:

- Age (except over 85 years)
- Hypotension
- Previous MI
- Anterior MI

In anterior MI, the survival benefit for rt-PA over streptokinase is **19 MORE LIVES SAVED PER THOUSAND PATIENTS TREATED**[2]

1. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.
2. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.
3. Holmes D, Califf R, Topol E. Lessons we have learned from the GUSTO trial. Journal of the American College of Cardiology. 1995;25(7):S10-S17.

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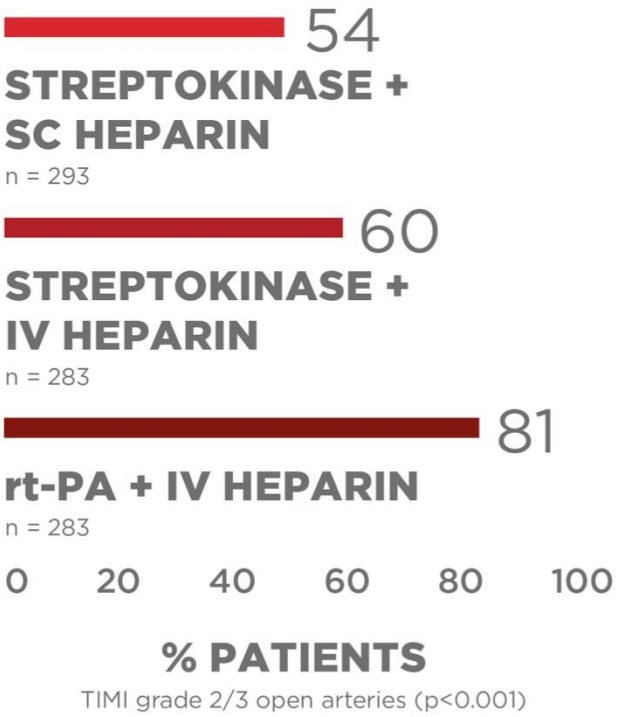
GUSTO-1 ANGIOGRAPHIC SUB-STUDY - FAST REPERFUSION WITH rt-PA

TIMI GRADE 2/3 AT 90 MINUTES



Significantly more **ARTERIES OPENED EARLY** with accelerated rt-PA than with streptokinase

Heparin used as **ADJUVANT THERAPY** to help prevent re-occlusion

The Effects of Tissue Plasminogen Activator, Streptokinase, or Both on Coronary-Artery Patency, Ventricular Function, and Survival after Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(22):1615-1622.

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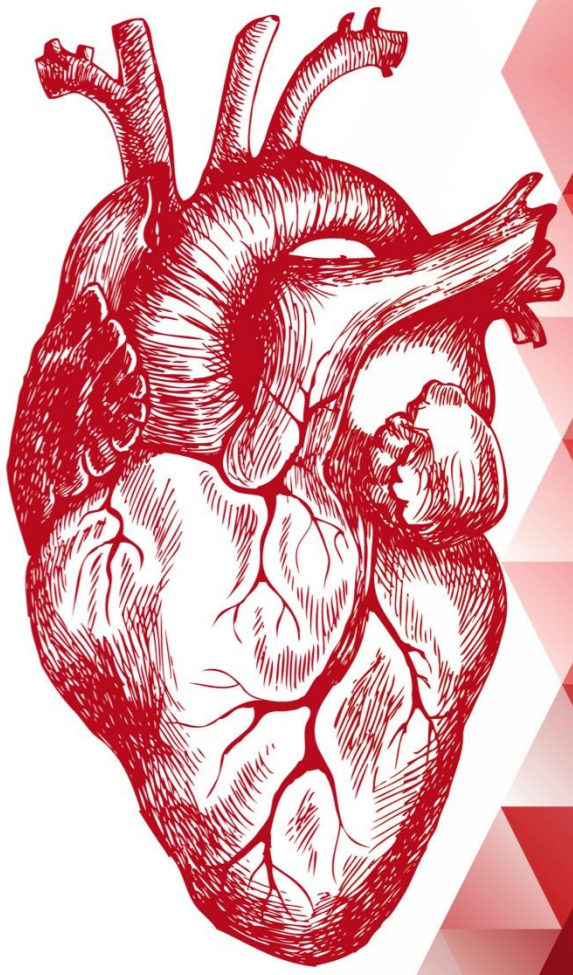
RESCUE THROMBOLYSIS WITH rt-PA - WHEN STREPTOKINASE FAILS

Streptokinase fails to restore full (TIMI 3) patency in **TWO-THIRDS OF PATIENTS**[1]

Only **ONE RANDOMISED STUDY** which evaluated patients who failed streptokinase therapy (rt-PA v placebo)[2]

Benefit shown in patients in the rt-PA arm in whom streptokinase failed to produce a **SYSTEMIC LYTIC STATE**[2]

Patients without **ECG EVIDENCE OF REPERFUSION AFTER THROMBOLYSIS** have been shown to benefit from further therapy with rt-PA[2]



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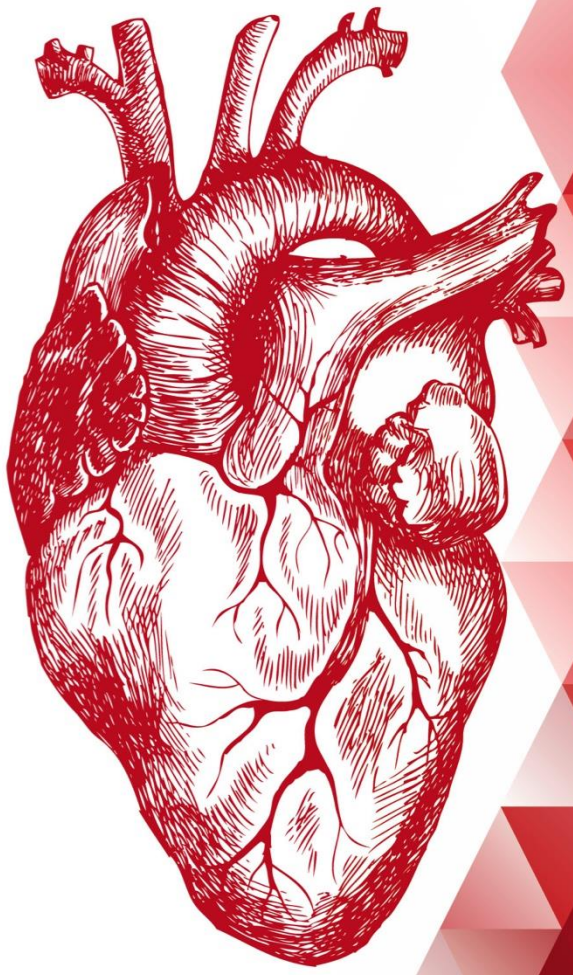
1. The Effects of Tissue Plasminogen Activator, Streptokinase, or Both on Coronary-Artery Patency, Ventricular Function, and Survival after Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(22):1615-1622.
2. Mounsey J, Skinner J, Hawkins T, MacDermott A, Furniss S, Adams P et al. Rescue thrombolysis: alteplase as adjuvant treatment after streptokinase in acute myocardial infarction. Heart. 1995;74(4):348-353.

STREPTOKINASE… NEVER AGAIN

A number of **PROPOSALS FOR SELECTION OF THROMBOLYTIC REGIMENS** after GUSTO have been suggested.

Additional considerations include **AVOIDING RE-USE** of Streptokinase indefinitely because of high prevalence of potentially **NEUTRALIZING ANTIBODY TITERS**.



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1. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. Circulation. 2004;110(9).
2. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

ACCELERATED rt-PA DOSAGE REGIMEN TO PATIENTS IN WHOM TREATMENT CAN BE STARTED WITHIN 6 HOURS AFTER SYMPTOM ONSET

Accelerated rt-PA

15mg
i.v. bolus

50mg
30 min infusion

35mg
60 min infusion

Total = 10mg
in 90 mins

i.v. heparin

5 000 IU
i.v. bolus

1000 IU/hr
30 min infusion
For patients over 65kg

Continue infusion for at least 48 hours

Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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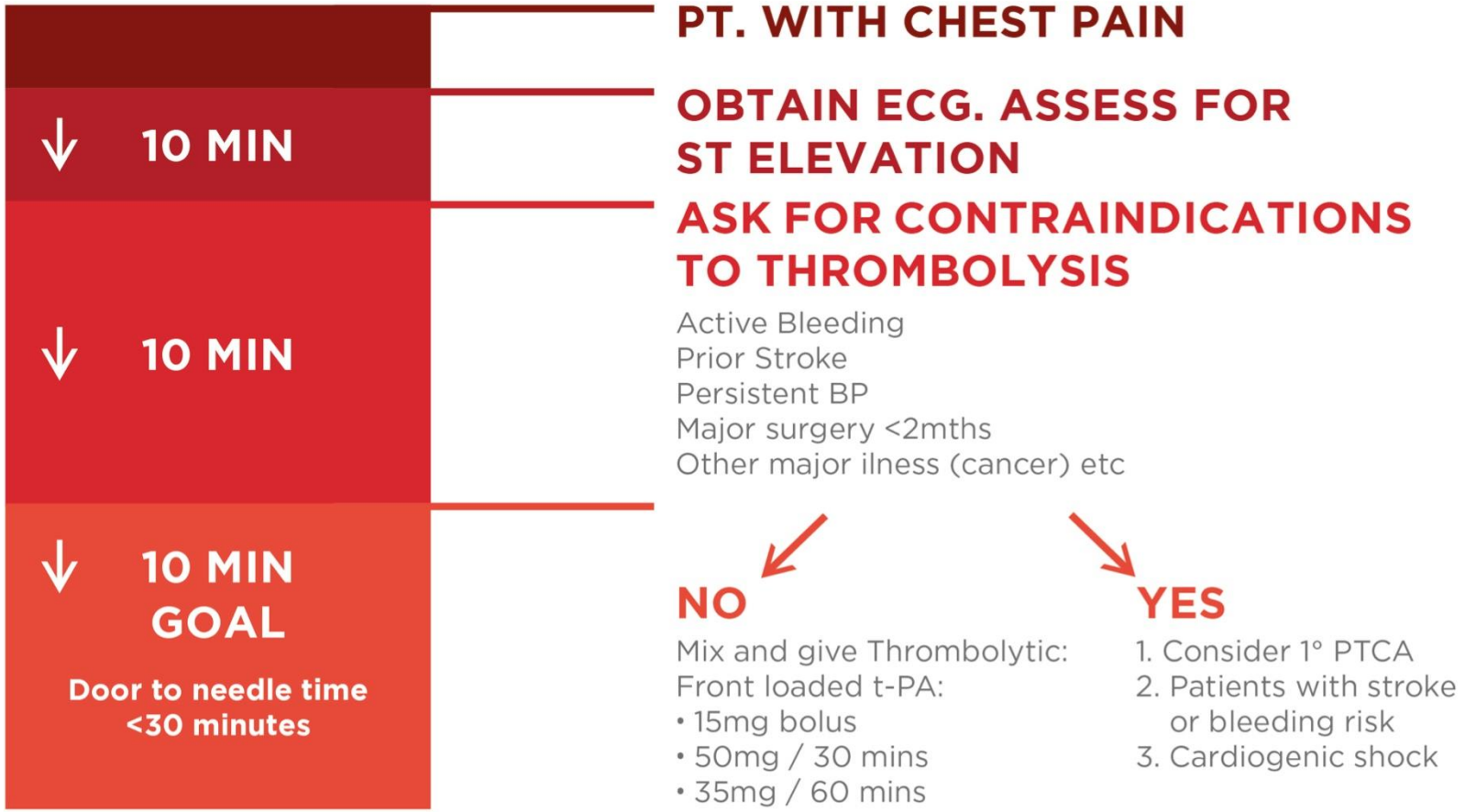
SPEEDING TIME TO TREATMENT WITH ALTEPLASE



Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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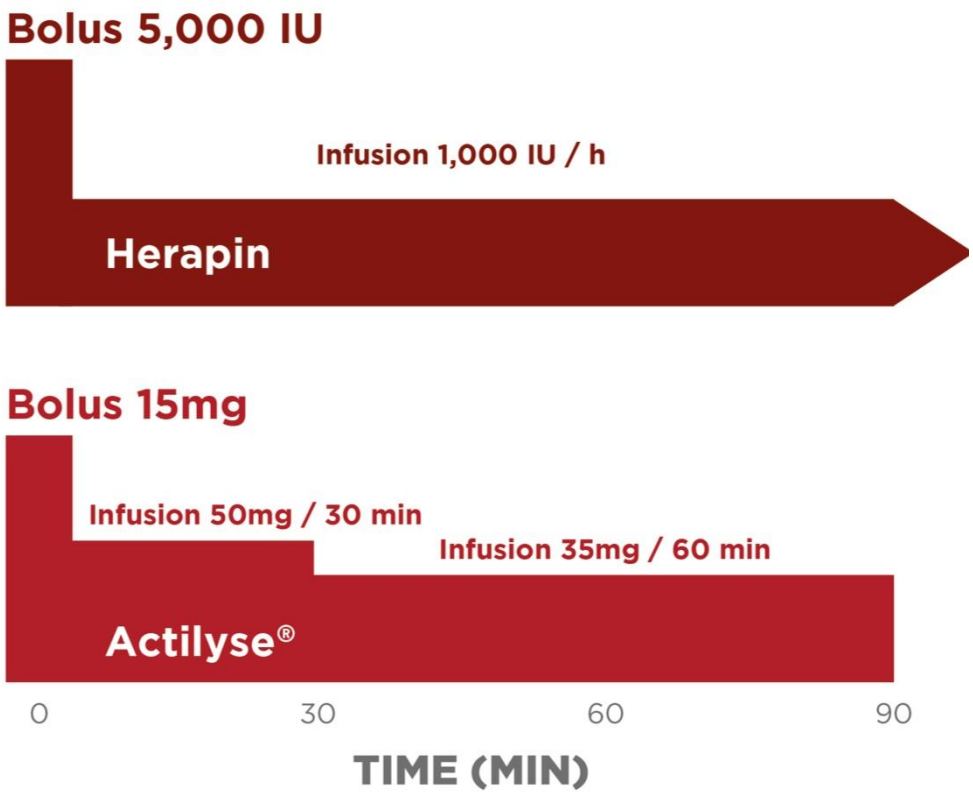
ACTILYSE® DOSAGE IN AMI



Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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ALTEPLASE VS RETEPLASE

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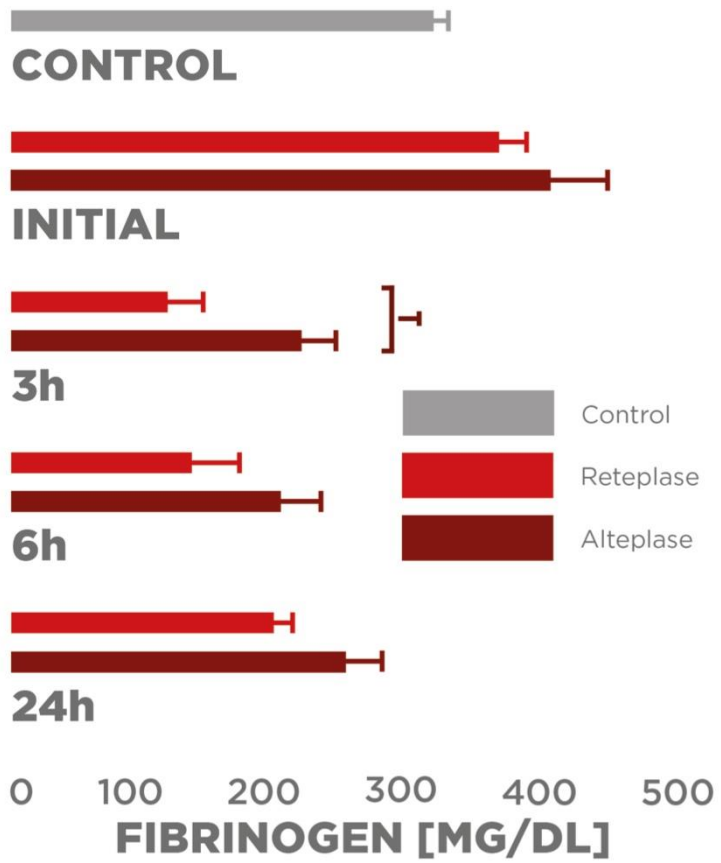
THE FIBRIN SPECIFICITY EVIDENCE: ALTEPLASE > RETEPLASE HIGHER THAN FIBRIN



Fibrinogen levels of patients with AMI treated either with **DOUBLE-BOLUS RETEPLASE** or with **FRONT-LOADED ALTEPLASE** in comparison to control subjects.

More marked reduction (†p <0.05 for direct comparison) after double-bolus reteplase indicates **LESS FIBRIN SPECIFICITY**.[1]

Means ± **SEM**; *p <0.05 , #p<0.01 versus controls (analysis of variance and Tuckey-Kramer-HSA test with Bonferroni-Holmes correction).[1]

1. Hoffmeister H, Kastner C, Szabo S, Beyer M, Helber U, Kazmaier S et al. Fibrin specificity and procoagulant effect related to the kallikrein-contact phase system and to plasmin generation with double-bolus reteplase and front-loaded alteplase thrombolysis in acute myocardial infarction. The American Journal of Cardiology. 2000;86(3):263-268.
2. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.

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THE FIBRIN SPECIFICITY EVIDENCE: ALTEPLASE > RETEPLASE HIGHER THE FIBRIN

FIBRIN SPECIFICITY: ALTEPLASE > RETEPLASE

GUSTO III Fibrin Specificity Sub-study: Sub group analysis of GUSTO III data showed significant **LOWER BLEEDING COMPLICATIONS** in low weight women treated with Actilyse compared to reteplase.[1]

In the GUSTO III Trial, Reteplase showed **SIGNIFICANTLY HIGHER MORTALITY** compared to Actilyse in this sub group. This is due to the poor fibrin specificity of reteplase thus showing poor efficacy in older thrombus.[2]

> Reteplase has proved to have significantly **LESS FIBRIN** specificity compared to front loaded Alteplase[1]

1. Hoffmeister H, Kastner C, Szabo S, Beyer M, Helber U, Kazmaier S et al. Fibrin specificity and procoagulant effect related to the kallikrein-contact phase system and to plasmin generation with double-bolus reteplase and front-loaded alteplase thrombolysis in acute myocardial infarction. The American Journal of Cardiology. 2000;86(3):263-268.
2. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16): 1118-1123.

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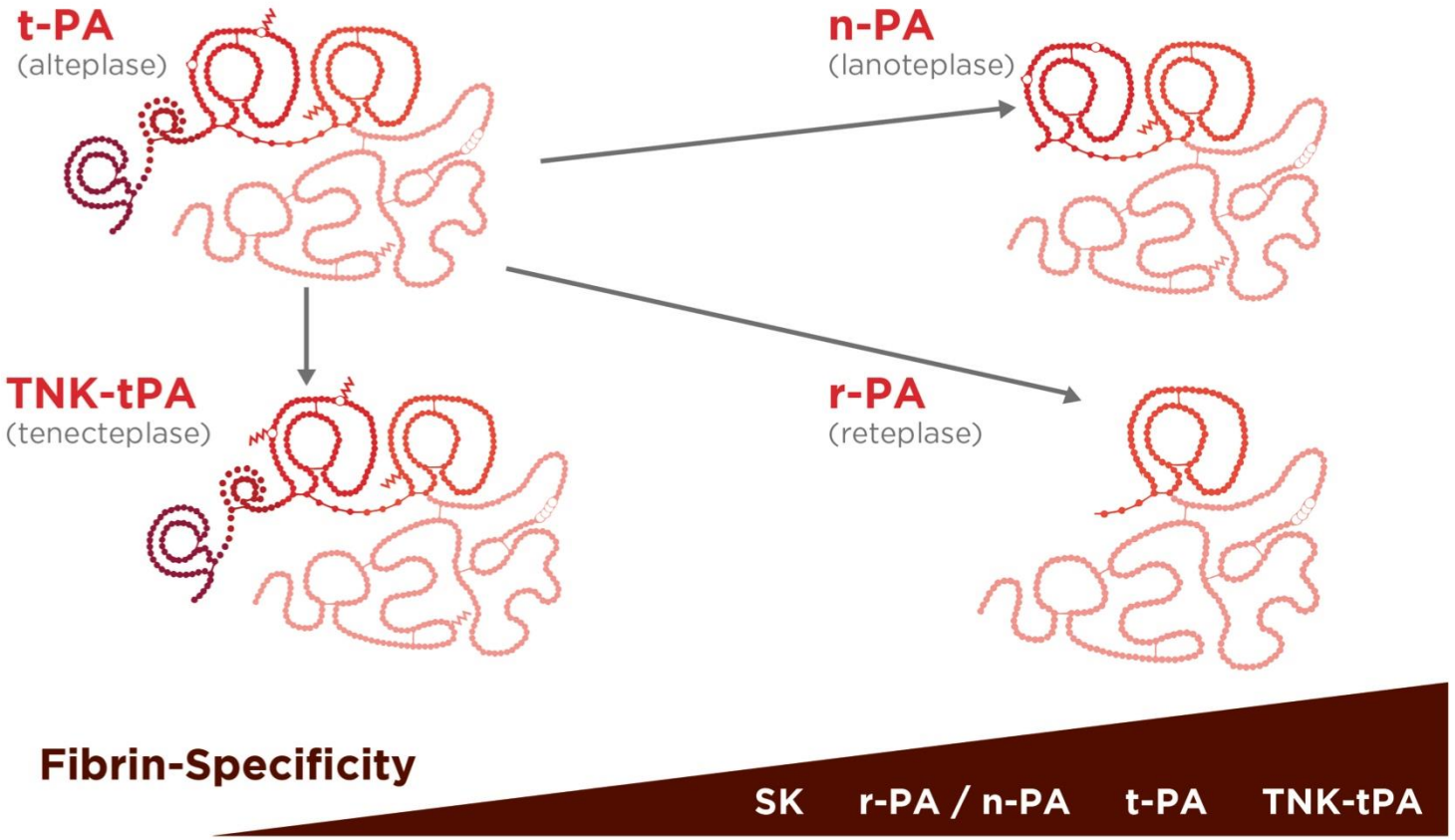
MOLECULAR STRUCTURE OF FIBRINOLYTICS



Adapted from:
Llevadot J. Bolus Fibrinolytic Therapy in Acute Myocardial Infarction. JAMA. 2001;286(4):442.

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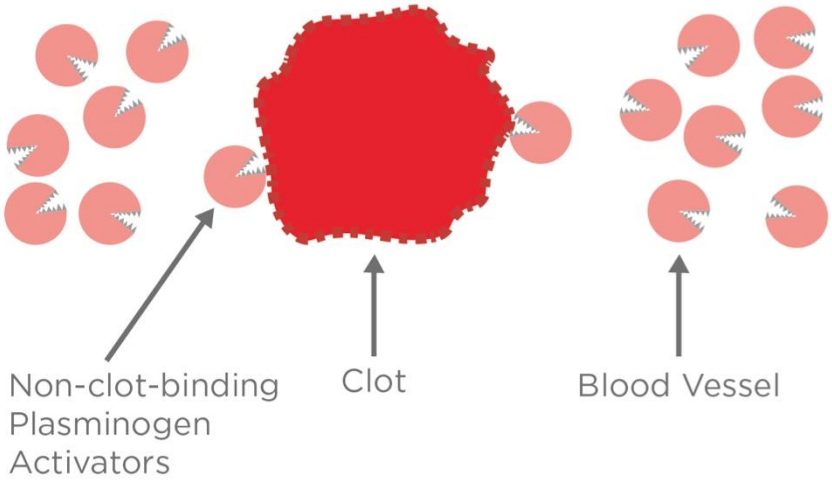
TYPES OF THROMBOLYTICS

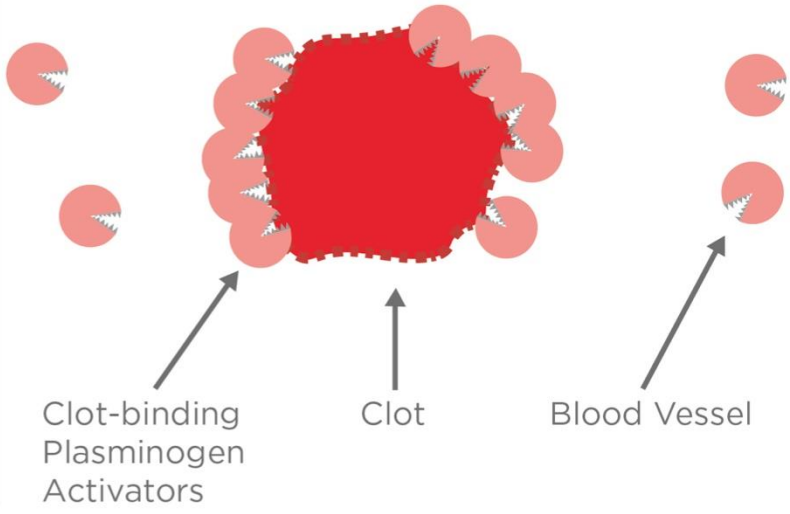
ACTIONS OF NON-CLOT-BINDING (LESS FIBRIN SPECIFIC) AGENTS

eg. Streptokinase, Reteplase, Urokinase



ACTIONS OF CLOT-BINDING (MORE FIBRIN SPECIFIC) AGENTS

eg. Alteplase, Tenecteplase



Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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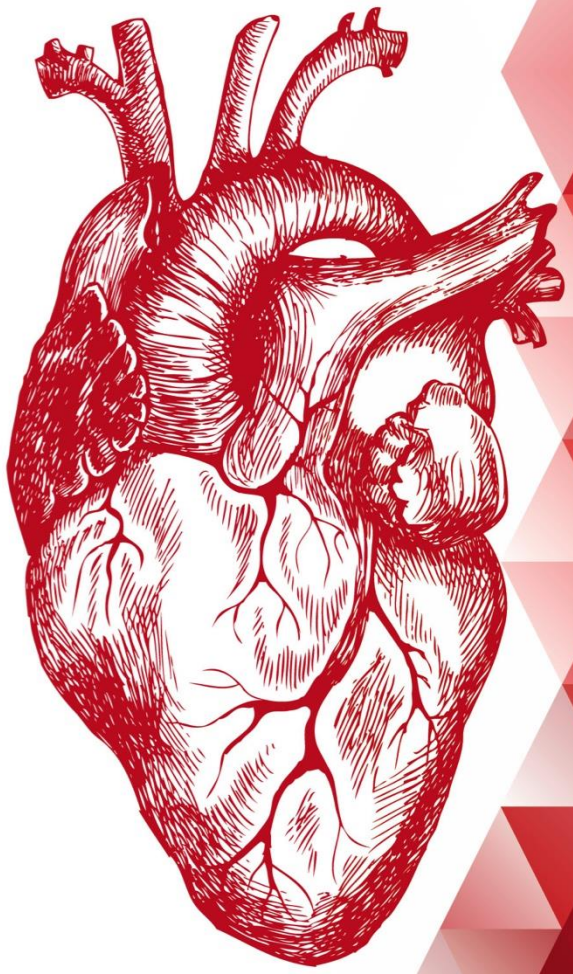
RETEPLASE

Reteplase: **SECOND GENERATION** thrombolytic-recombinant **FORM OF HUMAN TPA**

Half life of **18 MINUTES**

Given as 10ml + 10ml **BOLUS DOSE** 30 minutes apart

Launched in **1997**



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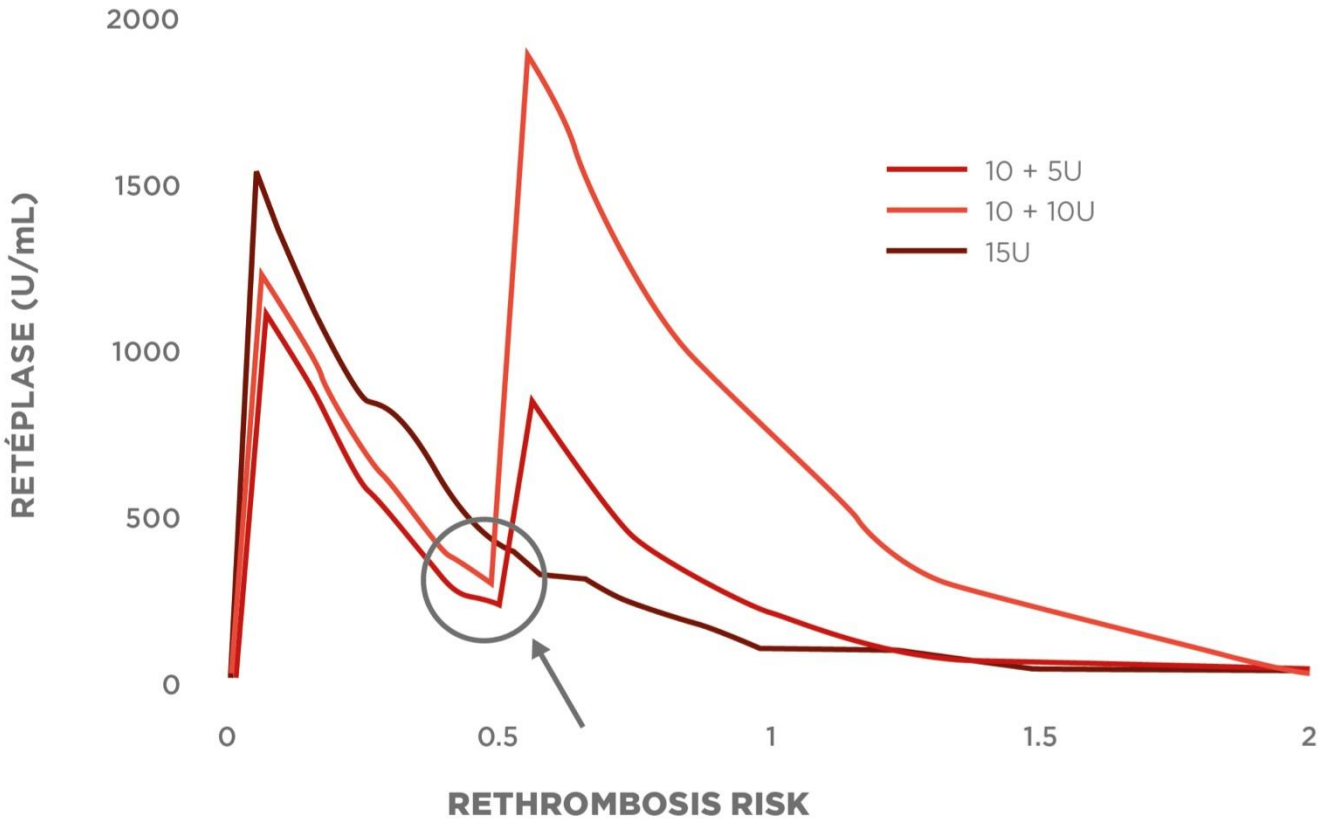
1. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.
2. Reteplase Product information

RETEPLASE IS GIVEN AS A DOUBLE BOLUS 30 MINUTES APART

WHY EXACTELY 30 MINUTES?



1. Hiremath JS D. Overview of Reteplase, A Novel Thrombolytic Agent in Indian Context. Cardiovascular Pharmacology: Open Access. 2015;04(02).
2. Product information document

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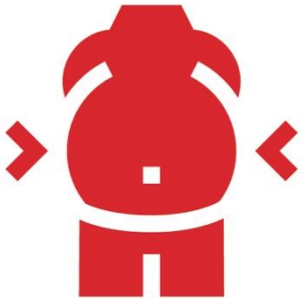
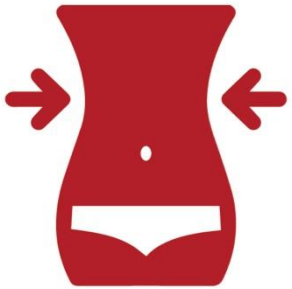
WEIGHT ADJUSTMENT

WEIGHT-ADJUSTMENT OF FIBRINOLYTICS IS CRITICAL FOR EFFICACY AND SAFETY





Giving a **FIXED DOSE OF THROMBOLYTIC** to all patients means effectively that:

Low body weight patients are potentially being **'OVERDOSED'**

Whilst heavy weight patients are being **'UNDER DOSED'**

Patients with **LOW BODY WEIGHT** have been shown to be at **HIGHER RISK** for stroke, haemorrhage and death when fixed dose, **WEIGHT UNADJUSTED THROMBOLYTIC AGENTS** was administered

Gibson C. GW Symposium. Presentation presented at; 2000; AHA 2000.

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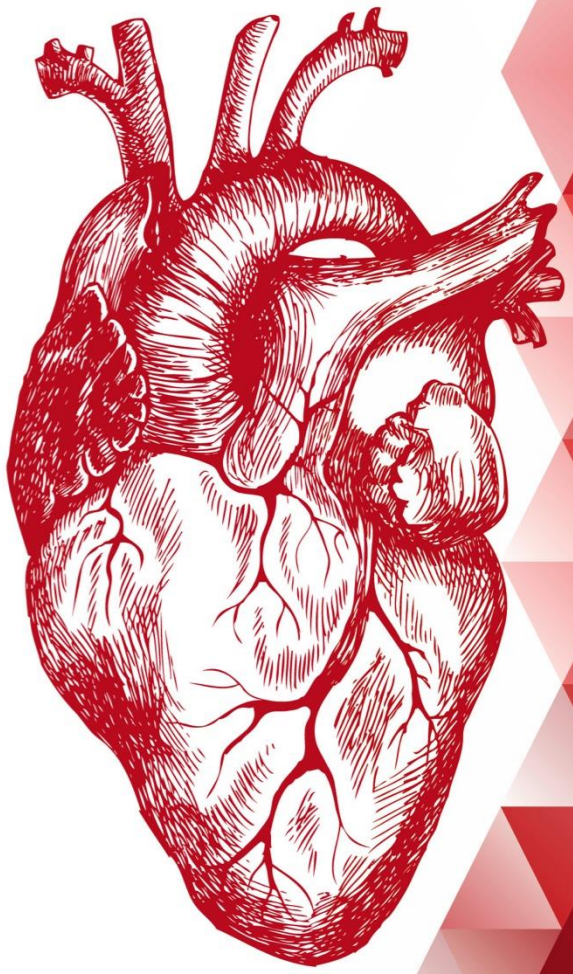
OTHER ACUTE MI REGIMENS USE WEIGHT ADJUSTED DOSING

- HEPARIN
- REOPRO
- INTEGRILIN
- AGGRASTAT
- LOW MOLECULAR WEIGHT
- HEPARINOIDS
- DOPAMINE, DOBUTAMINE



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1. Gibson C. GW Symposium. Presentation presented at; 2000; AHA 2000.
2. Characteristics of the Ideal Fibrinolytic Agent [Internet]. SlideServe. 2019 [cited 17 January 2019]. Available from: https://www.slideserve.com/kalin/characteristics-of-the-ideal-fibrinolytic-agent

WOULD YOU GIVE THESE PEOPLE THE SAME DOSE?

HEAVY PATIENTS

These patients would receive relatively less drug[1]

LIGHT PATIENTS

These patients would receive relatively more drug

HIGH RISK PATIENTS

Females, elderly > 75 years, low weight < 65 kgs patients are at high risk for ICH complications associated with thrombolytic therapy[2]

1. Gibson C. GW Symposium. Presentation presented at; 2000; AHA 2000.
2. Estess J. Fibrinolytic treatment for elderly patients with acute myocardial infarction. Heart. 2002;87(4):308-311
3. Characteristics of the Ideal Fibrinolytic Agent [Internet]. SlideServe. 2019 [cited 17 January 2019]. Available from: https://www.slideserve.com/kalin/characteristics-of-the-ideal-fibrinolytic-agent

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RETEPLASE UNDERWENT WEIGHT OPTIMIZED DOSING IN TWO PIVOTAL CLINICAL TRIALS

RAPID - 1

- For individuals weighing less than 65 kg the dose was decreased to 8MU+8MU 30 minutes apart[3]

GUSTO V

- GUSTO V excluded certain high risk patients
- Patients weighing >120kg were not enrolled because r-PA was not dosed according to weight[1]

1. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. The Lancet. 2001;357(9272):1905-1914.
2. Characteristics of the Ideal Fibrinolytic Agent [Internet]. SlideServe. 2019 [cited 17 January 2019]. Available from: https://www.slideserve.com/kalin/characteristics-of-the-ideal-fibrinolytic-agent
3. Smalling R, Bode C, Kalbfleisch J, Sen S, Limbourg P, Forycki F et al. More Rapid, Complete, and Stable Coronary Thrombolysis With Bolus Administration of Reteplase Compared With Alteplase Infusion in Acute Myocardial Infarction. Circulation. 1995;91(11):2725-2732.

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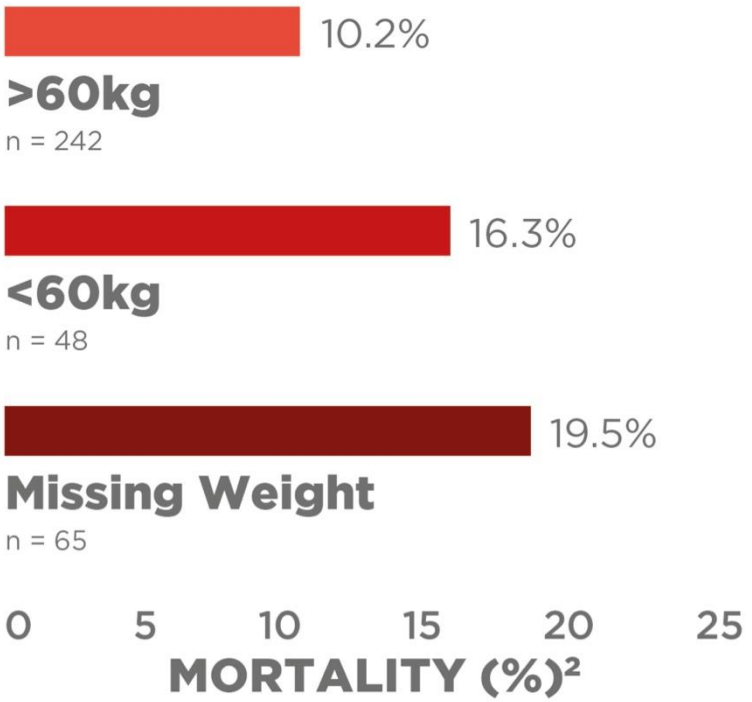
AMONG RETEPLASE TREATED PATIENTS, MISSING WEIGHT IS ASSOCIATED

WEIGHT NOT RECORDED IN 11% OF INJECT TRIAL PATIENTS[1]



MORTALITY HIGHEST if no weight recorded

No biologically plausible reason why there should be a higher mortality among patients receiving a **FIXED LYTIC DOSE** in whom no weight was recorded

Likely explanation is **STATISTICAL CONFOUNDING**: Missing weight is a marker of a sicker patient, or the patient died before weight obtained

1. Wilcox R. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. The Lancet. 1995;346(8971):329-336.
2. Characteristics of the Ideal Fibrinolytic Agent [Internet]. SlideServe. 2019 [cited 17 January 2019]. Available from: https://www.slideserve.com/kalin/characteristics-of-the-ideal-fibrinolytic-agent

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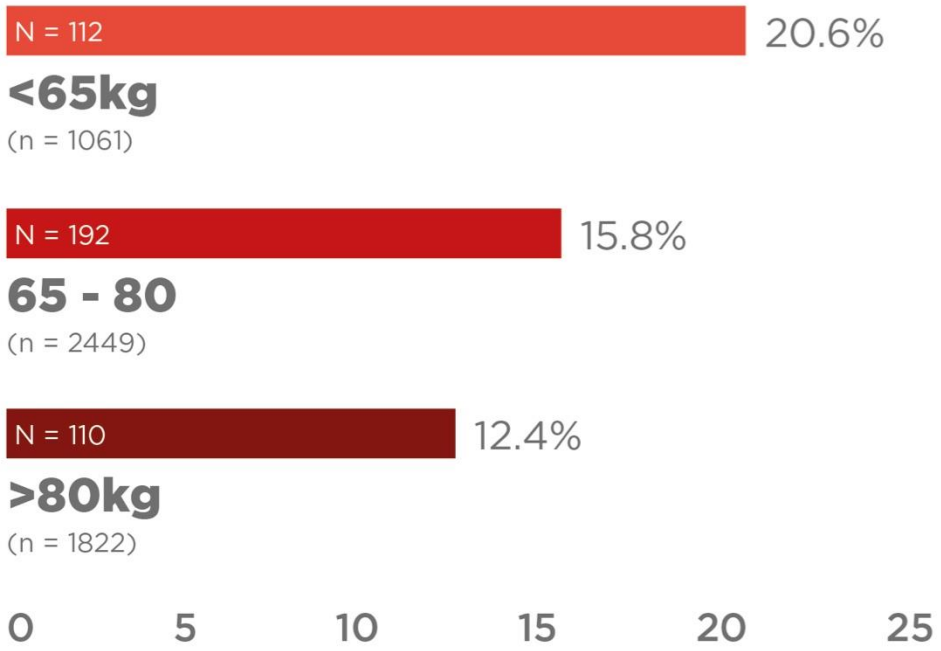
AMONG RETEPLASE TREATED PATIENTS, MISSING WEIGHT IS ASSOCIATED WITH

RETEPLASE*: PATIENTS WITH BLEEDS STRATIED BY WEIGHT



Characteristics of the Ideal Fibrinolytic Agent [Internet]. SlideServe. 2019 [cited 17 January 2019]. Available from: https://www.slideserve.com/kalin/characteristics-of-the-ideal-fibrinolytic-agent

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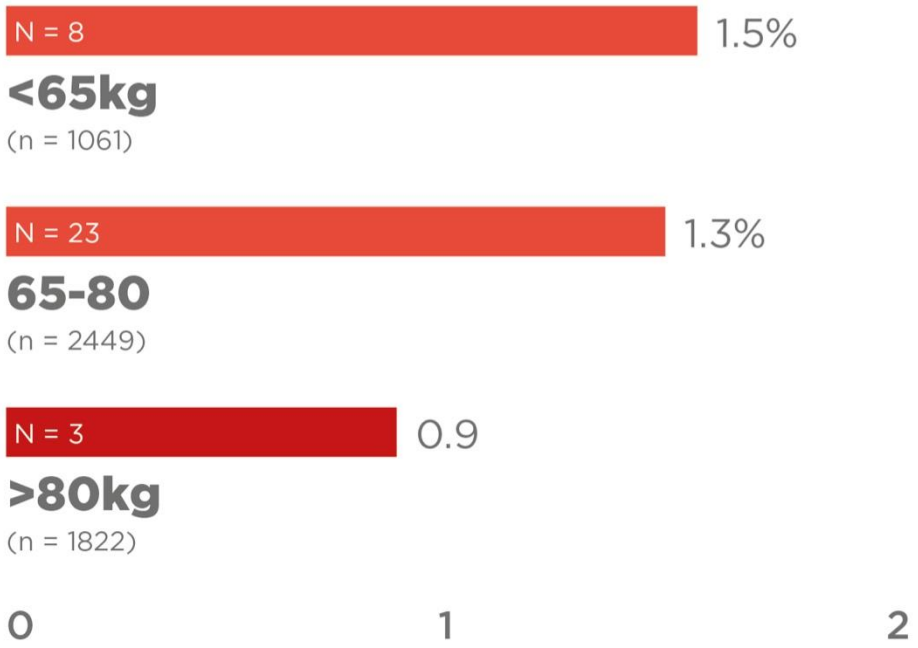
EVIDENCE OF HIGH RISK OF STROKE IN LOW WEIGHT PATIENTS WITH RETEPLASE WEIGHT

RETEPLASE*: PATIENTS WITH STROKES STRATED BY WEIGHT



Characteristics of the Ideal Fibrinolytic Agent [Internet]. SlideServe. 2019 [cited 17 January 2019]. Available from: https://www.slideserve.com/kalin/characteristics-of-the-ideal-fibrinolytic-agent

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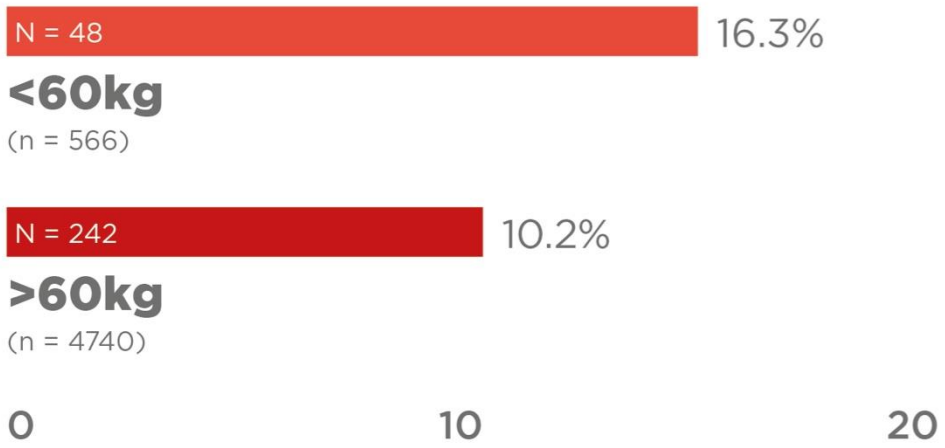
EVIDENCE OF HIGH 35 DAY MORTALITY IN LOW WEIGHT PATIENTS

RETEPLASE*: 35 DAYS MORTALITY RATES BY WEIGHT



Characteristics of the Ideal Fibrinolytic Agent [Internet]. SlideServe. 2019 [cited 17 January 2019]. Available from: https://www.slideserve.com/kalin/characteristics-of-the-ideal-fibrinolytic-agent

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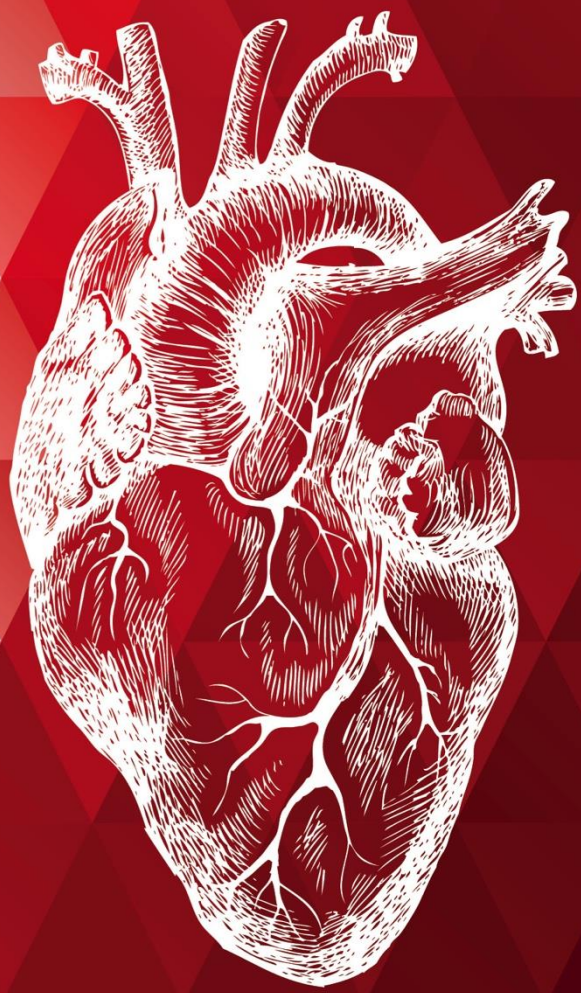
GUSTO 3

THE GUSTO III CLINICAL TRIAL

Open-labeled trial to assess whether reteplase is superior to alteplase (Actilyse) concerning reduction of mortality after MI.



1. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.
2. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with Stsegment elevation. European Heart Journal. 2017;39(2):119-177.

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GUSTO III TRIAL :
RETEPLASE COMPARED TO ALTEPLASE

GUSTO III trial was designed to test the **PRIMARY HYPOTHESIS** that reteplase would significantly reduce 30 day mortality compared with accelerated alteplase in AMI treated within 6 hours*[1]

Reteplase failed to demonstrate **SURVIVAL SUPERIORITY** over alteplase Subgroup analysis of GUSTO III data showed significant **LOWER BLEEDING COMPLICATIONS** in low weight women treated with alteplase compared to reteplase.

No improvement of **CARDIOGENIC SHOCK** with Reteplase compared to Alteplase[2]

Medication errors for Reteplase in GUSTO III comprised of **EARLY DISCONTINUATION** or **ERROR IN TIME** duration between the first and the second bolus. <25 minutes or >35 minutes[3]

Reteplase showed **HIGHER ADVERSE OUTCOME** due to medication errors compared to Alteplase

1. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.
2. Hasdai D. Frequency and clinical outcome of cardiogenic shock during acute myocardial infarction among patients receiving reteplase or alteplase. Results from GUSTO-III. European Heart Journal. 1999;20(2):128-135.
3. Medication errors and outcomes with fixed double-bolus r-PA versus bolus plus weight-adjusted infusion t-PA fibrinolysis: The GUSTO-III experience Shaun G. Goodman, Aiala Barr, Christopher Granger, Magnus Ohman, Anatoly Langer, Paul Armstrong, Brian Gibler, Eric Topol. Canadian Heart Research Centre, Toronto, ON, Canada, Duke University Medical Center, Durham, NC. Journal of the American College of Cardiology. 2001;37(2):A351.

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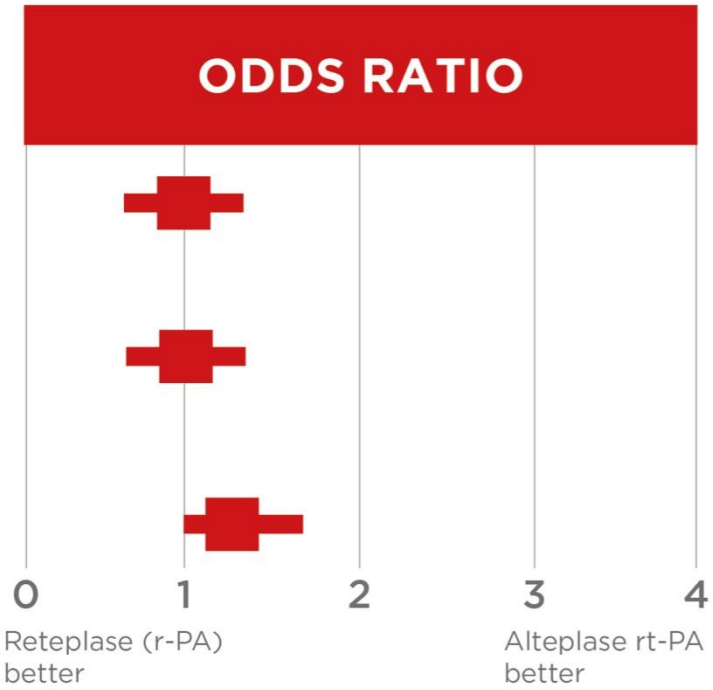
GUSTO III TRIAL 30-DAY MORTALITY BY TIME TO RANDOMIZATION

MORTALITY

Time to Randomisation	% pts	Reteplase n-= 10,139	Alteplase n = 4,921
0 - 2 hours	31.0%	5.9%	6.2%
2 - 4 hours	46.5%	7.7%	7.7%
> 4 hours	22.5%	10.1%	7.5%



“Alteplase is more fibrin specific and is associated with better outcome in late patients (>4hours) than RETEPLASE, A less fibrin specific agent”

1. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.
2. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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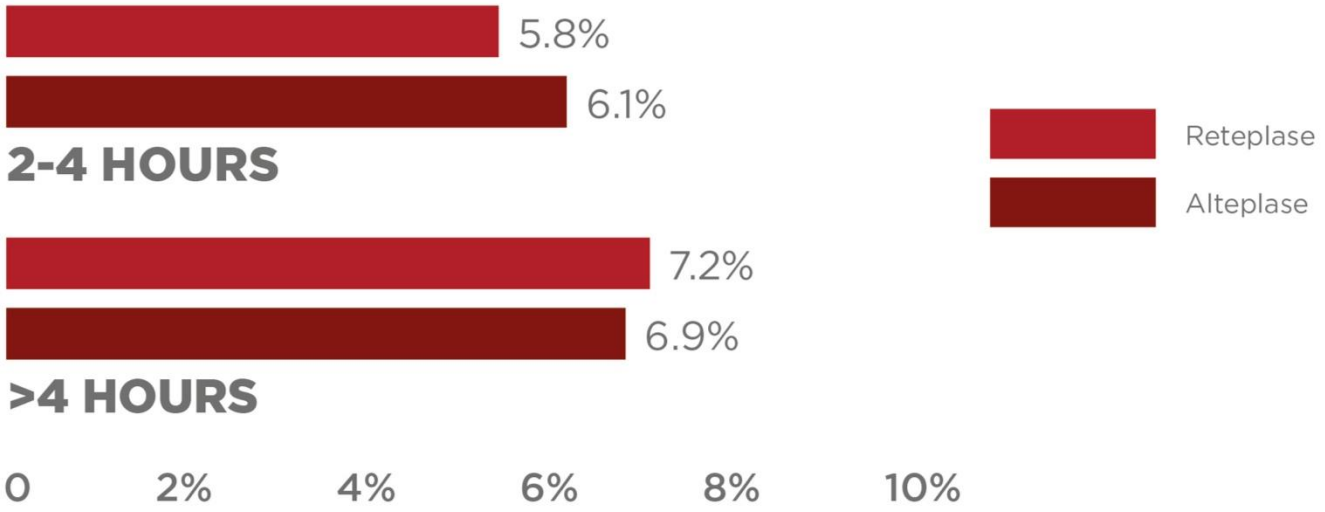
GUSTO III
30-DAYS MORTALITY ACCORDING TO TIME TO RANDOMIZATION



1. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.
2. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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CONCLUSIONS OF GUSTO III TRIAL

Reteplase and Actilyse are **NOT EQUIVALENT**

Actilyse saves **2 ADDITIONAL LIVES** per 1000 patients compared to Reteplase

For **ANTERIOR INFARCTIONS**, Alteplase saves **7 ADDITIONAL LIVES** per 1000 patients compared to Reteplase

GUSTO III failed to prove its **PRIMARY HYPOTHESIS**, i.e. **RETEPLASE DOES NOT PROVIDE ANY ADDITIONAL SURVIVAL BENEFIT IN THE TREATMENT OF STEMI**

GUSTO III results **DO NOT PROVE** that reteplase **IS EQUIVALENT TO** alteplase (GUSTO III was not designed to assess equivalency nor does it have the power to do so)

Accelerated dose of ACTILYSE¨ is still the **GOLD STANDARD THROMBOLYTIC REGIMEN**

A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.

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IS RETEPLASE A STREPTOKINASE?

GUSTO I

EFFICACY

RAPID-2

Alteplase is superior to streptokinase
Reteplase is equivalent to streptokinase ...
... but not superior to alteplase

INJECT

GUSTO III

1. Ohman E, Harrington R, Cannon C, Agnelli G, Cairns J, Kennedy J. Intravenous Thrombolysis in Acute Myocardial Infarction. Chest. 2001;119(1):253S-277S.
2. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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SUMMARY

Actilyse has been shown to work **FASTER** and with a **HIGHER DEGREE OF REPERFUSION** with **BETTER EFFICACY RATES** than streptokinase with reteplase[1,2,3]

This translates into a **MORTALITY ADVANTAGE** over streptokinase & reteplase which no other thrombolytic can claim[1,2,3]

1. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.
2. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.
3. Topol E, Ohman E, Armstrong P, Wilcox R, Skene A, Aylward P et al. Survival Outcomes 1 Year After Reperfusion Therapy With Either Alteplase or Reteplase for Acute Myocardial Infarction. Circulation. 2000;102(15):1761-1765.
4. Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with Stsegment elevation. European Heart Journal. 2017;39(2):119-177.

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KEY ACTILYSE CLINICAL EVIDENCE SUMMARY

Streptokinase + SC heparin	Supporting Evidence (references)
Superior Mortality Reduction at 24 Hours and 30 Days with Actilyse. In the landmark GUSTO I trial (n = 41,021), the accelerated infusion of Actilyse (<100mg / 90min) with IV heparin proved to be clinically and statistically superior to the standard dose of streptokinase with either IV or SC heparin in reducing mortality at 24 hours and 30 days[1]	
Mortality Reduction sustained at 1 Year. The benefit in mortality reduction achieved with the accelerated infusion of Actilyse with IV heparin in GUSTO I was sustained at 1-Year follow up[1]	
Superior 90-Minute Patency: TIMI 2/3 and TIMI 3 More than two thirds of the 90-minute patency achieved with Actilyse in this study was TIMI grade 3 flow[2]	
Actilyse provides significant benefit to patients arriving "late" i.e. presenting > 6 hours after symptom onset. Patients treated with Actilyse between 6-12 hours after symptom onset had a 25% relative reduction in morality versus placebo.[3] Actilyse is therefore indicated for lysis of occlusive coronary thrombi within 12 hours of the onset of symptoms	

1. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.
2. Neuhaus K, Von Essen R, Tebbe U, Vogt A, Roth M, Riess M et al. Improved thrombolysis in acute myocardial infarction with front loaded administration of alteplase: Results of the rt-PA-APSAC patency study (TAPS). Journal of the American College of Cardiology. 1992;19(5):885-891.
3. Paolasso E, Ravizzini G, Martin E, Diaz R. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. The Lancet [Internet]. 1993 [cited 20 January 2019];342(8874):767-772. Available from: https://www.sciencedirect.com/science/article/pii/014067369391539X

Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2017;39(2):119-177.

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LANDMARK TRIALS

GUSTO-1 (1993) a trial of 41,021 of AMI showed that **accelerated t-PA** + i.v. UFH **reduced mortality** in comparison to SK in combination with either s.c. or i.v. UFH.[1]

ASSENT-2 (1999) a trial of 16,949 of AMI showed that a **single bolus** of TNK was as **safe and effective** as accelerated t-PA.[2]

GUSTO-V (2001) a trial of 16,600 patients with AMI showed that there is **no reduction in mortality** with half dose reteplase plus abciximab in comparison to full dose- reteplase.[3]

GUSTO-1: tPA. 15% reduction in 30-day mortality compared to Streptokinase[1]

GUSTO-3: Reteplase had **no benefit** over tPA but is **easier to use** (double bolus)[1]

ASSENT: TNK is similar to tPA but with less non-cerebral bleeding and better mortality with symptoms>4 hrs: **Single bolus, fibrin selective, resistance to PAI-14**

1. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.
2. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial.
3. Topol E. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. The Lancet. 2001;357(9272):1905-1914.
4. Van de Werf F, Cannon C, Luyten A, Houbracken K, McCabe C, Berioli S et al. Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: The ASSENT-1 trial. American Heart Journal. 1999;137(5):786-791.

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metalyse®

tenecteplase 8 000 U / 10 000 U

Boehringer Ingelheim

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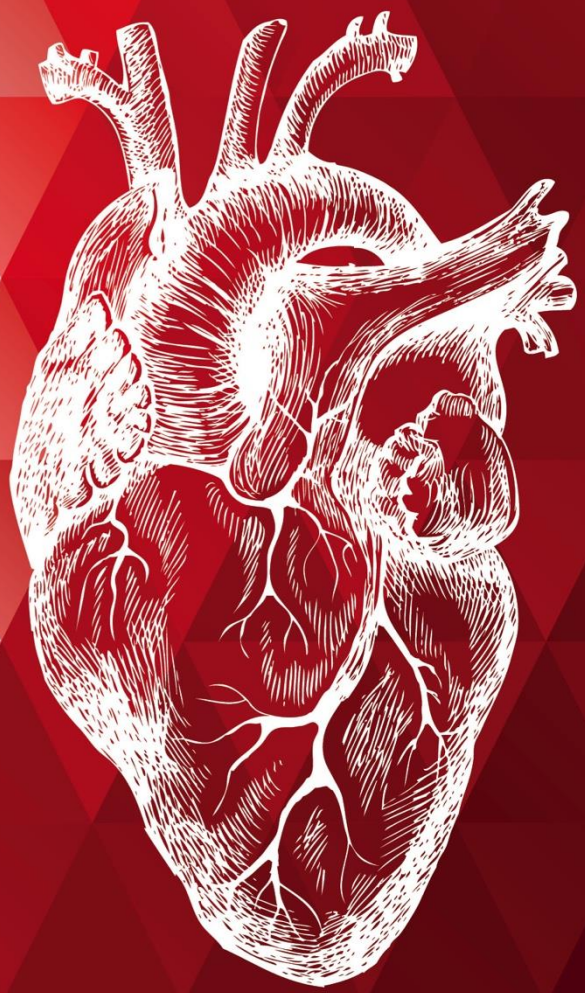

ASSENT-2

Assessment of the Safety and Efficacy of a New Thrombolytic

Results and implications

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Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

ASSENT-2 TRIAL

Assessment of the **SAFETY AND EFFICACY** of a New Thrombolytic (ASSENT-2) Investigators.

LANCET 1999; 354: 716-22 **MAJOR PHASE III TRIAL** on TNK t-PA

16,949 **PATIENTS**, 1021 **HOSPITALS**, 29 **COUNTRIES WORLDWIDE.**

EQUIVALENCE TRIAL

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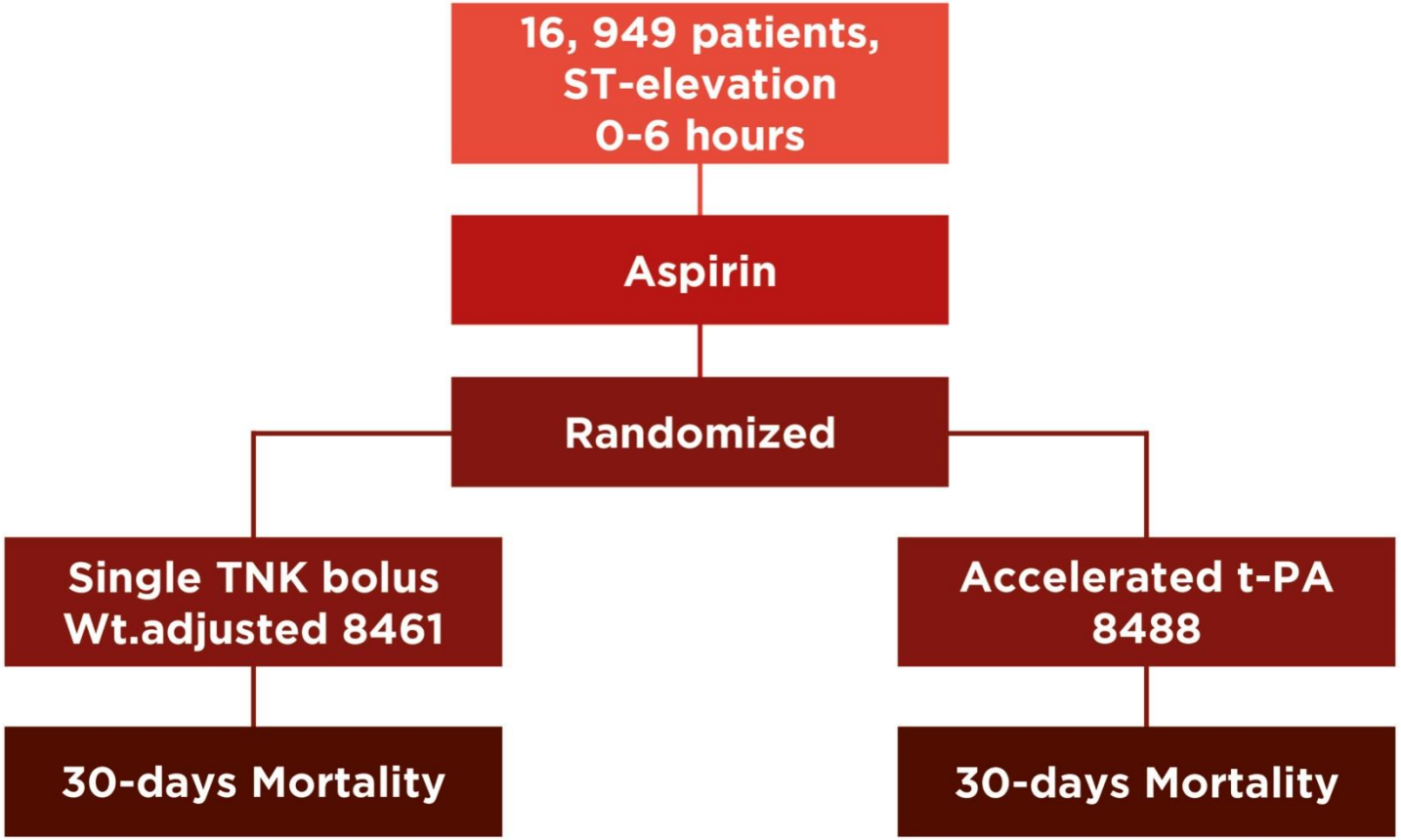
Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

STUDY DESIGN



Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial.

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ASSENT II -
AIM OF THE STUDY

PRIMARY OBJECTIVE:

To demonstrate **EQUIVALENCE** in **30-DAY MORTALITY** between bolus administration of TNK-tPA and an **ACCELERATED INFUSION** of rt-PA.

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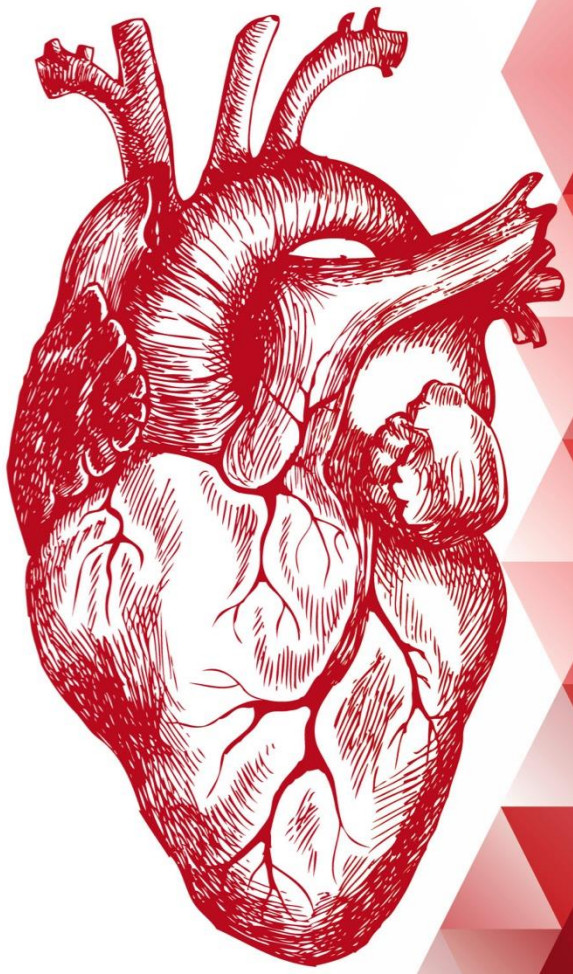
Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 doubleblind randomised trial.

TRIAL DESIGN

A phase III, **RANDOMIZED**, **DOUBLEBLIND**, **PARALLEL-GROUP**, international trial of single bolus of TNK-tissue plasminogen activator (TNK-tPA) versus **ACCELERATED INFUSION** of rt-PA (Alteplase, Activase) in **ACUTE MYOCARDIAL INFARCTION**.



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Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 doubleblind randomised trial.

WEIGHT ADJUSTED DOSAGE OF METALYSE

TNK-tPA DOSE
SINGLE I.V. BOLUS OVER 5 – 10 SECONDS

Body Weight Category kg	Tenecteplase (mg)	Tenecteplase (ml)
< 60	30	6
≥ 60 to < 70	35	7
≥ 70 to < 80	40	8
≥ 70 to < 80	45	9
≥ 90	50	10

1. TNKase¨ ASSENT-2 Clinical Trial Design and Methodology [Internet]. Tnkase.com. 2019 [cited 20 January 2019]. Available from: https://www.tnkase.com/ami-treatment-clinical-trial-data/assent-2-clinical-trial.html
2. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial.

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WORLDWIDE TRIAL

Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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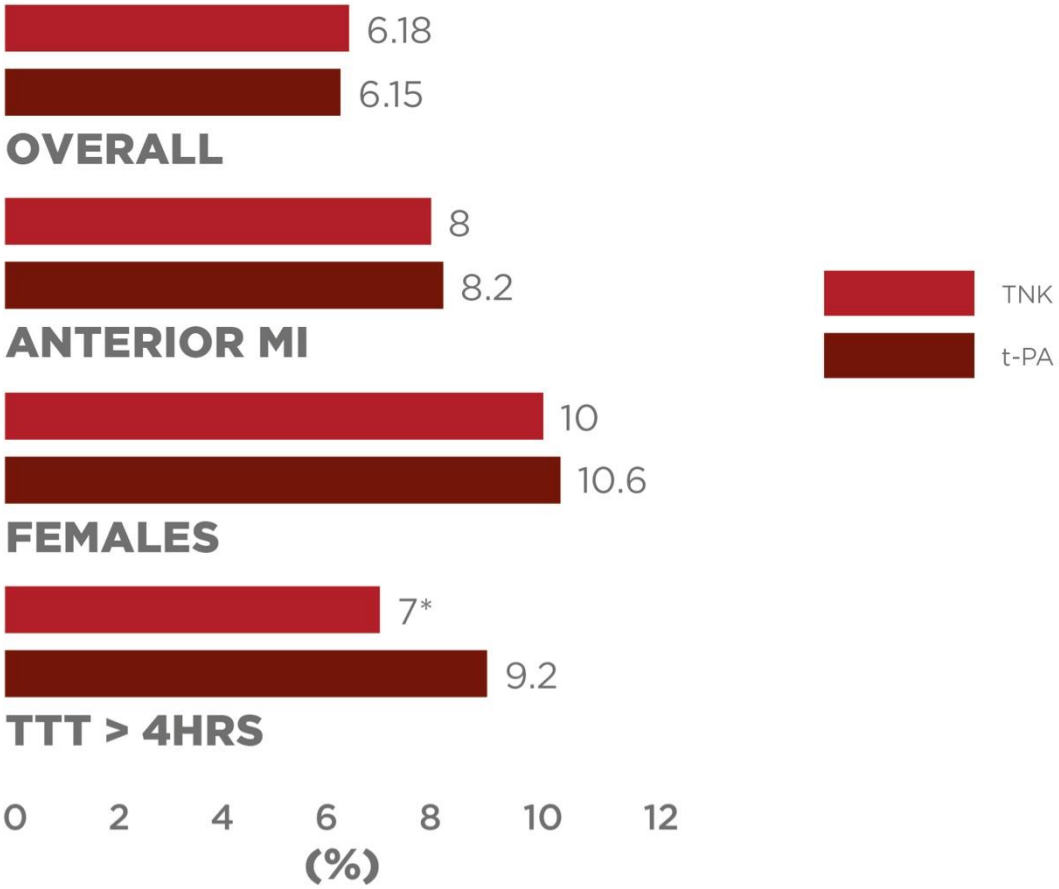
30-DAYS MORTALITY



Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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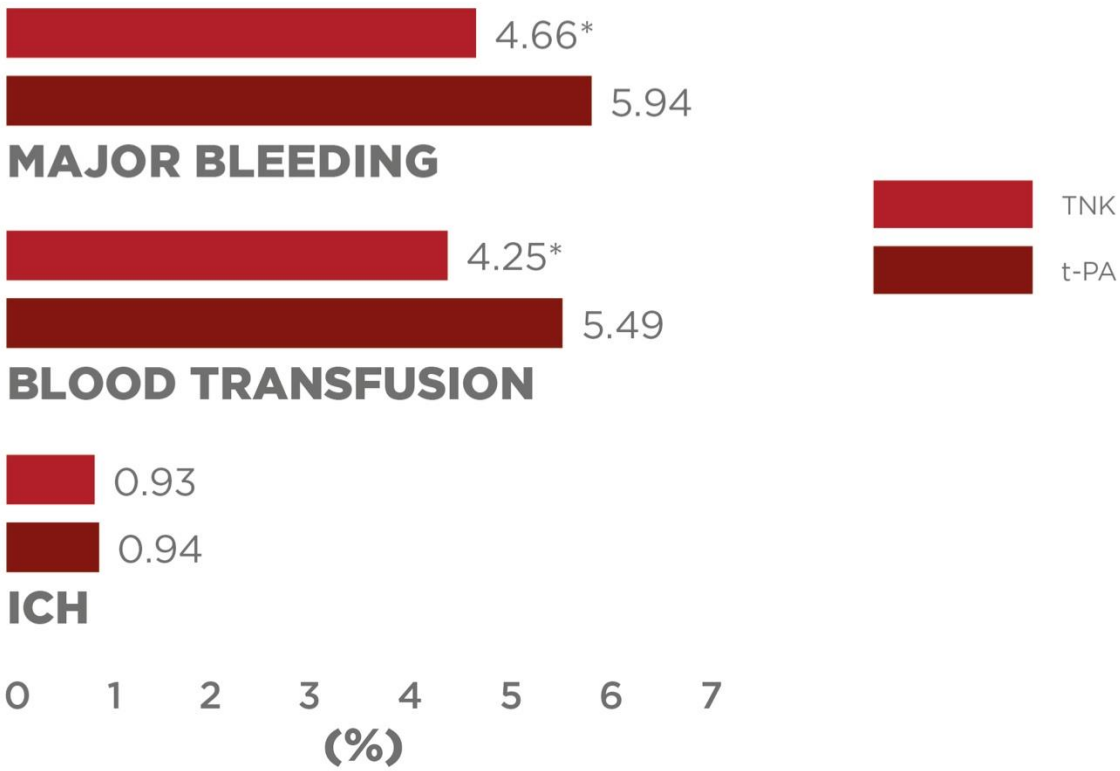
BLEEDING COMPLICATIONS



* p = 0.0002

Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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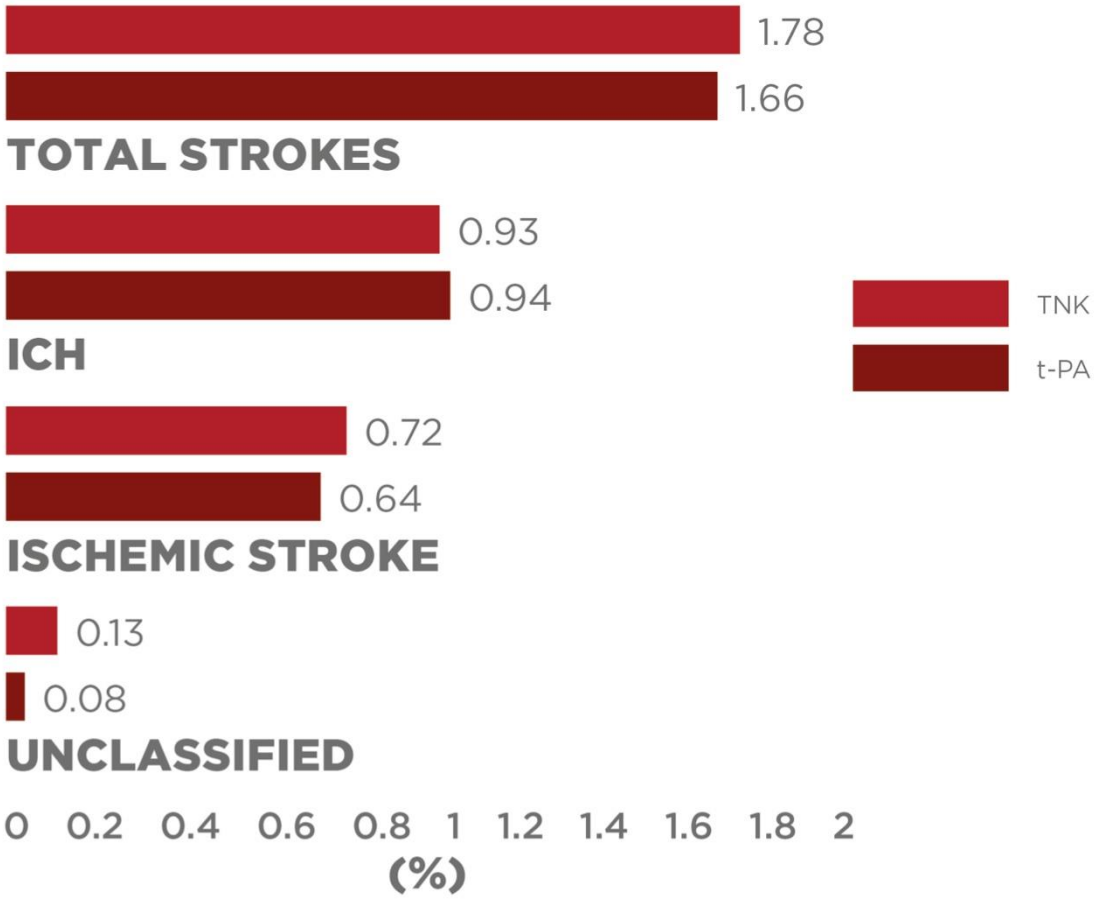
FREQUENCY OF STROKES



Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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PRINCIPAL FINDINGS

	TNK-tPA	T-PA
30 days mortality	6.2%	6.2%
Intracranial HG	0.93%	0.94%
Stroke	1.78%	1.66%
Major Bleeds	4.7%	5.9%
Needs transfusion	4.3%	5.5%
Mortality 4-6 hrs	7%	9.2%

1. Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.
2. TNKase¨ ASSENT-2 Clinical Trial Design and Methodology [Internet]. Tnkase.com. 2019 [cited 20 January 2019]. Available from: https://www.tnkase.com/ami-treatment-clinical-trial-data/assent-2-clinical-trial.html

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CONCLUSION

TNK-tPA (tenecteplase and rt-PA (alteplase) are **EQUIVALENT AT 30 DAY MORTALITY**

- **STRINGENT CRITERIA** for equivalence
- Mortality rates **VIRTUALLY IDENTICAL**
- **FIRST TIME EQUIVALENCE** shown with new fibrinolytic

The risk of **CEREBRAL BLEEDING** is very similar with both agents

The risk of other **BLEEDING COMPLICATIONS** is lower after TNK-tPA

The ease of administration of tenecteplase may facilitate more **RAPID TREATMENT** in and out of hospital

Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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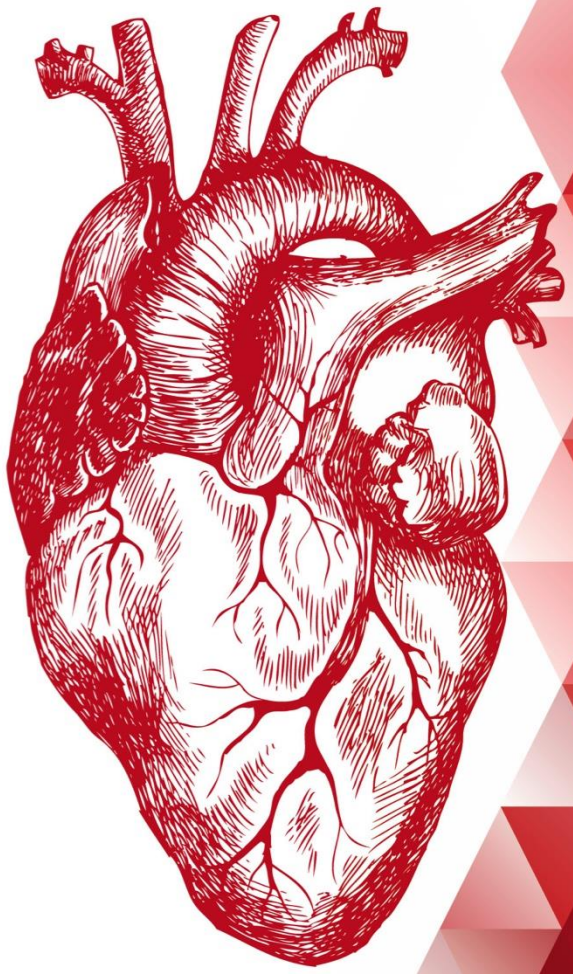
IMPLICATION

> What these findings mean is that the two drugs are **VIRTUALLY IDENTICAL** for **MORTALITY REDUCTION**, while TNK-t-PA has the added advantage of being given as a single bolus, rather than as an intravenous infusion

– ASSENT 2 principal investigator
Frans J. Van de Werf, MD,
Chairman, Department of Cardiology,
University Hospital Gasthuisberg, Leuven, Belgium



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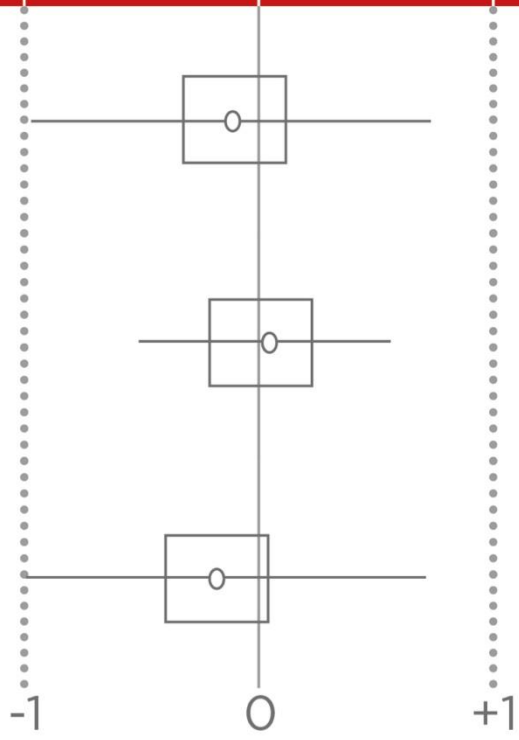
Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

COMPARISON AMONG EQUIVALENCY ANALYSES FOR 30-DAY MORTALITY

	Mortality (%)		Absolute difference (95% CI)	p value for equivalence
InTIME-2	n-PA	t-PA	-0.14	0.004
	6.75	6.61	(-1.0, 0.68)	
ASSENT-2	TNK-tPA	t-PA	0.02	0.006
	6.16	6.18	(-0.59, 0.62)	
GUSTO-III	r-PA	t-PA	-0.23	NS
	7.47	7.24	(-1.11, 0.66)	



1. Intravenous NPA for the treatment of infarcting myocardium early. InTIME-II, a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction. European Heart Journal. 2000;21(24):2005-2013.
2. Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 doubleblind randomised trial. The Lancet. 1999;354(9180):716-722.
3. A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.

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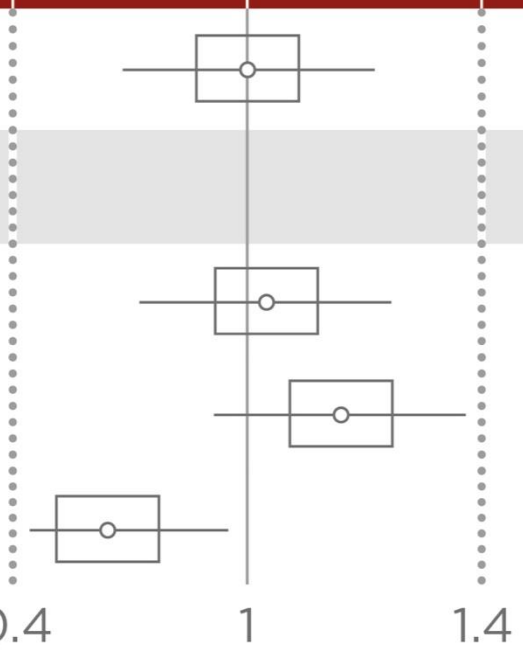
ASSENT-2: IMPROVED SURVIVAL FOR TNK-TPA IN LATE-TREATED PATIENTS

	TNK-tPA (n=8,461)	t-PA (n=8,488)	Relative risk (95% CI)	p value
Total population (%)	6.16	6.18	1.00 (0.89, 1.12)	0.975
Time to therapy (h)				
0-2 (%)	5.0	4.9	1.017 (0.799, 1.296)	0.897
>2-4 (%)	6.3	5.5	1.157 (0.970, 1.379)	0.106
>4 (%)	7.0	9.2	0.766 (0.617, 0.952)	0.018



Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 doubleblind randomised trial. The Lancet. 1999;354(9180):716-722.

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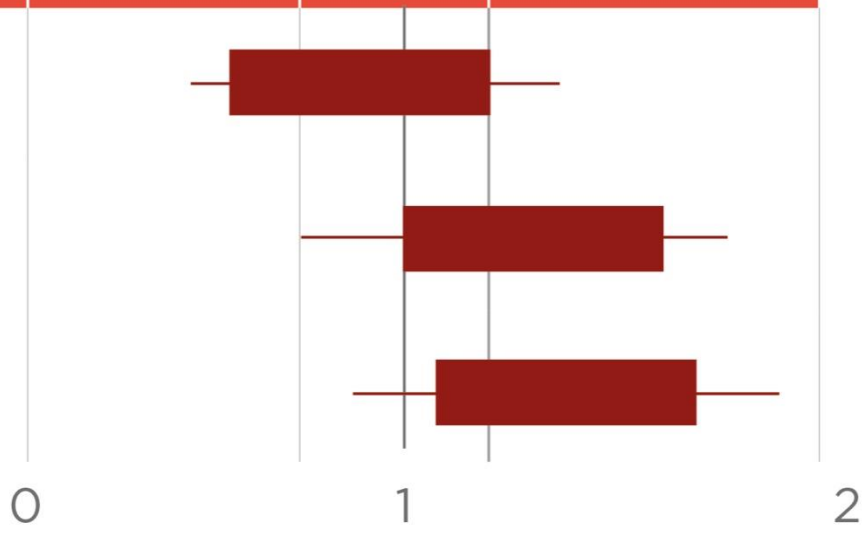
GUSTO III: TIME-TO-TREATMENT AND 30-DAY MORTALITY

Time to Rx (h)	r-PA	t-PA
0-2	5.8%	6.2%
2-4	7.2%	6.9%
>4	9.7%	7.9%



* * p=0.02 for interaction time to Rx

A Comparison of Reteplase with Alteplase for Acute Myocardial Infarction. New England Journal of Medicine. 1997;337(16):1118-1123.A

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ASSENT-2: SIGNIFICANTLY FEWER NONCEREBRAL BLEEDING EVENTS WITH TNK-TPA

	TNK-tPA (n=8,461)	t-PA (n=8,488)	p value
Total bleeds (%)	26.4	29.0	0.0003
Major bleeds (%)	4.7	5.9	0.0002
Minor bleeds (%)	21.8	23.0	0.0553
Units transfused			
Any	4.3	5.5	0.0002
1-2 units	2.6	3.2	–
>2 units	1.7	2.2	–

1. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial.
2. TNKase¨ ASSENT-2 Clinical Trial Design and Methodology [Internet]. Tnkase.com. 2019 [cited 20 January 2019]. Available from: https://www.tnkase.com/ami-treatment-clinical-trial-data/assent-2-clinical-trial.html

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NON-CEREBRAL BLEEDINGS AND FIBRIN-SPECIFICITY

Less **FIBRIN-SPECIFIC AGENTS** are associated with more **NON-CEREBRAL BLEEDING COMPLICATIONS**

- SK > t-PA (GUSTO-I and GISSI-2 International)
- t-PA > TNK (ASSENT-2)

1. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. New England Journal of Medicine. 1993;329(10):673-682.
2. GRUPPOITALIANOPERLOSTUDIODELL. MEDICAL SCIENCE GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. The Lancet. 1990;336(8707).
3. Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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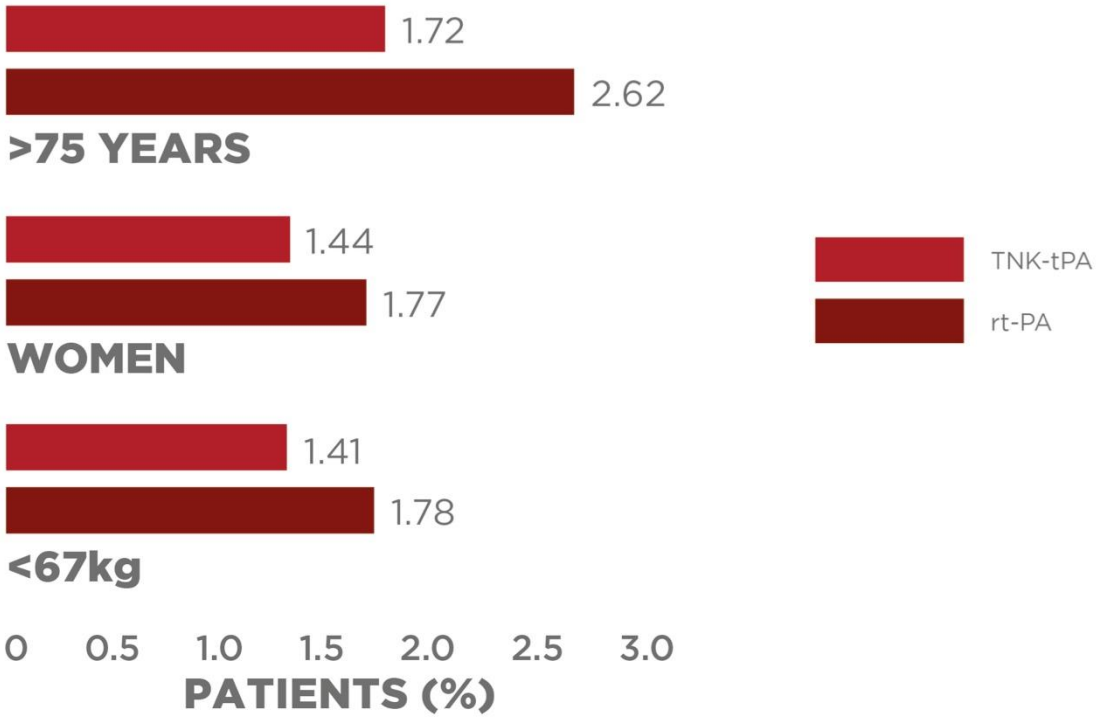
ICH RATES: ASSENT-2



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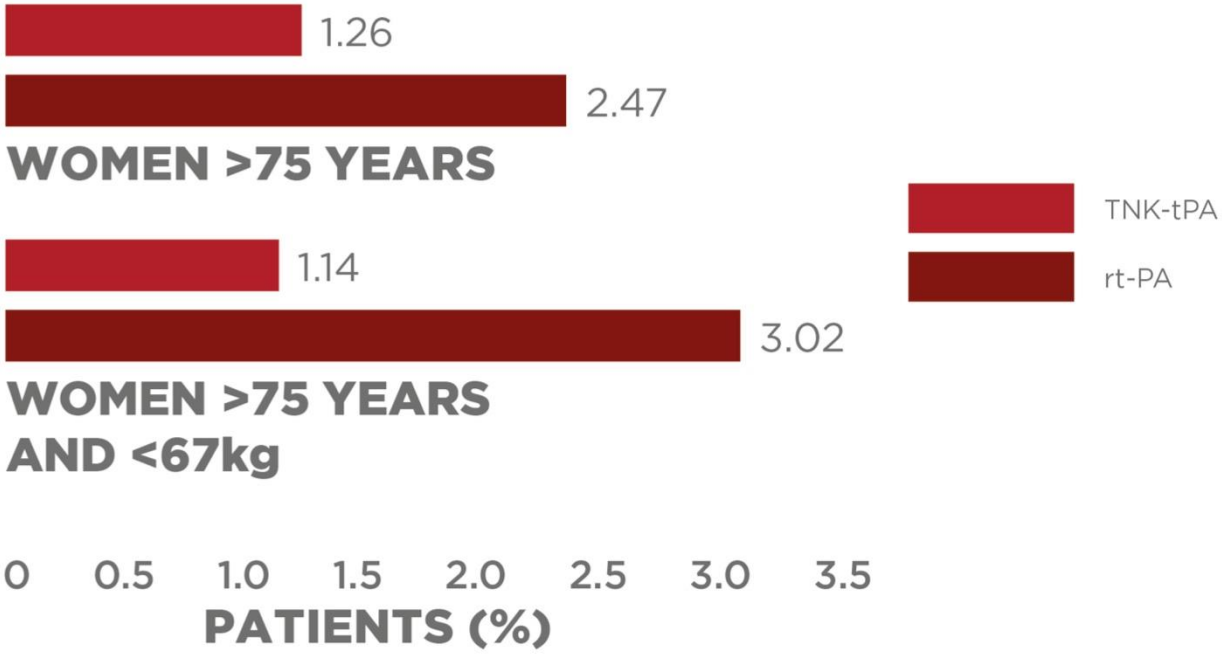
ICH RATES: ASSENT-2



Van de Werf F. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999;354(9180):716-722.

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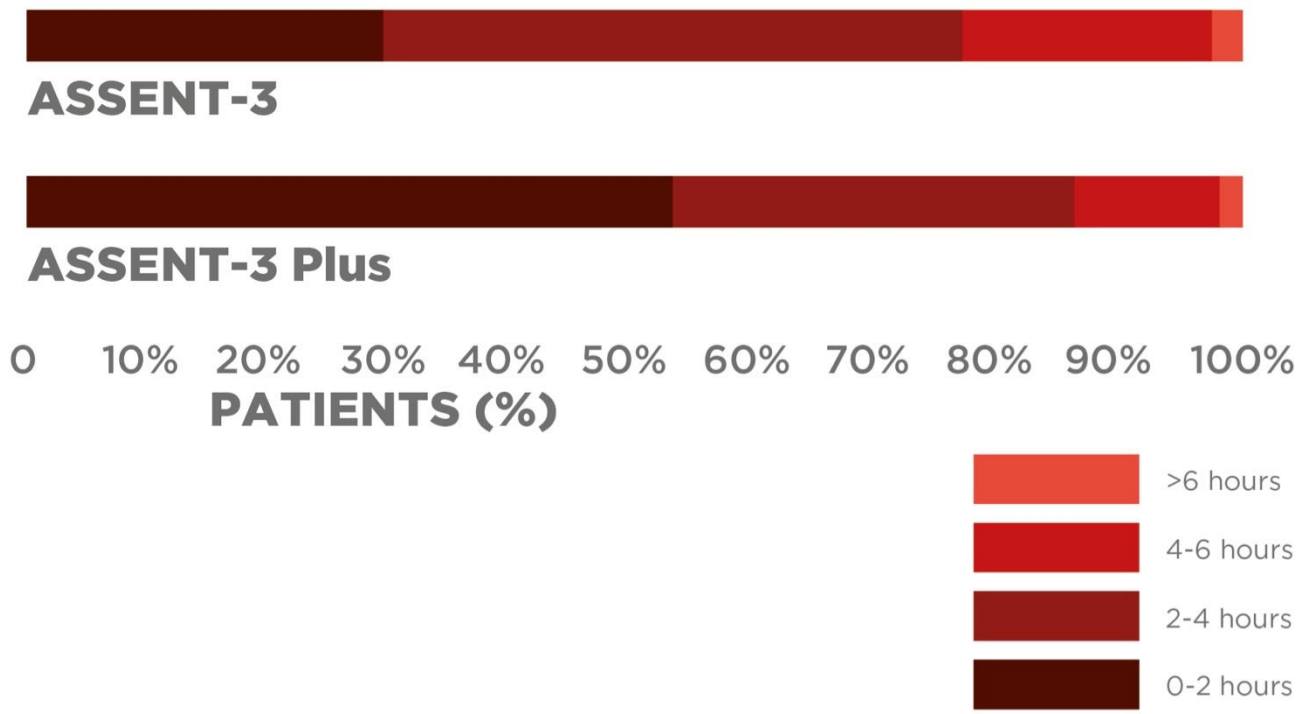
ONSET OF SYMPTOMS TO TNK-TPA BOLUS: ASSENT-3 VS. ASSENT-3 PLUS



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2. Wallentin L, Goldstein P, Armstrong P. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the assessment of the safety and efficacy of a new thrombolytic regimen (ASSENT) 3 plus randomized trial in acute myocardial infarction. ACC Current Journal Review. 2003;12(6):12.

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WHY METALYSE?

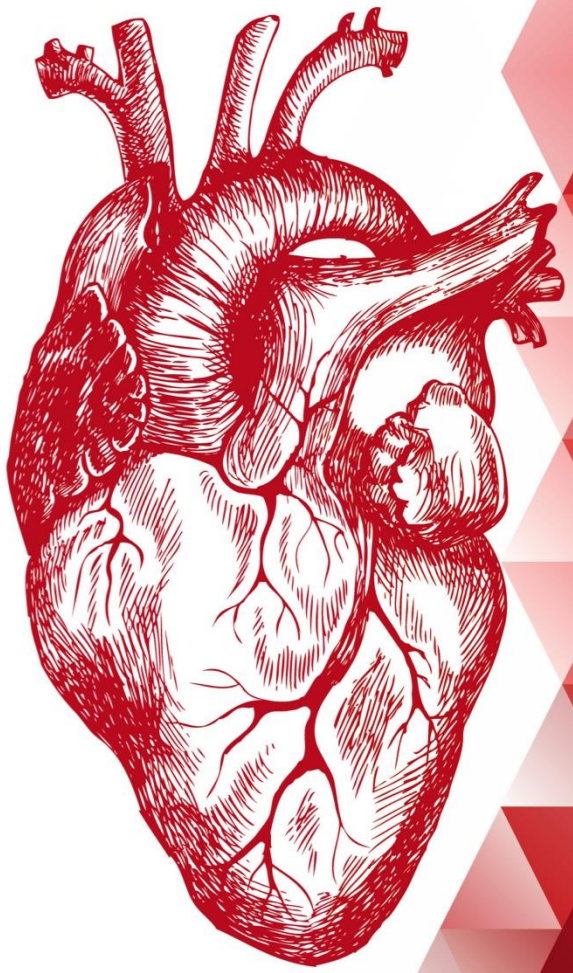
SINGLE BOLUS ADMINISTRATION:

- **CONVENIENCE[1]**
- **TIME / IMPROVED OUTCOMES[1]**

CLOT SPECIFIC FIBRINOLYSIS[2]

PREDICTABLE ELIMINATION[2]

HIGH PAI-1* RESISTANCE[2]



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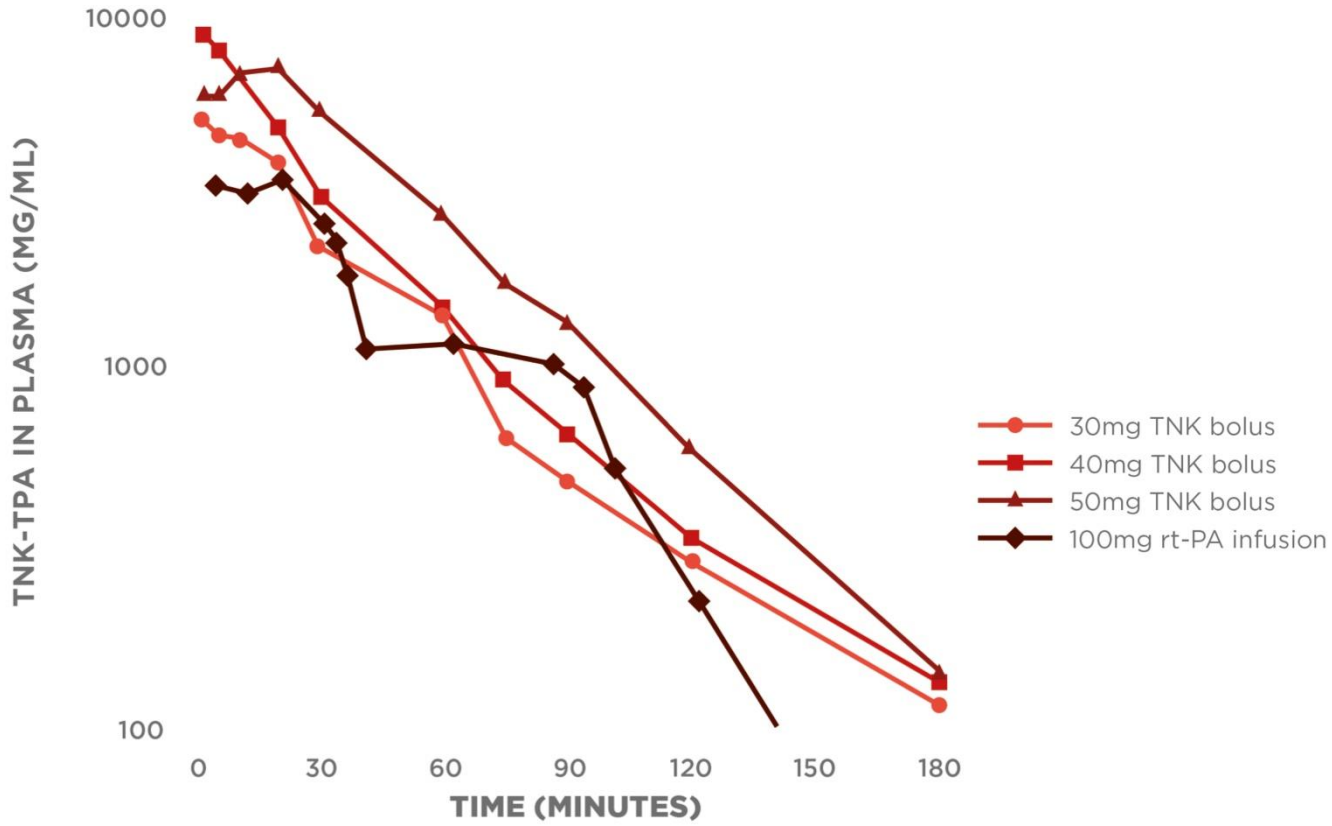
1. Wallentin L, Goldstein P, Armstrong P. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the assessment of the safety and efficacy of a new thrombolytic regimen (ASSENT) 3 plus randomized trial in acute myocardial infarction. ACC Current Journal Review. 2003;12(6):12.
2. Kliche W, Krech I, Michel M, Sangole N, Sathaye S. Comparison of clot lysis activity and biochemical properties of originator tenecteplase (Metalyse¨) with those of an alleged biosimilar. Frontiers in Pharmacology. 2014;5. *plasminogen activator inhibitor 1

WHY METALYSE?

SINGLE DOSE METALYSE = t-PA 90 MIN INFUSION



Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and Pharmacodynamics of Tenecteplase in Fibrinolytic Therapy of Acute Myocardial Infarction. Clinical Pharmacokinetics. 2002;41(15):1229-1245.

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HIGH PAI-1 RESISTANCE

What is PAI-1?: Plasminogen activator inhibitor 1 (PAI-1)[1]

What does PAI-1 do?: Inhibitor of tissue plasminogen activator (t-PA)

Where does PAI-1 come from? Mainly activated platelets[2]

How does PAI-1 work? PAI-1 binds to t-PA to inhibit its action – Metalyse has mutations than decrease PAI-1 ability to bind and inhibit.

↓

RESULT: **80-fold higher resistance** to inhibition by PAI-1 for Metalyse. vs. Alteplase

↓

Easy administration of Metalyse as a single bolus

1. Llevadot J. Bolus Fibrinolytic Therapy in Acute Myocardial Infarction. JAMA. 2001;286(4):442.
2. Cesari M, Pahor M, Incalzi R. REVIEW: Plasminogen Activator Inhibitor-1 (PAI-1): A Key Factor Linking Fibrinolysis and Age-Related Subclinical and Clinical Conditions. Cardiovascular Therapeutics. 2010;28(5):e72-e91.
3. Kliche W, Krech I, Michel M, Sangole N, Sathaye S. Comparison of clot lysis activity and biochemical properties of originatortenecteplase (Metalyse¨) with those of an alleged biosimilar. Frontiers in Pharmacology. 2014;5.

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