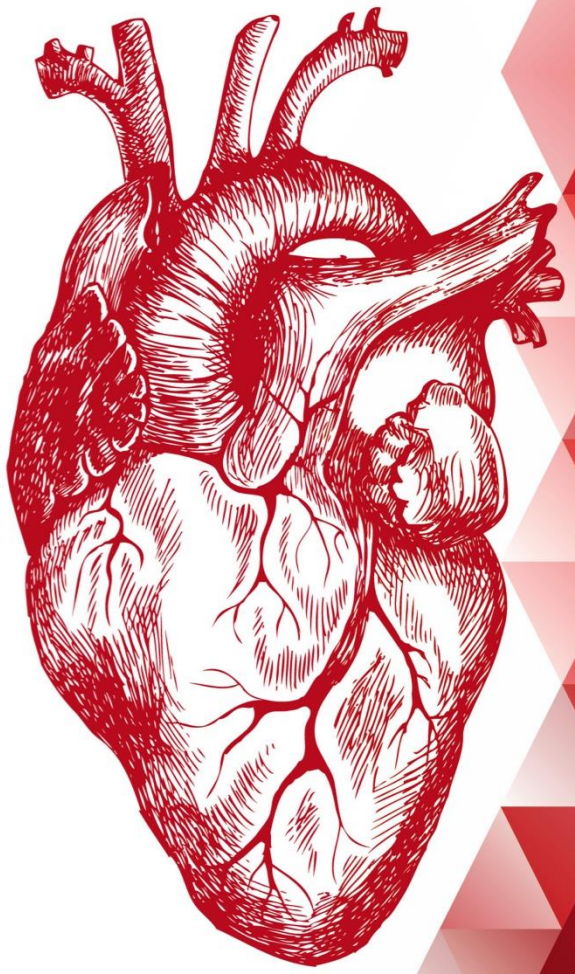
guardian
guard your heart

PHARMACEUTICAL TREATMENT OPTIONS

OVERVIEW

1. Importance of time
2. Role of fibrinolytics
3. Tenecteplase (Metalyse®)
4. Alteplase (Actilyse®)
5. Clinical trials in summary



guardian
guard your heart

IMPORTANCE OF TIME

MANAGEMENT OF ACUTE MI AND RATIONALE FOR EARLY REPERFUSION

AIMS

- Prevent death
- Limit extent of myocardial damage
- Minimise patient's discomfort and distress

STRATEGY[1]

Re-establish myocardial reperfusion before irreversible damage occurs:

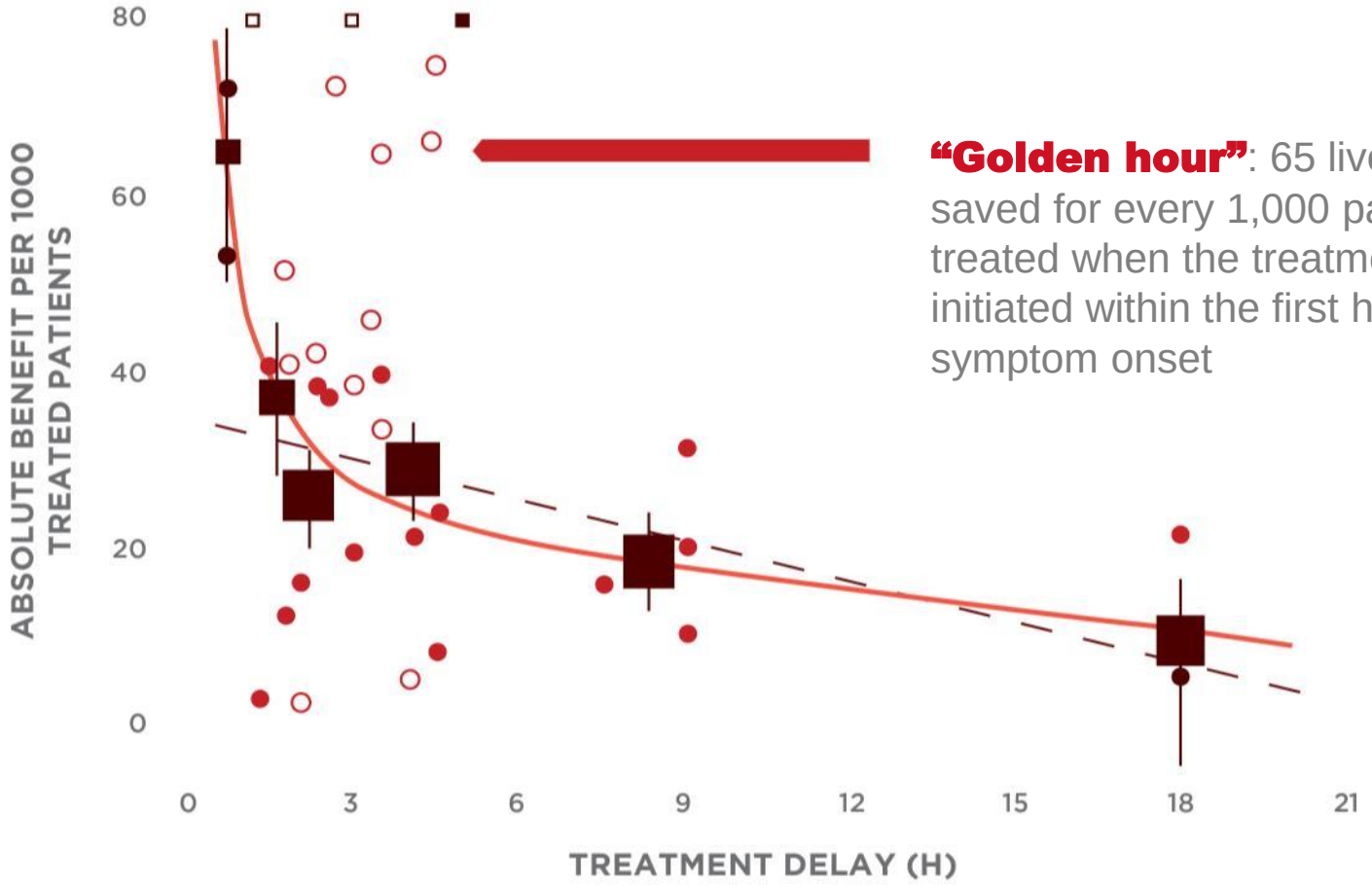
- mechanically (PPCI, primary percutaneous coronary intervention)
- pharmacologically (induction of thrombolysis by thrombolytic agent)
- pharmaco-invasive (combination of pharmacological and mechanical intervention)

TIME IS MUSCLE!

1. Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). European heart journal. 2012 Aug 24;33(20):2569-619.

guardian guard your heart

MANAGEMENT OF ACUTE MI AND RATIONALE FOR EARLY REPERFUSION



"Golden hour": 65 lives are saved for every 1,000 patients treated when the treatment is initiated within the first hour of symptom onset

Adapted from:

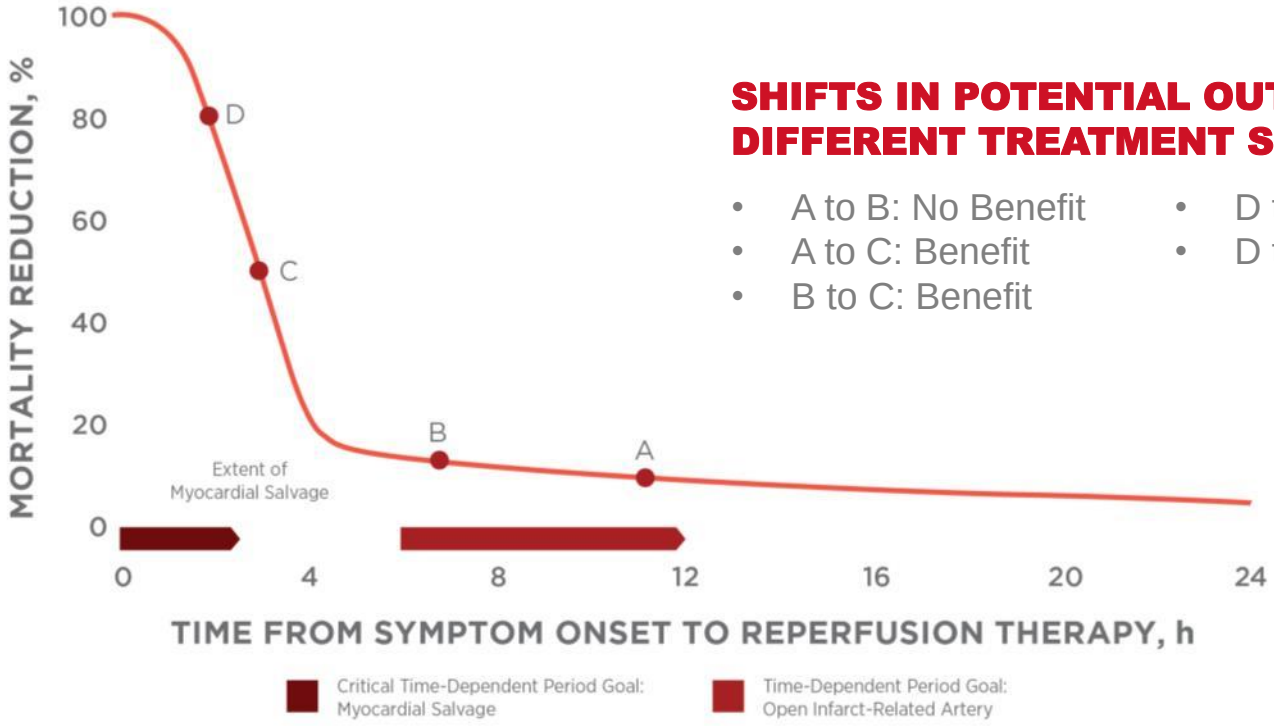
Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. The Lancet. 1996 Sep 21;348(9030):771-5.

guardian
guard your heart

BENEFIT OF EARLY THROMBOLYSIS

LIMIT THE FINAL EXTENT OF INFARCTION WITH EARLY THROMBOLYSIS

Relationship between mortality and extent of salvage



SHIFTS IN POTENTIAL OUTCOMES WITH DIFFERENT TREATMENT STRATEGIES:

- A to B: No Benefit
- A to C: Benefit
- B to C: Benefit
- D to B: Harm
- D to C: Harm

Adapted from:

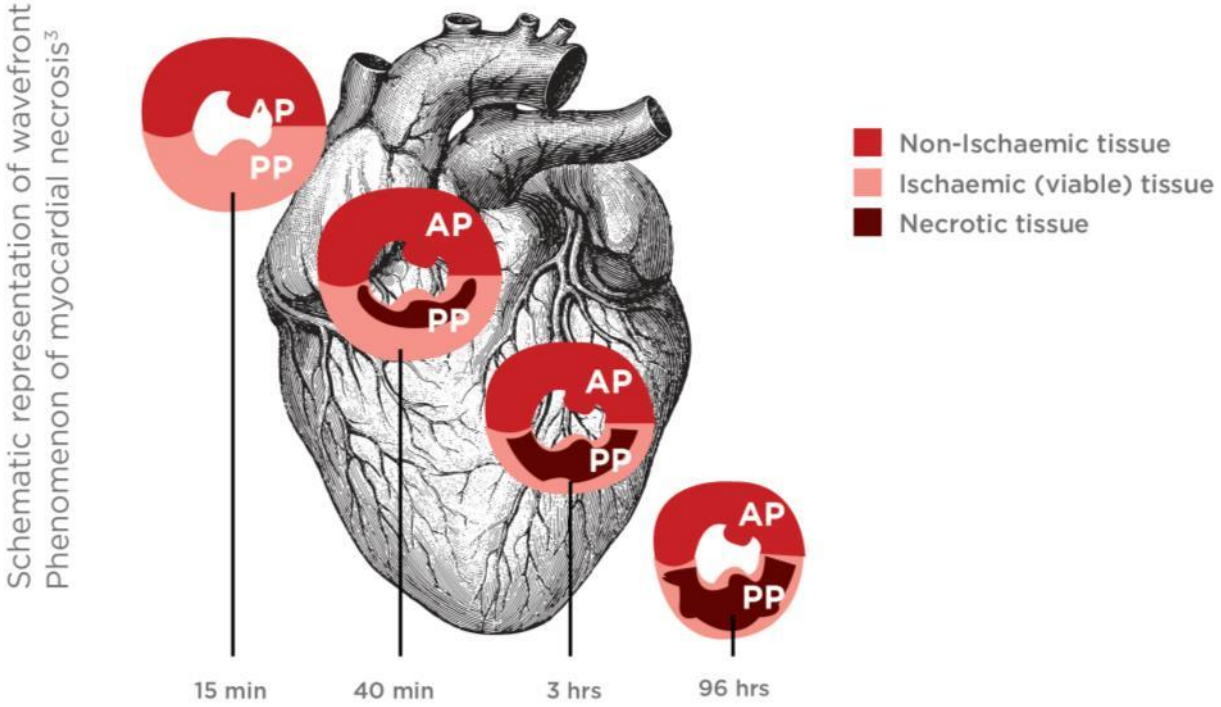
Gersh BJ, Stone GW, White HD, Holmes DR. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future?. Jama. 2005 Feb 23;293(8):979-86.

guardian
guard your heart

BENEFIT OF EARLY THROMBOLYSIS

LIMIT THE FINAL EXTENT OF INFARCTION WITH EARLY THROMBOLYSIS

Progression after cell death



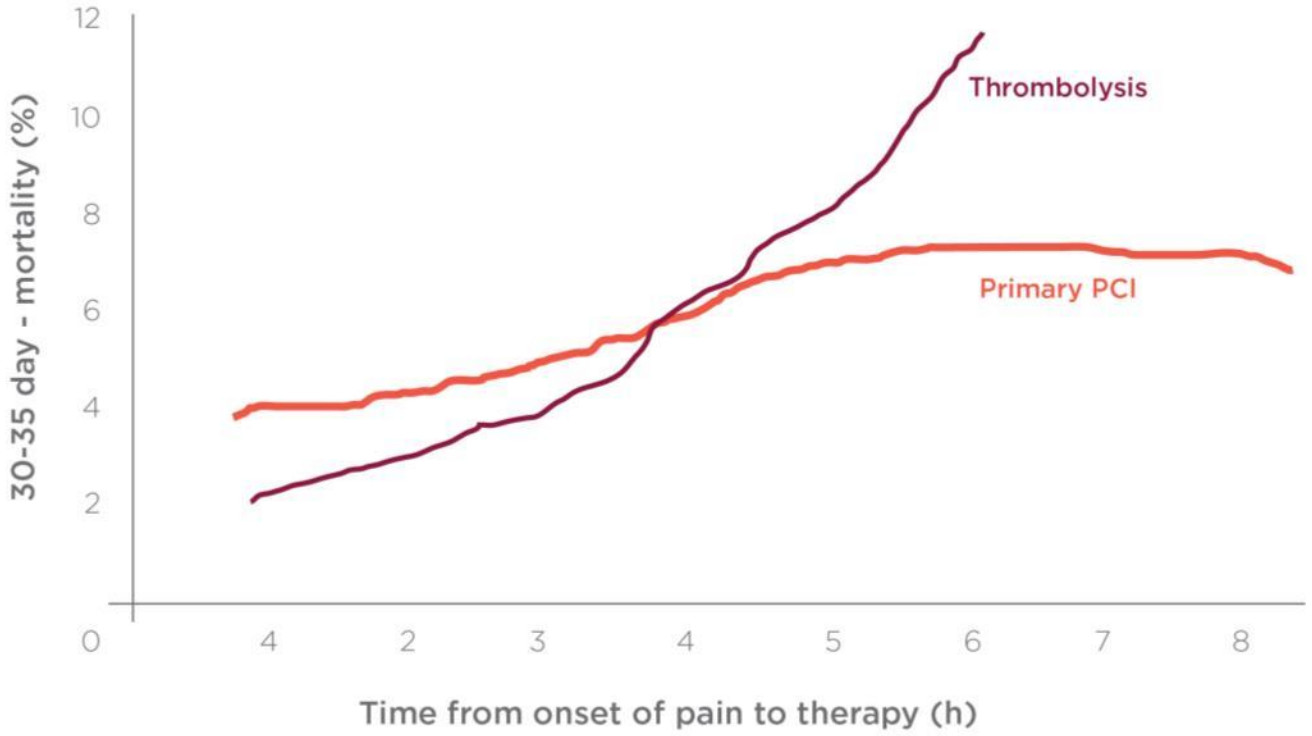
AP = Anterior papillary muscle; PP = Posterior papillary muscle

Adapted from:
Jennings RB, Reimer KA. Factors involved in salvaging ischemic myocardium: effect of reperfusion of arterial blood. Circulation.1983 Aug 1;68:I-25.

guardian
guard your heart

BENEFIT OF EARLY THROMBOLYSIS

TIME AND MORTALITY: EARLY REPERFUSION IS CRITICAL



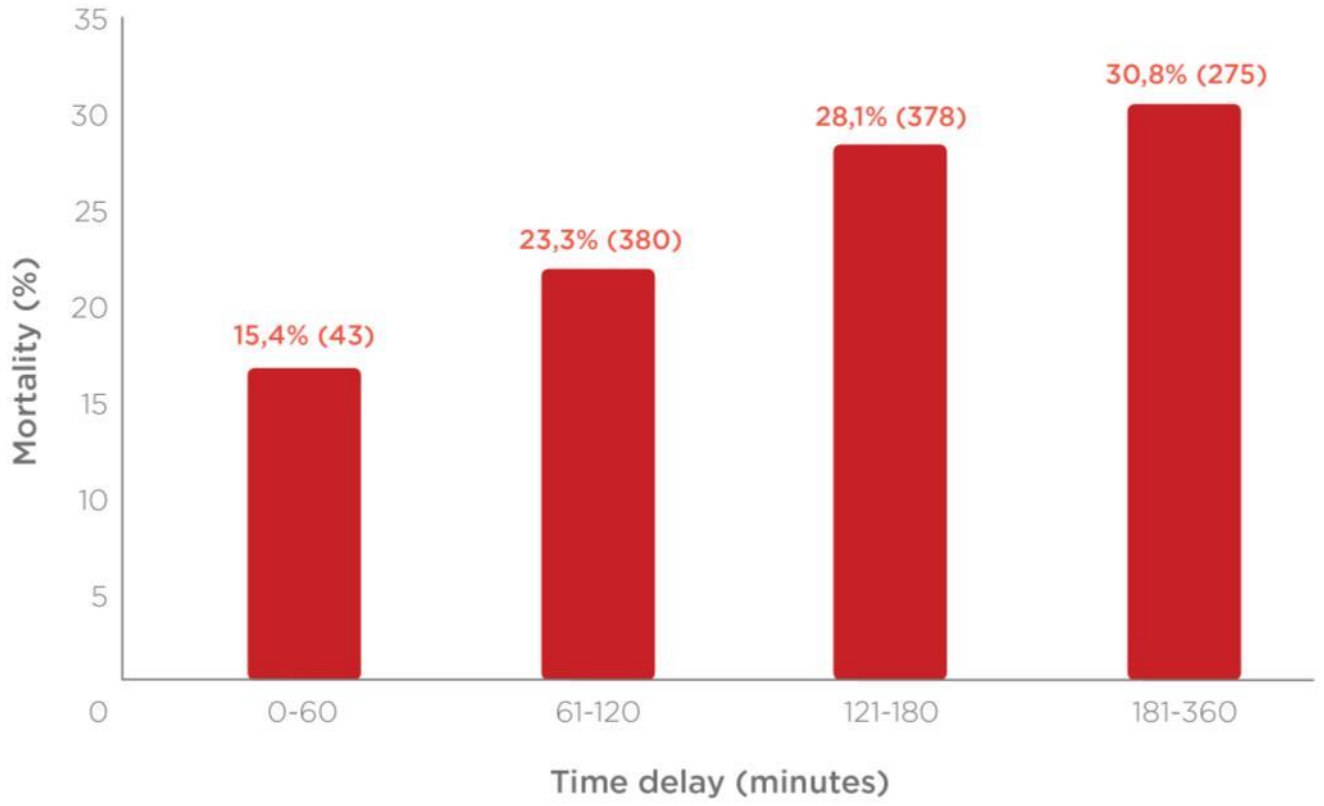
PCI: Percutaneous coronary intervention

Huber K, Caterina RD, Kristensen SD, Verheugt FW, Montalescot G, Maestro LB, Werf FV. Pre-hospital reperfusion therapy: a strategy to improve therapeutic outcome in patients with ST-elevation myocardial infarction. European heart journal. 2005 Jul 29;26(19):2063-74.

guardian
guard your heart

BENEFIT OF EARLY THROMBOLYSIS[1]

MEDIAN FOLLOW UP: 3,4 YEARS (1,8 - 5,2 YEARS)

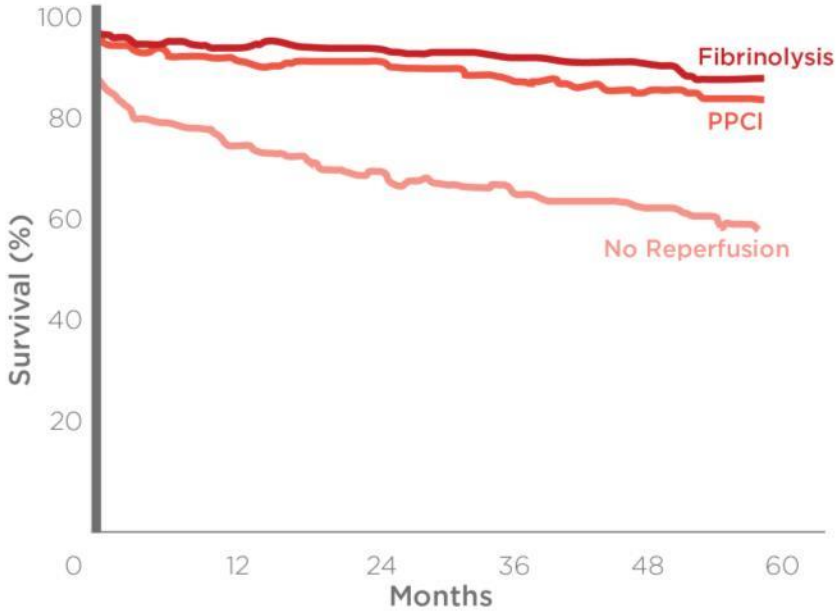


Adapted from:

Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, Vach W, Johnsen SP, Thuesen L, Lassen JF. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. Jama. 2010 Aug 18;304(7):763-71.

guardian
guard your heart

FAST-MI: FIVE YEAR CUMULATIVE SURVIVAL IN PATIENTS WITH STEMI ACCORDING TO REPERFUSION THERAPY*



Adjusted HR [95% CI] (reference no reperfusion)
PPCI 0,57 [0,43 - 0,74]
IV fibrinolysis 0,48 [0,35 - 0,68]

Adjusted HR [95% CI] fibrinolysis vs PPCI
0,73 [0,50 - 1,05]

Number of Risk	Months			
No Reperfusion	462	314	277	248
Fibrinolysis	447	413	395	362
PPCI	583	524	476	439

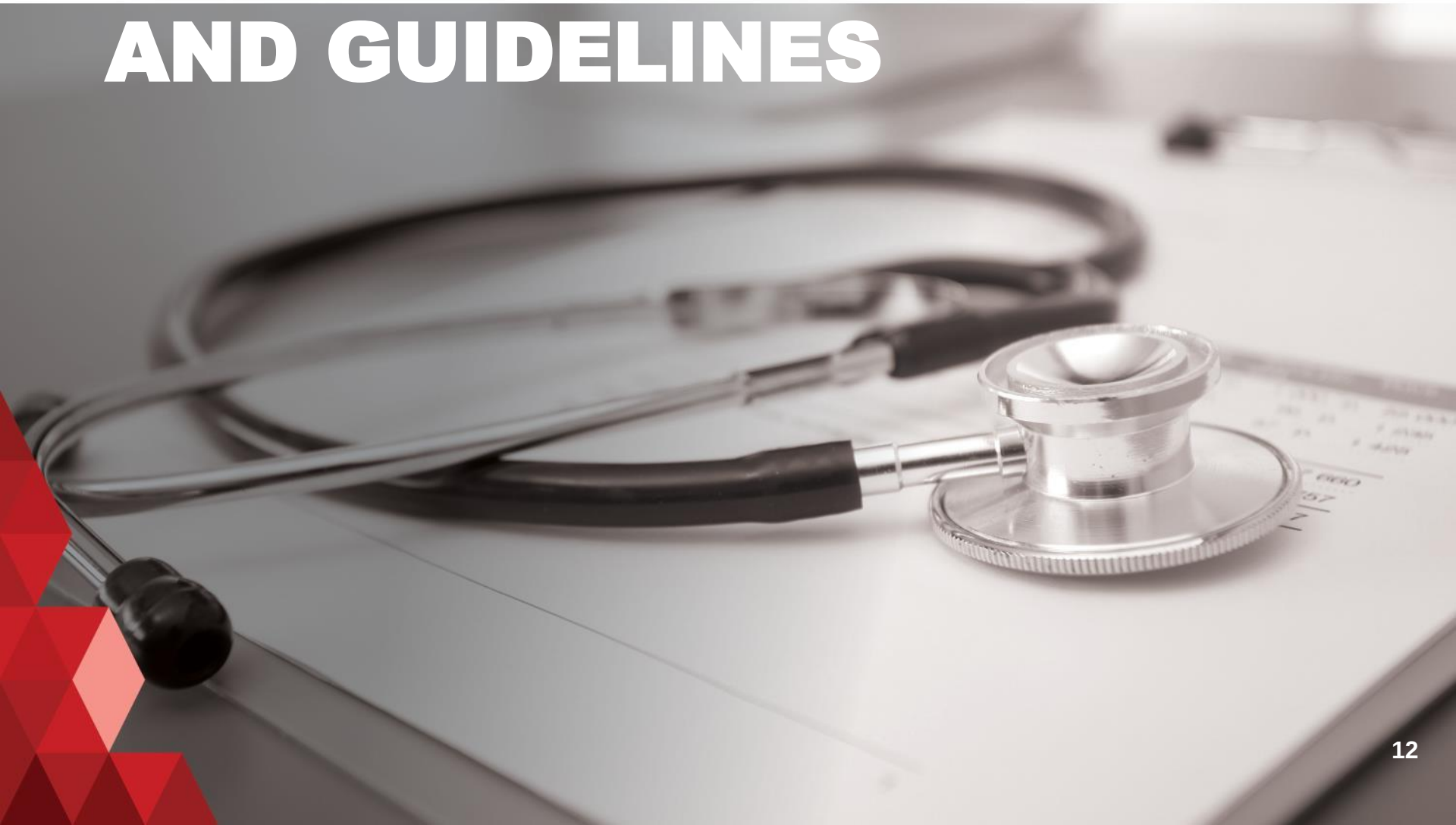
*FAST-MI: The Fench Registry on Acute ST-Elevation Myocardial Infarction; PPCI: Primary percutaneous coronary intervention

Danchin N, Puymirat E, Steg PG, Goldstein P, Schiele F, Belle L, Cottin Y, Fajadet J, Khalife K, Coste P, Ferrieres J. Five-year survival in patients with ST-segment elevation myocardial infarction according to modalities of reperfusion therapy: the French Registry on Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) 2005 cohort. Circulation. 2014 Mar 21:CIRCULATIONAHA-113.

guardian
guard your heart

TREATMENT STRATEGIES AND GUIDELINES

guardian
guard your heart



REPERFUSION TREATMENT

Mechanical Reperfusion

Primary percutaneous coronary intervention (PPCI)

Pharmacological Reperfusion

Pre-hospital/in-hospital thrombolysis (PHT/IHT)

Pharmaco-invasive Therapy

Thrombolysis followed by early angiography and mechanical intervention if indicated

TIME IS CRITICAL FOR STEMI MANAGEMENT!

Organised STEMI networks can be an invaluable asset in enabling STEMI patients to undergo coronary reperfusion in a timely manner

REFERENCE

STEMI TREATMENT GUIDELINES

STEMI guidelines state that acute myocardial ischaemia (<12hrs) should be treated with reperfusion therapy[1,2]

GUIDELINES FROM THE ACC/AHA AND ESC AGREE THAT:

1. Primary PCI (PPCI) is the gold-standard of reperfusion treatment for STEMI if delivered <120 minutes of diagnosis[1,2]
2. Where this is not possible, fibrinolysis should be performed with a fibrin-specific agent (tenecteplase, alteplase or reteplase, as soon as possible within 10 min from STEMI diagnosis, preferably pre-hospital, and patients should be transferred to a PCI-capable centre for subsequent therapy.[2]

ACC/AHA = American College of Cardiology/American Heart Association;
ESC = European Society of Cardiology; PPCI = primary percutaneous coronary intervention

1. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013 Jan 29;61(4):e78-140.2. ESC Task Force. Eur HEart J 2018;39(2):119-177.
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Crea F, Goudevenos JA, Halvorsen S, Hindricks G. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2017 Aug 26;39(2):119-77.

guardian
guard your heart

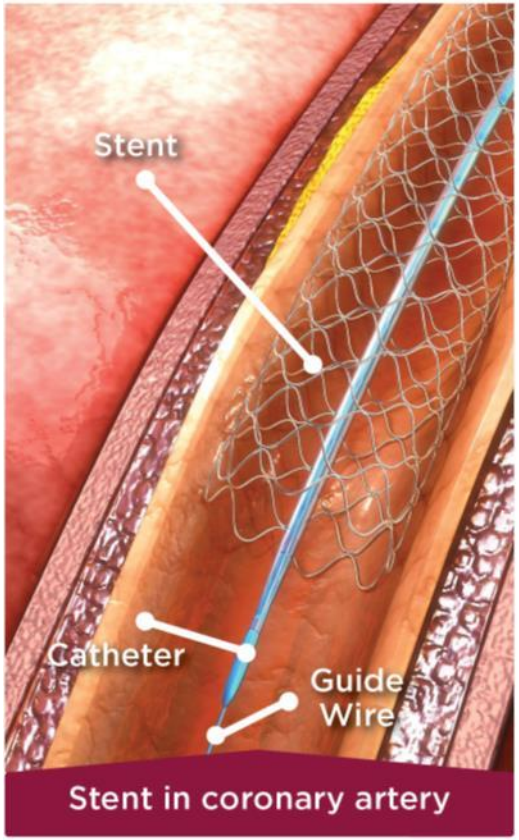
PERCUTANEOUS CORONARY INTERVENTION (PCI) AND PRIMARY PCI (PPCI)

PPCI IS THE GOLD STANDARD IN STEMI CARE – IF PERFORMED WITHIN 120 MIN OF FMC[1]

- Timely PPCI is difficult to achieve in many regions, when patients do not present directly to a PCI-capable facility via EMS or arrival at a facility is delayed[1]

PPCI INVOLVES REVASCULARISATION OF THE BLOCKED CORONARY ARTERY BY MECHANICAL MEANS

- Using the femoral or radial artery as an access point, a catheter with a balloon (and often a stent) is passed through the occulsion[2]
- The balloon is then inflated to open up the vessel, and the stent is put in place to maintain the revascularisation[2]

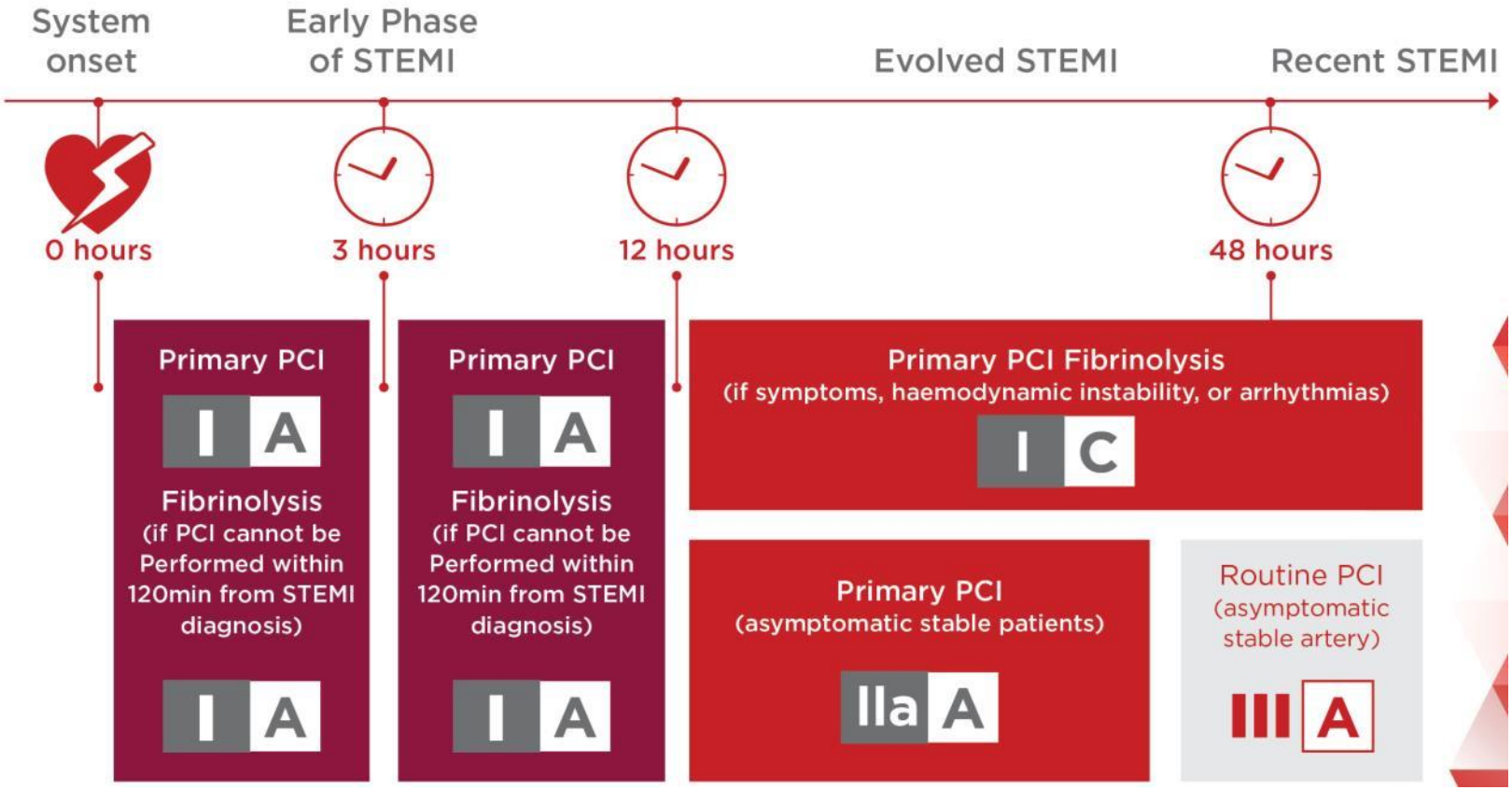


EMS = emergency medical services; FMC, first medical contact; PPCI = primary percutaneous coronary intervention

1. Sinnaeve PR, Van de Werf F. Transporting STEMI patients for primary PCI: a long and winding road paved with good intentions?. European heart journal. 2016 Apr 1;37(13):1041.
2. Keeley EC, Hillis LD. Primary PCI for myocardial infarction with ST-segment elevation. New England Journal of Medicine. 2007 Jan 4;356(1):47-54.

guardian guard your heart

ESC STEMI GUIDELINES 2017: REPERFUSION STRATEGIES



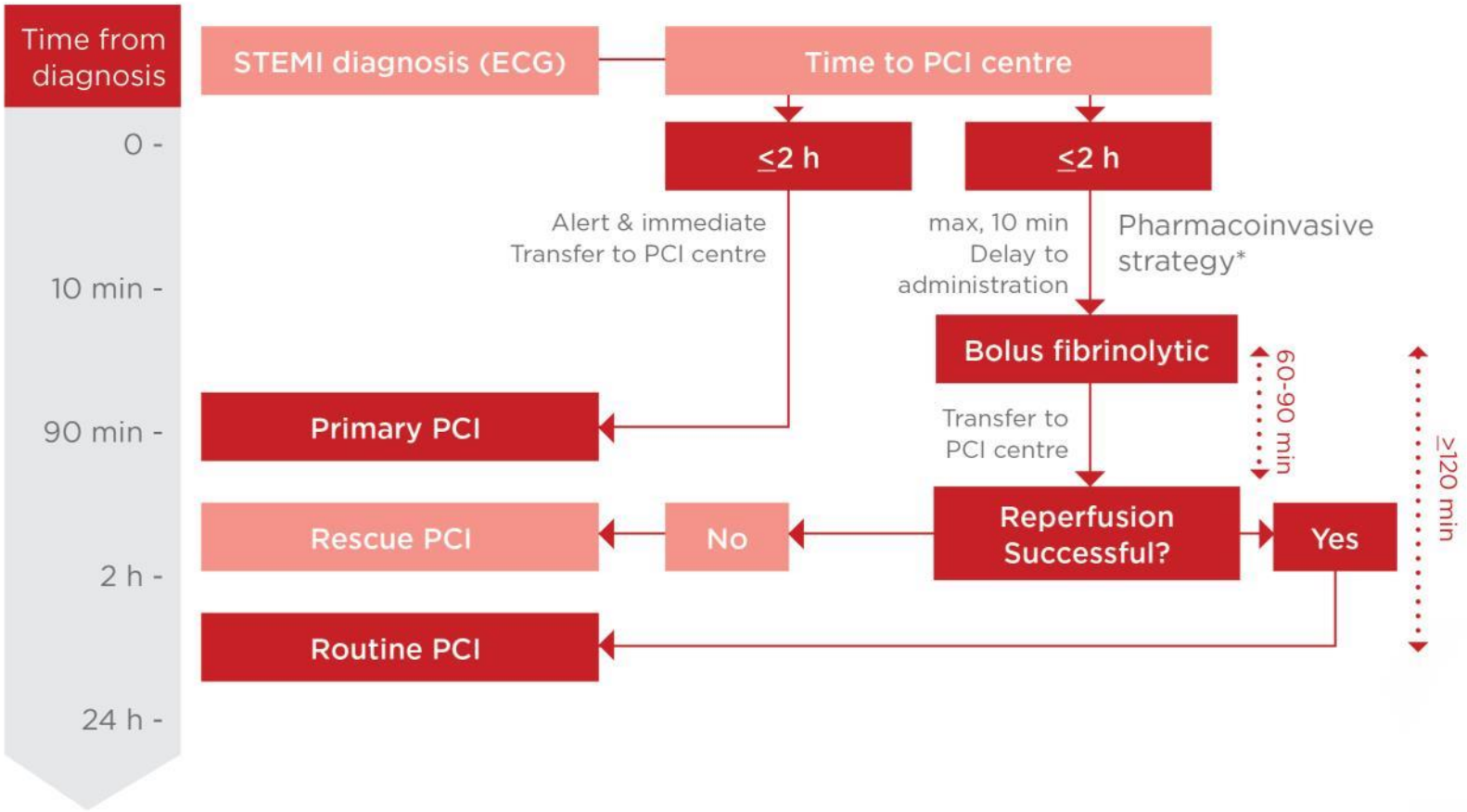
Levels and class of evidence as per ESC guidelines 2018

Adapted from:

Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Crea F, Goudevenos JA, Halvorsen S, Hindricks G. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2017 Aug 26;39(2):119-77.

guardian guard your heart

ESC STEMI GUIDELINES 2017: REPERFUSION STRATEGIES



*If fibrinolysis is contraindicated, transfer to PCI centre regardless of time to PCI

Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Crea F, Goudevenos JA, Halvorsen S, Hindricks G. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2017 Aug 26;39(2):119-77.

SUMMARY OF RATIONALE FOR PRE-HOSPITAL THROMBOLYSIS (PHT) AND PHARMACO-INVASIVE STRATEGY

Not all medical centres are PPCI-capable &/or pre-hospital delays often prevent patients from receiving timely PPCI[1]

No specialist equipment required and PHT has been established as a safe and effective treatment for STEMI[2]

PHT reduces time to reperfusion and improves outcomes if PPCI is not possible within 2h[3,4]

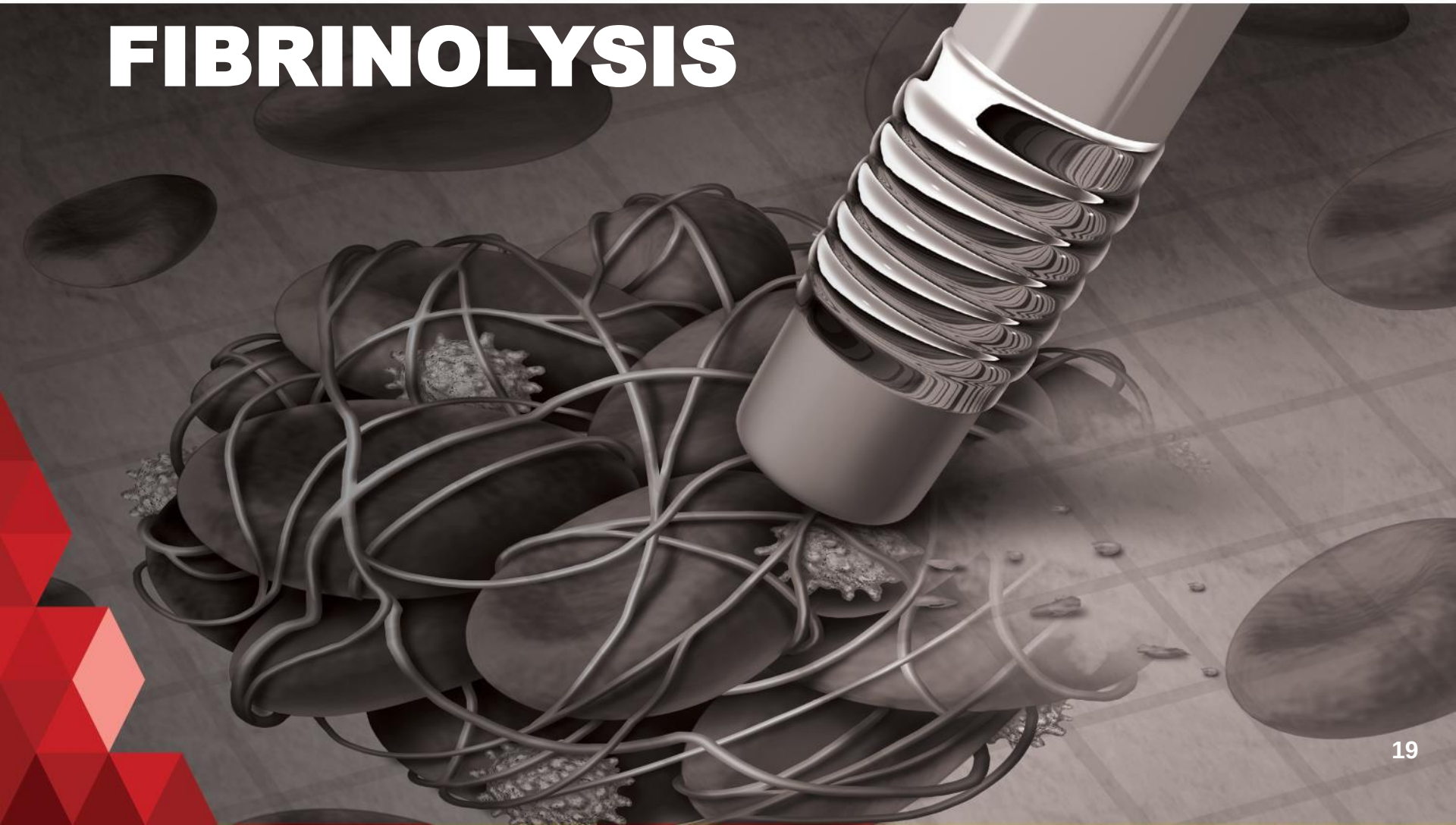
Pharmaco-invasive strategy may achieve reperfusion directly:
in case of thrombolysis failure, reperfusion can be achieved with subsequent rescue PCI[5]

PPCI: primary percutaneous coronary intervention

1. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. New England Journal of Medicine. 2013 Apr 11;368(15):1379-87.
2. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013 Jan 29;61(4):e78-140.
3. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. Jama. 2000 May 24;283(20):2686-92.
4. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F. 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. Circulation. 2003 Jul 15;108(2):135-42.
5. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Crea F, Goudevenos JA, Halvorsen S, Hindricks G. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2017 Aug 26;39(2):119-77.

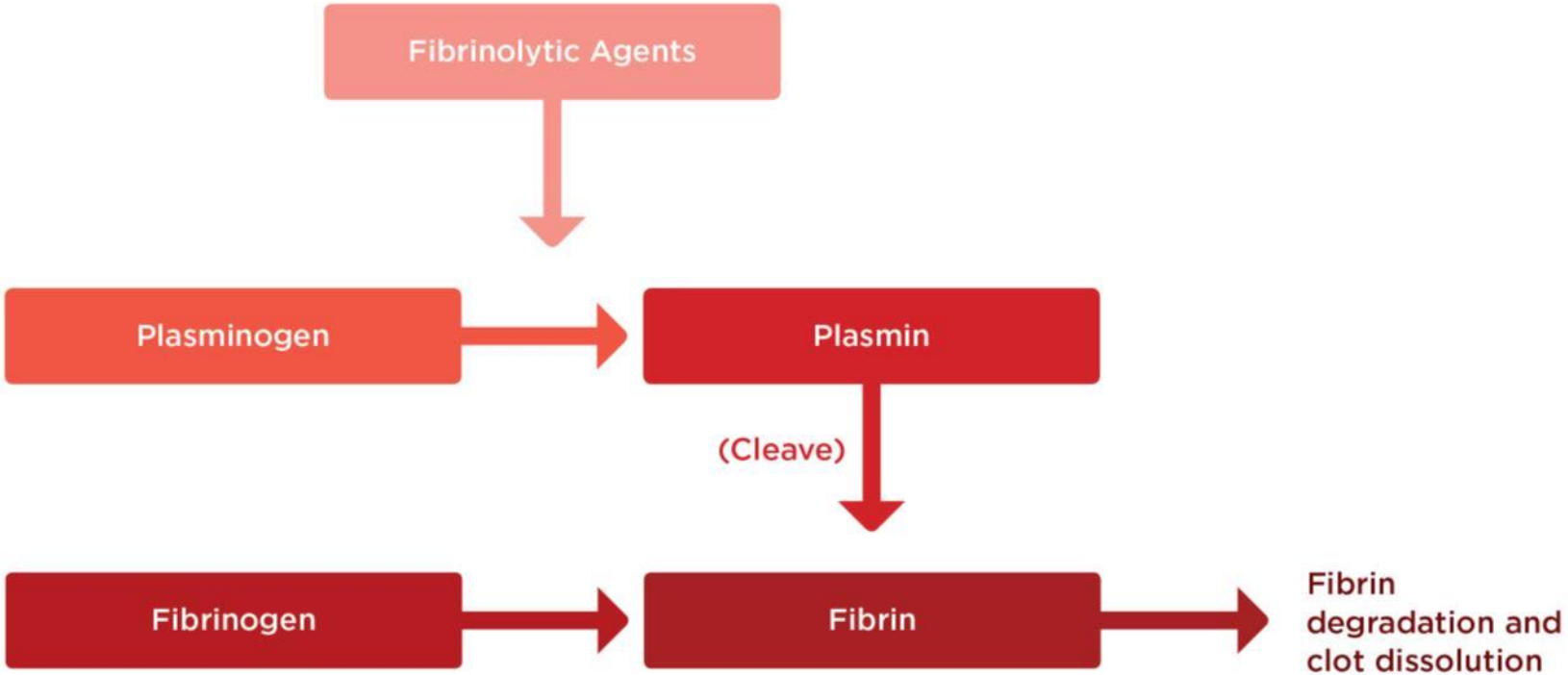
guardian guard your heart

ROLE OF FIBRINOLYSIS



THROMBOLYTIC AGENTS

MECHANISM OF ACTION OF FIBRINOLYTIC AGENTS IN CLOT DISSOLUTION



Adapted from:

Hilleman DE, Tsikouris JP, Seals AA, Marmur JD. Fibrinolytic Agents for the Management of ST-Segment Elevation Myocardial Infarction. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2007 Nov;27(11):1558-70.

guardian
guard your heart

CHARACTERISTICS OF THE IDEAL THROMBOLYTIC AGENTS

- RAPID REPERFUSION
- 100% TIMI GRADE 3 FLOW REPERFUSION
- ADMINISTRATION AS AN INTRAVENOUS BOLUS
- FIBRIN SPECIFIC
- LOW INCIDENCE OF SYSTEMIC BLEEDING
- LOW INCIDENCE OF INTRACRANIAL HEMORRHAGE
- RESISTANT TO PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1)
- LOW REOCCLUSION RATE
- NO EFFECT ON BLOOD PRESSURE
- NO ANTIGENICITY
- REASONABLE COST

Van de Werf FJ. The ideal fibrinolytic: can drug design improve clinical results?. European heart journal. 1999 Oct 1;20(20):1452-8.

guardian
guard your heart

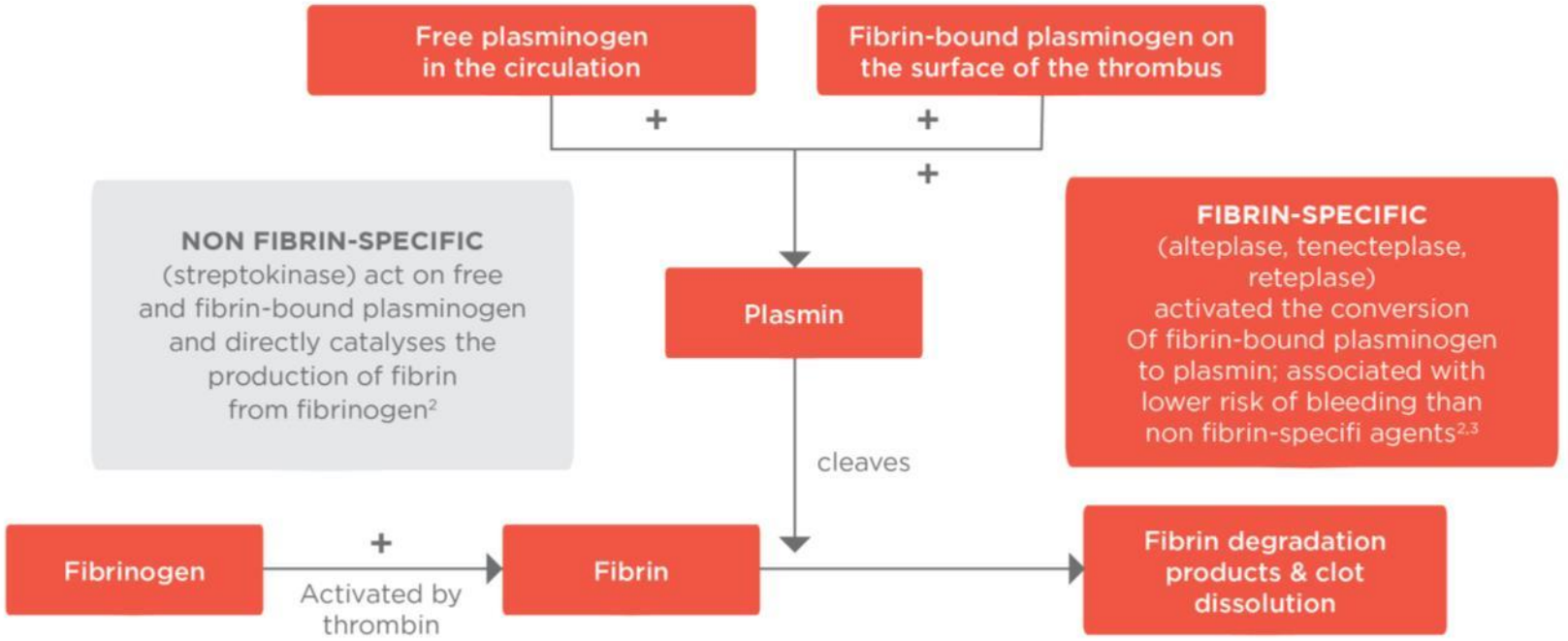
THE IDEAL THROMBOLYTIC AGENT

- Rapid acting
- High efficacy in terms of both 60-90 minute vessel patency (TIMI.grade flow)
- Low incidence of adverse reactions, particularly bleeding and stroke
- Low re-occlusion rate
- Easy to administer (bolus vs. infusion)
- Simple, patient-tailored dosage regimen
- Good long-term effects on clinical outcome
- Cost effective

Adapted from:
Van de Werf FJ. The ideal fibrinolytic: can drug design improve clinical results?. European heart journal. 1999 Oct 1;20(20):1452-8.

guardian
guard your heart

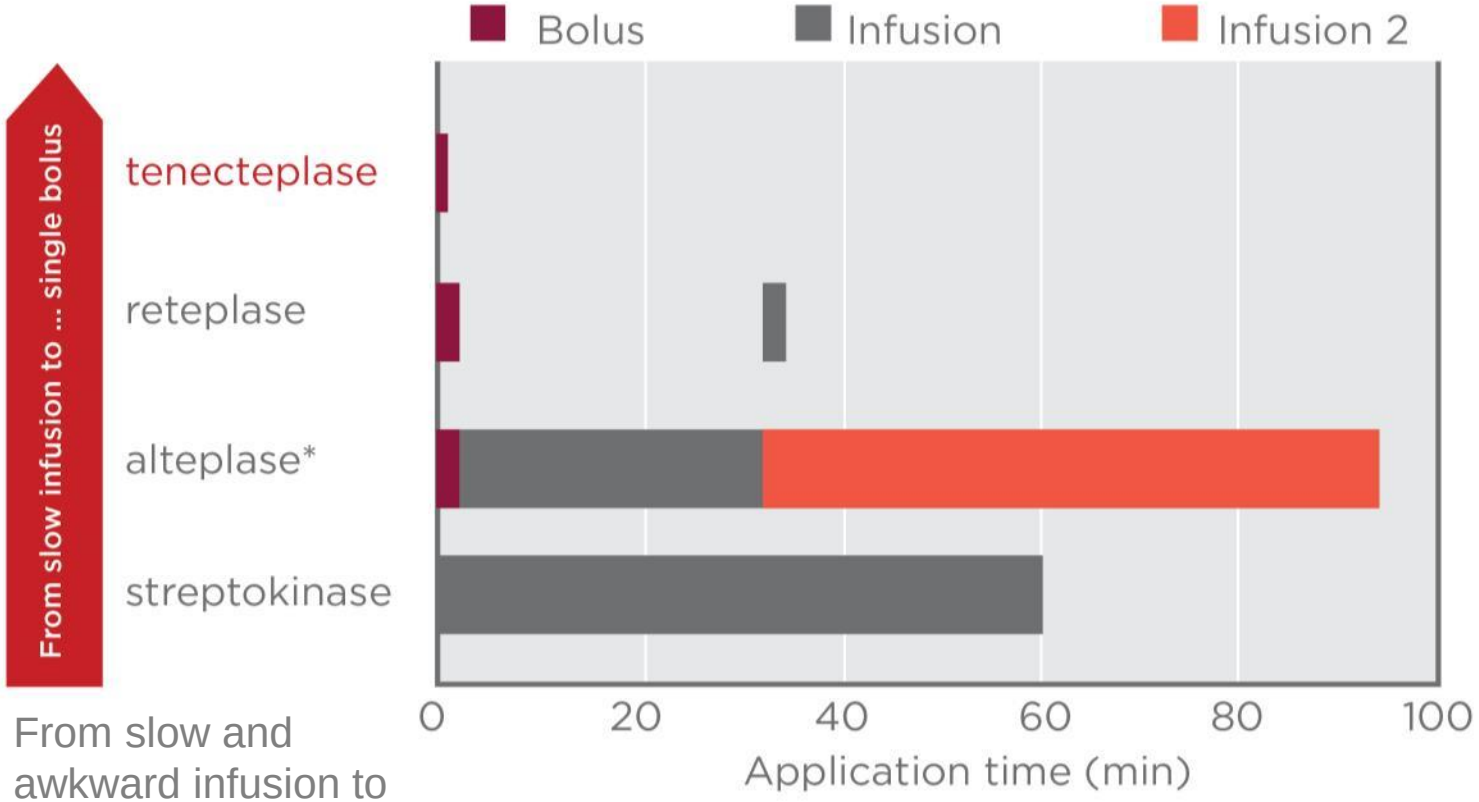
FIBRIN-SPECIFIC AND NON FIBRIN-SPECIFIC FIBRINOLYTICS MODE OF ACTION



1. Hilleman DE, Tsikouris JP, Seals AA, Marmur JD. Fibrinolytic Agents for the Management of ST-Segment Elevation Myocardial Infarction. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2007 Nov;27(11):1558-70.
2. Thrombolytic Therapy: Background, Thrombolytic Agents, Thrombolytic Therapy for Acute Myocardial Infarction [Internet]. Emedicine.medscape.com. 2019 [cited 15 January 2019]. Available from: https://emedicine.medscape.com/article/811234-overview#a2.
3. Tsikouris JP, Tsikouris AP. A review of available fibrin-specific thrombolytic agents used in acute myocardial infarction. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2001 Feb;21(2):207-17.

guardian
guard your heart

THROMBOLYTICS: FROM INFUSION TO SINGLE BOLUS



From slow and awkward infusion to fast easy single bolus

Adapted from:

Thrombolytic Therapy: Background, Thrombolytic Agents, Thrombolytic Therapy for Acute Myocardial Infarction [Internet]. Emedicine.medscape.com. 2019 [cited 15 January 2019]. Available from: https://emedicine.medscape.com/article/811234-overview#a2.

guardian
guard your heart

THROMBOLYTICS

STREPTOKINASE (AND DERIVATIVES)
Considered an inferior thrombolytic drug to tPA compounds as it is not given as a bolus and lacks fibrin specificity and antigenicity[1]

ALTEPLASE (RT-PA)
Recombinant form of human tissue plasminogen activator (tPA) with a 5 min plasma half-life.1 Improved outcomes in myocardial infarction treatment vs. streptokinase[1]

RETEPLASE (R-PA)
Genetically modified rt-PA with longer half-life (13-16 min)1 and simplified administration. Failed to show clinical benefit over alteplase[1]

TENECTEPLASE (TNK)
Longer plasma half-life, highest fibrin specificity, and resistance to plasminogen activator inhabitor-1 (PAI-1) vs rt-PA. Single bolus pharmacological reperfusion therapy, with equivalent efficacy and improved safety profile to alteplase[1]

1. Hilleman DE, Tsikouris JP, Seals AA, Marmur JD. Fibrinolytic Agents for the Management of ST-Segment Elevation Myocardial Infarction. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2007 Nov;27(11):1558-70.

COMPARISON ALTEPLASE-RETEPLASE-TENECTPLASE[1]

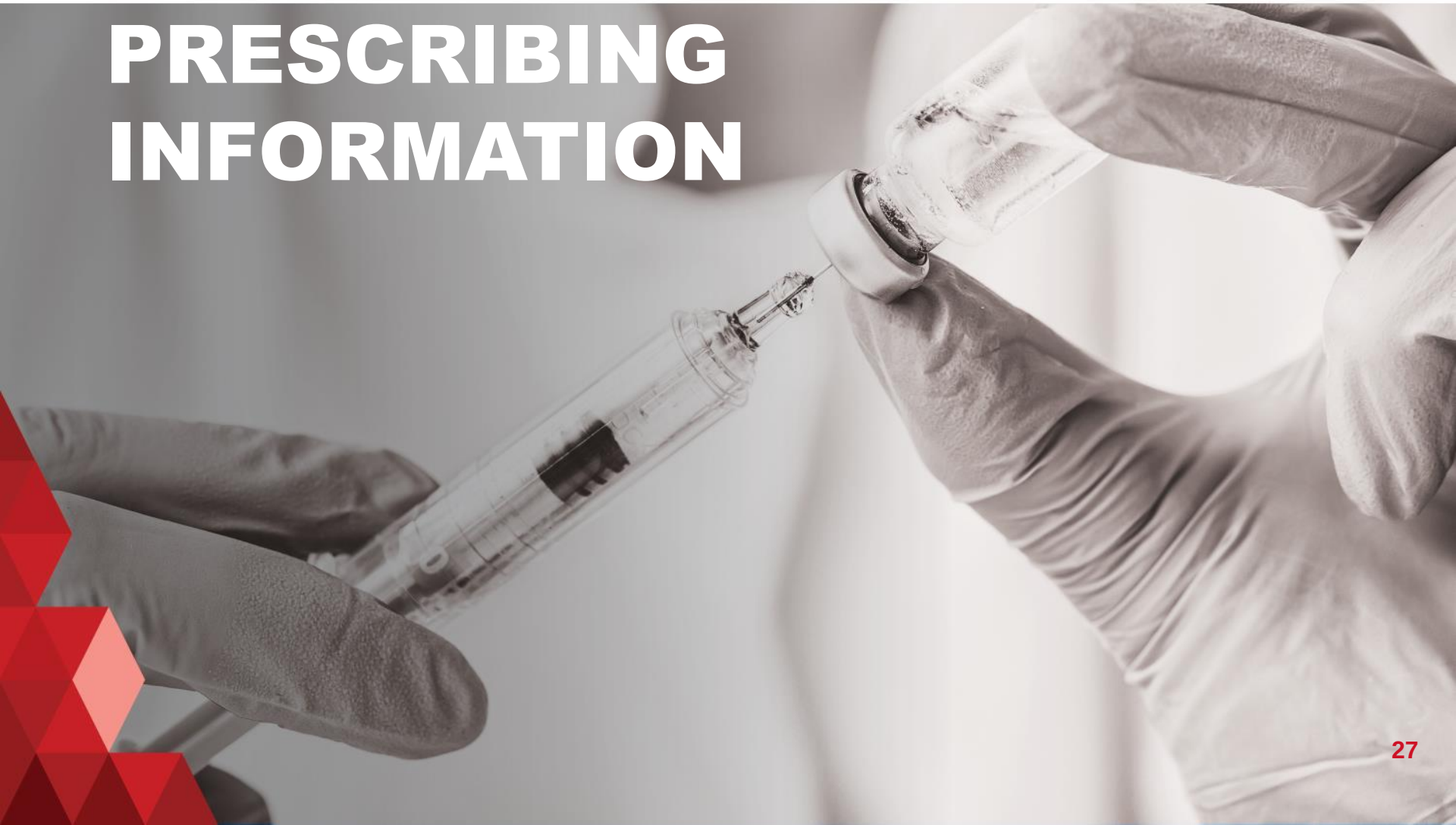
Characteristic	Alteplase (rPA)	Reteplase (rPA)	Tenecteplase (TNK-tPA)
Immunogenicty	No	No	No
Plasminogen Activation	Direct	Direct	Direct
Fibrin specificity	++	+	+++
Plasma half-life	4-6 mm	18 mm	20 mm
Dose	15 mg bolus plus 90 min infusion up to 85 mg	10+10MU double bolus 30 min apart	+-0.5 mg/kg single Bolus over approx. 10 seconds
PAI-1 resistance	Low	Low[2]	80-fold higher than rt-PA
Genetic alteration to native tPA	No (recombinant version)	Yes	Yes

1. Ross AM. New plasminogen activators: a clinical review. Clinical cardiology. 1999 Mar;22(3):165-71.
2. Nordt TK, Bode C. Thrombolysis: newer thrombolytic agents and their role in clinical medicine. Heart. 2003 Nov 1;89(11):1358-62.

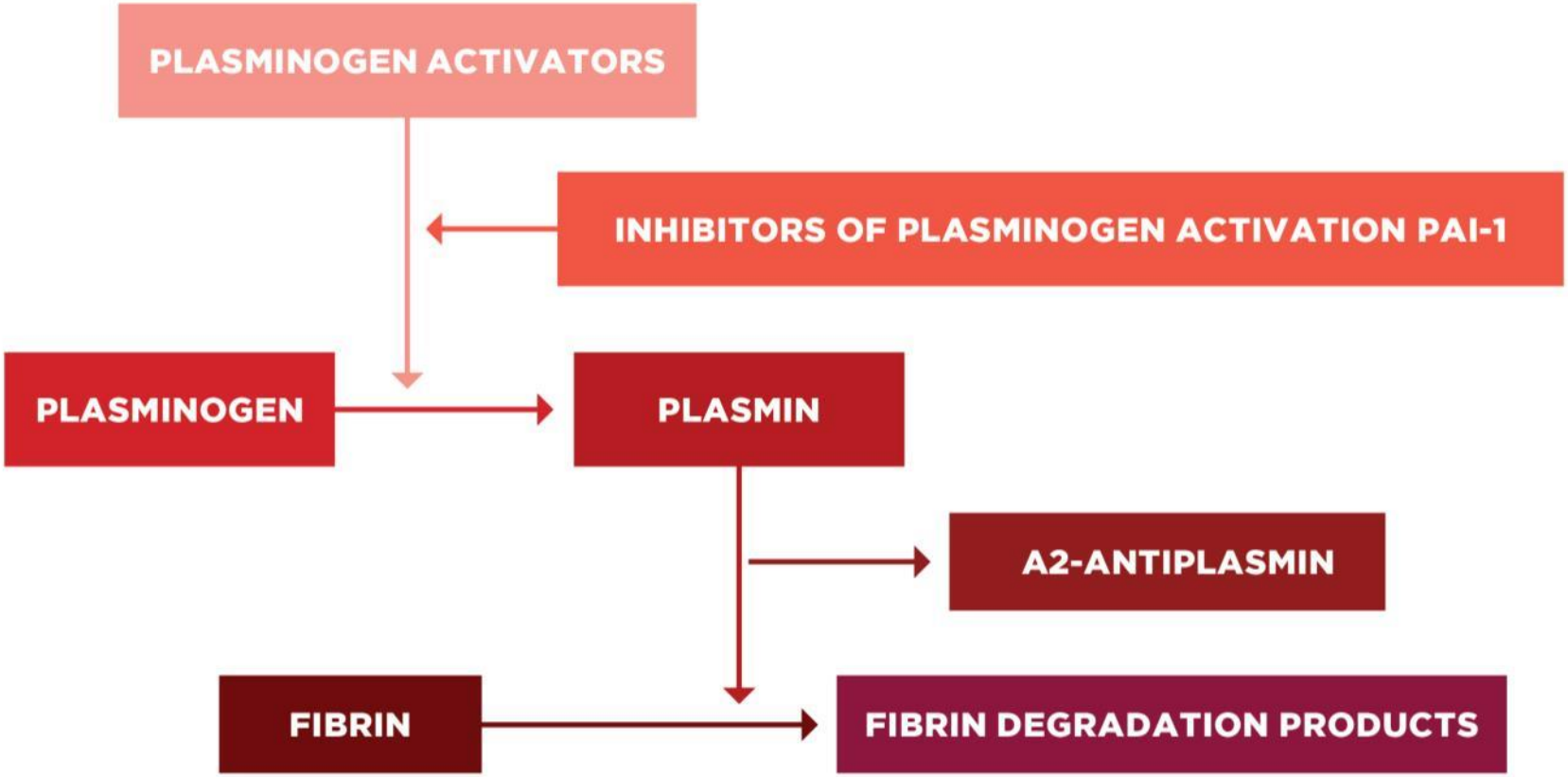
guardian
guard your heart

METALYSE

PRESCRIBING INFORMATION



NATURAL FIBRINOLYTIC SYSTEM



Armstrong PW. New advances in the management of acute coronary syndromes: 2. Fibrinolytic therapy for acute ST-segment elevation myocardial infarction. Cmaj. 2001 Sep 18;165(6):791-7.

guardian
guard your heart

TENECTEPLASE — IS A NEW GENERATION THROMBOLYTIC

SEVERAL POTENTIAL ADVANTAGES ARE ACQUIRED BECAUSE OF STRUCTURAL CHANGES

- 80 fold increase in resistance to in-vitro inhibition by PAI -1 (plasminogen activator inhibitor -1).
- More fibrin-specific than t-PA.
- 3-fold more potent at fibrinolysis than the t-PA molecule on a mg/kg body weight basis.
- Longer mean terminal half-life thus allowing administration as a single IV bolus

Melandri G, Vagnarelli F, Calabrese D, Semprini F, Nanni S, Branzi A. Review of tenecteplase (TNKase) in the treatment of acute myocardial infarction. Vascular health and risk management. 2009;5:249.

guardian
guard your heart

METALYSE® (TENECTEPLASE) IN BRIEF[1]

- The only single bolus thrombolytic commercially available
- The only thrombolytic proven to be equivalent to rt-PA-regardless of patient subgroup[2]
- Fast and easy to administer: administered over 5-10 seconds in a single case
- Optimal efficacy through tailored, weight-adjusted dosing
- Fast acting
- Reduced risk of bleeding complications when used to treat STEMI 2
- Increased resistance to PAI-1 compare to rt-PA

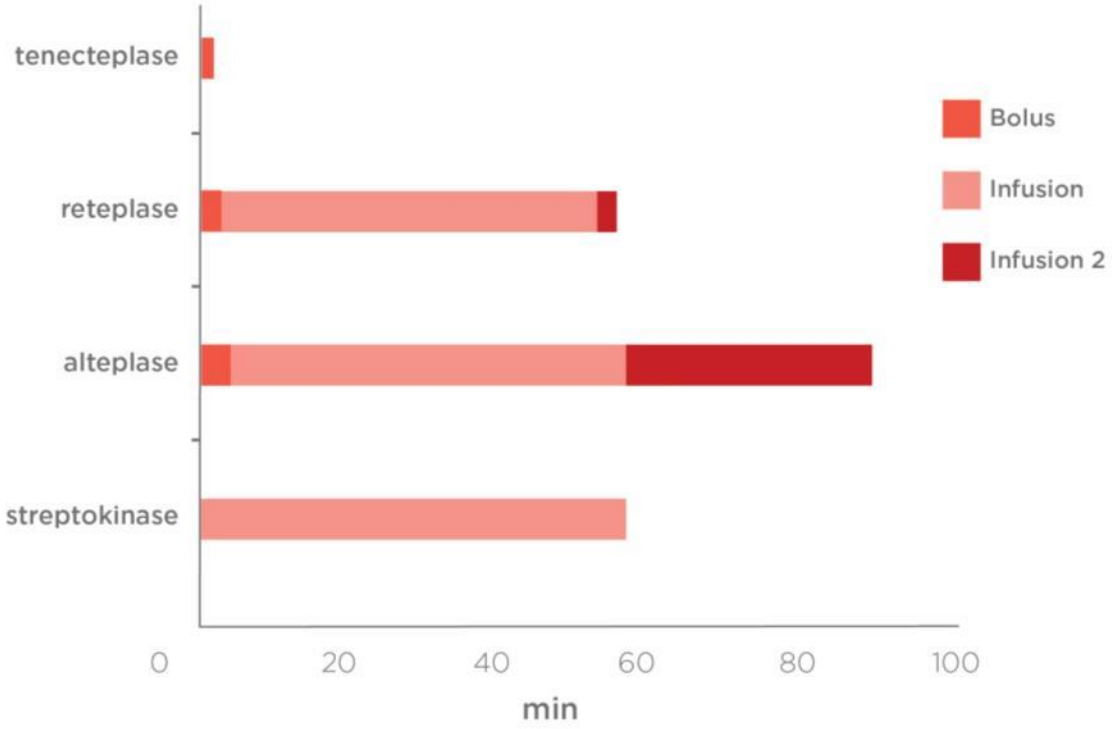
Reference 1 missing

1.
2. Van de Werf F, of the Safety A. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. The Lancet. 1999 Aug 28;354(9180):716-22.

guardian guard your heart

SINGLE BOLUS: CONVENIENCE

FIRST THROMBOLYTIC AGENT THAT CAN BE ADMINISTERED OVER 5-10 SECONDS IN A SINGLE DOSE



Adapted from:

Thrombolytic Therapy: Background, Thrombolytic Agents, Thrombolytic Therapy for Acute Myocardial Infarction [Internet]. Emedicine. medscape.com. 2019 [cited 15 January 2019]. Available from: https://emedicine.medscape.com/article/811234-overview#a2.

guardian
guard your heart

HIGH PAI-1 RESISTANCE

What is PAI-1? Plasminogen activator inhibitor 1 (PAI-1)

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

How does PAI-1 work? PAR-1 binds to t-PA to inhibit its action - Metalyse (r) (Tenecteplase) 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

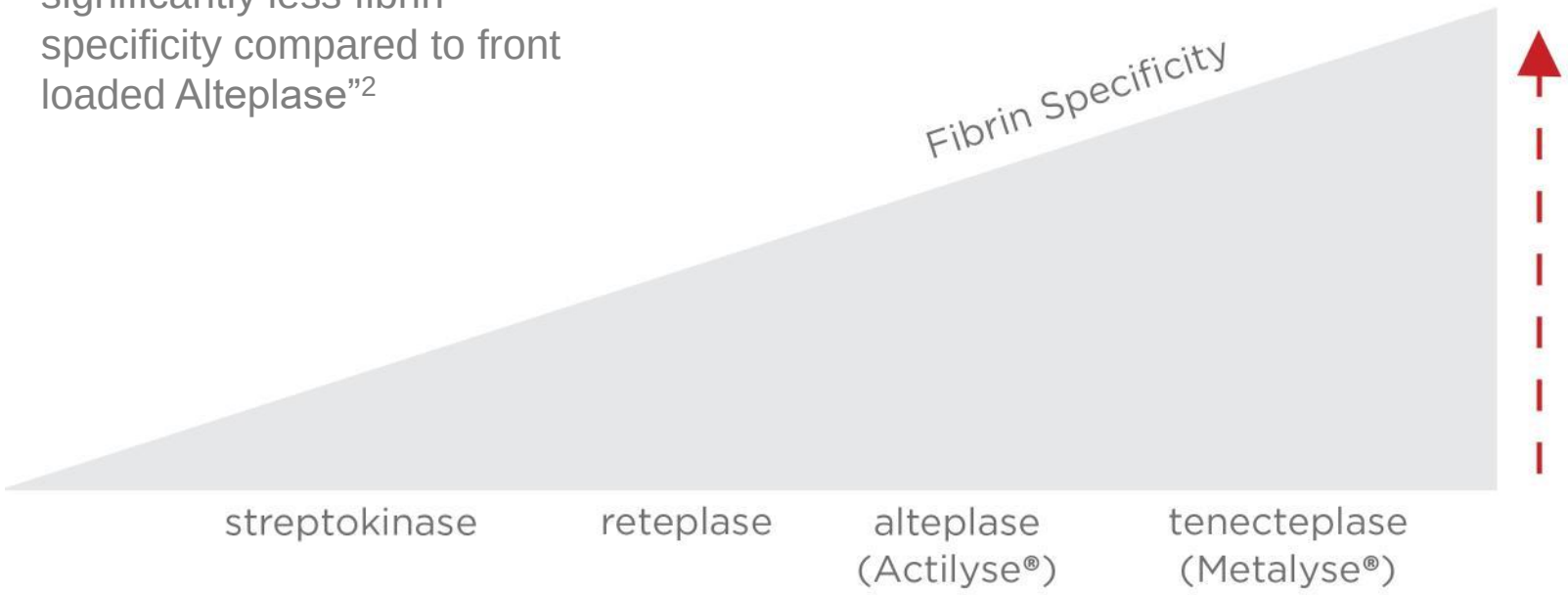
Easy administration of Metalyse as a single bolus

Davydov L, Cheng JW. Tenecteplase: a review. Clinical therapeutics. 2001 Jul 1;23(7):982-97.

guardian
guard your heart

HIGH FIBRIN SPECIFIC THROMBOLYTICS ARE PREFERRED CHOICE ACCORDING TO US AND EUROPEAN STEMI GUIDELINES[1]

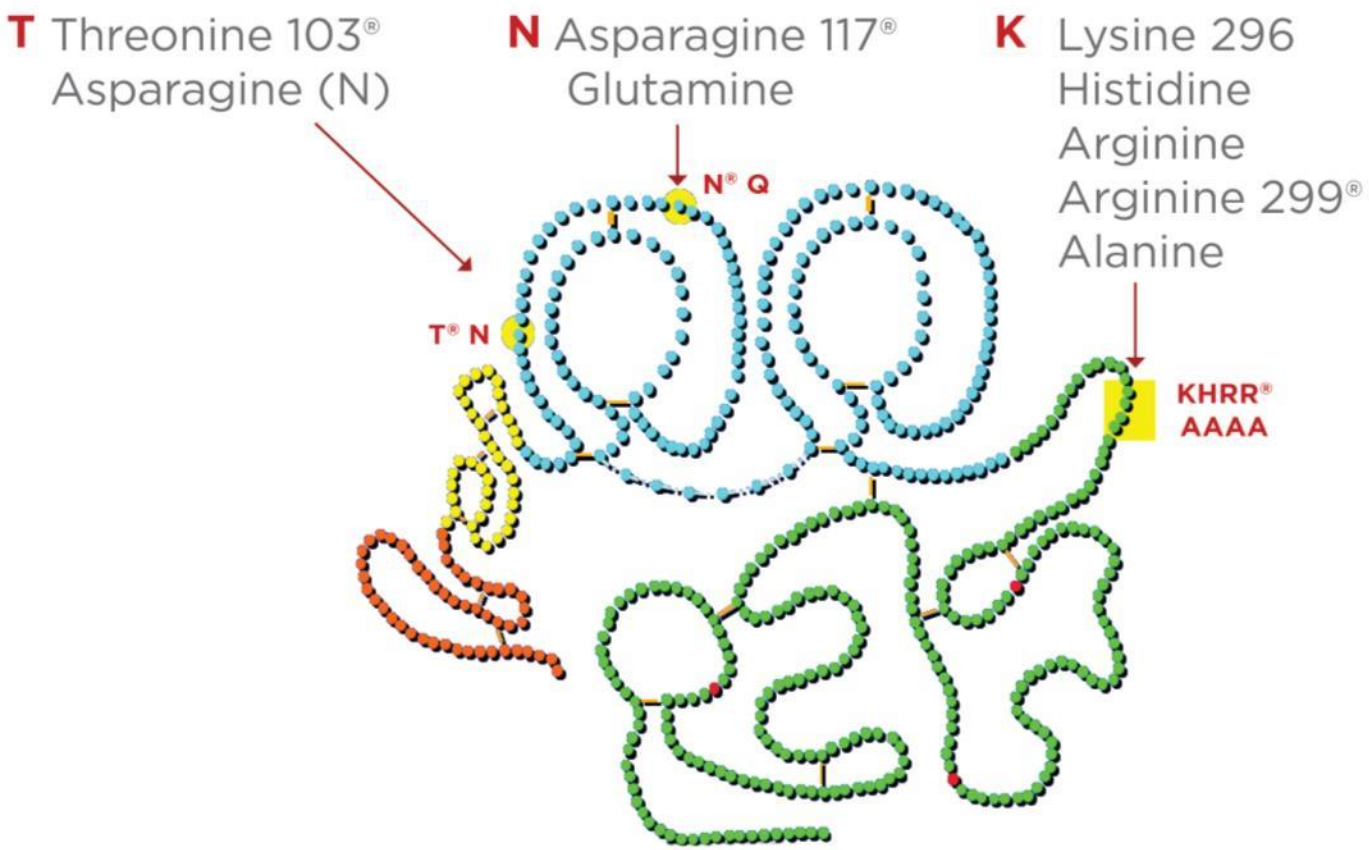
"Reteplase has proved to have significantly less fibrin specificity compared to front loaded Alteplase"[2]



1. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013 Jan 29;61(4):e78-140.2. ESC Task Force. Eur HEart J 2018;39(2):119-177.
2. Hoffmeister HM, Kastner C, Szabo S, Beyer ME, Helber U, Kazmaier S, Baumbach A, Wendel HP, Heller W. 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 Aug 1;86(3):263-8.

guardian
guard your heart

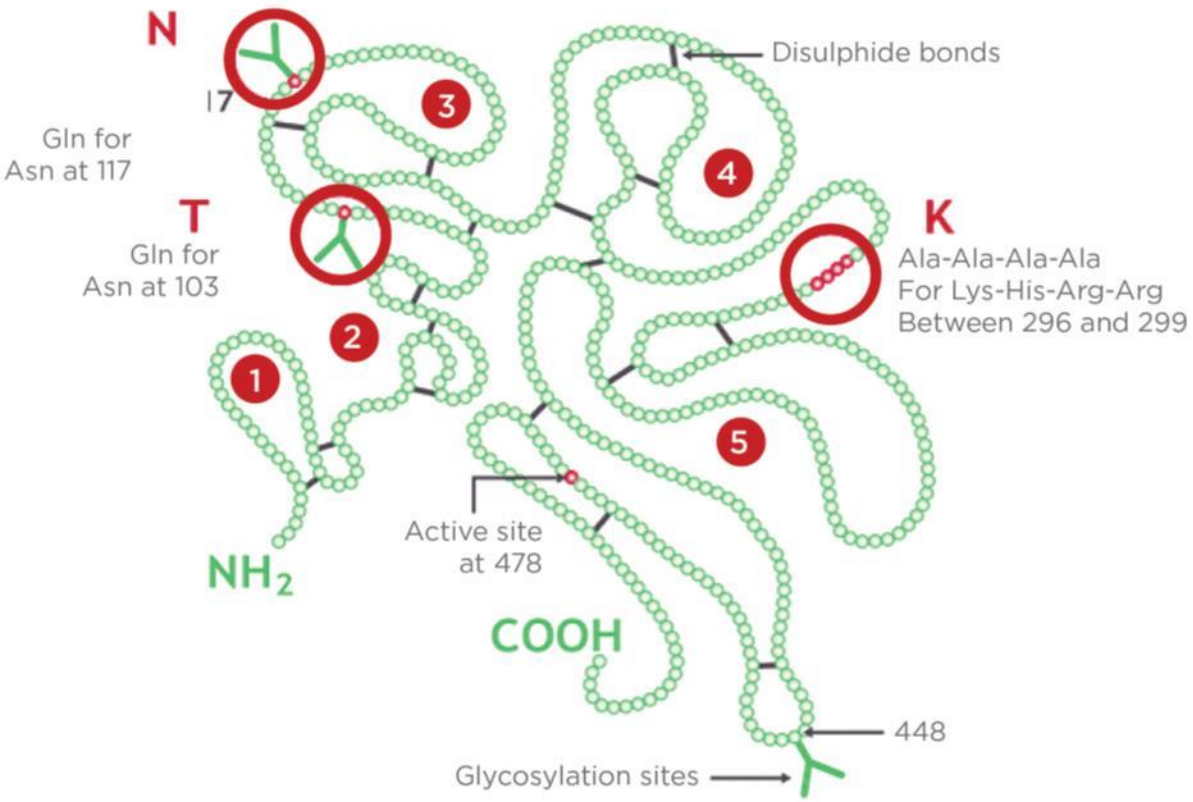
TENECTEPLASE, TNK-TPA: SPECIFIC MUTATIONS



Biochemistry of Metalyse [Internet]. metalyse (tenecteplase). 2019 [cited 5 February 2019]. Available from: http://www.metalyse.com/metalyse/biochemistry

guardian
guard your heart

TENECTEPLASE STRUCTURE



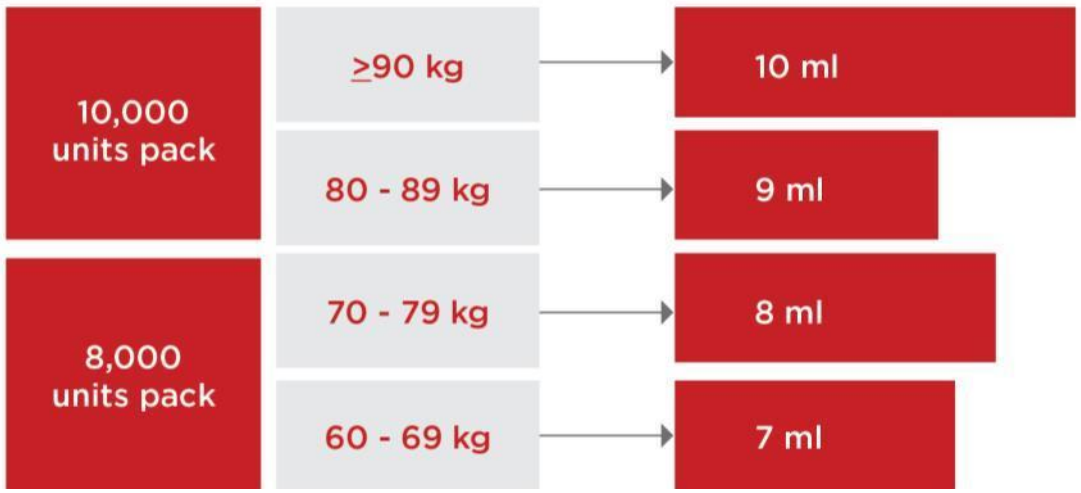
1. Finger'
2. Growth Factor
3. 'Kringle 1'
4. 'Kringle 2'
5. Protease

- Greater fibrin specificity than alteplase
- Longer plasma half-life than alteplase (20 minutes vs 4-6 minutes)
- Higher resistance to PAI-1 than alteplase

Biochemistry of Metalyse [Internet]. metalyse (tenecteplase). 2019 [cited 5 February 2019]. Available from: http://www.metalyse.com/metalyse/biochemistry

WEIGHT-ADAPTED DOSAGE OF TENECTEPLASE (TNK)

THE REQUIRED DOSE SHOULD BE ADMINISTERED AS A SINGLE INTRAVENOUS BOLUS OVER APPROXIMATELY 10 SECONDS



A pre-existing intravenous line may be used for administration of TNK in 0.9% sodium chloride solution only.

TNK is incompatible with dextrose solution. No other medicinal product should be added to the injection solution.

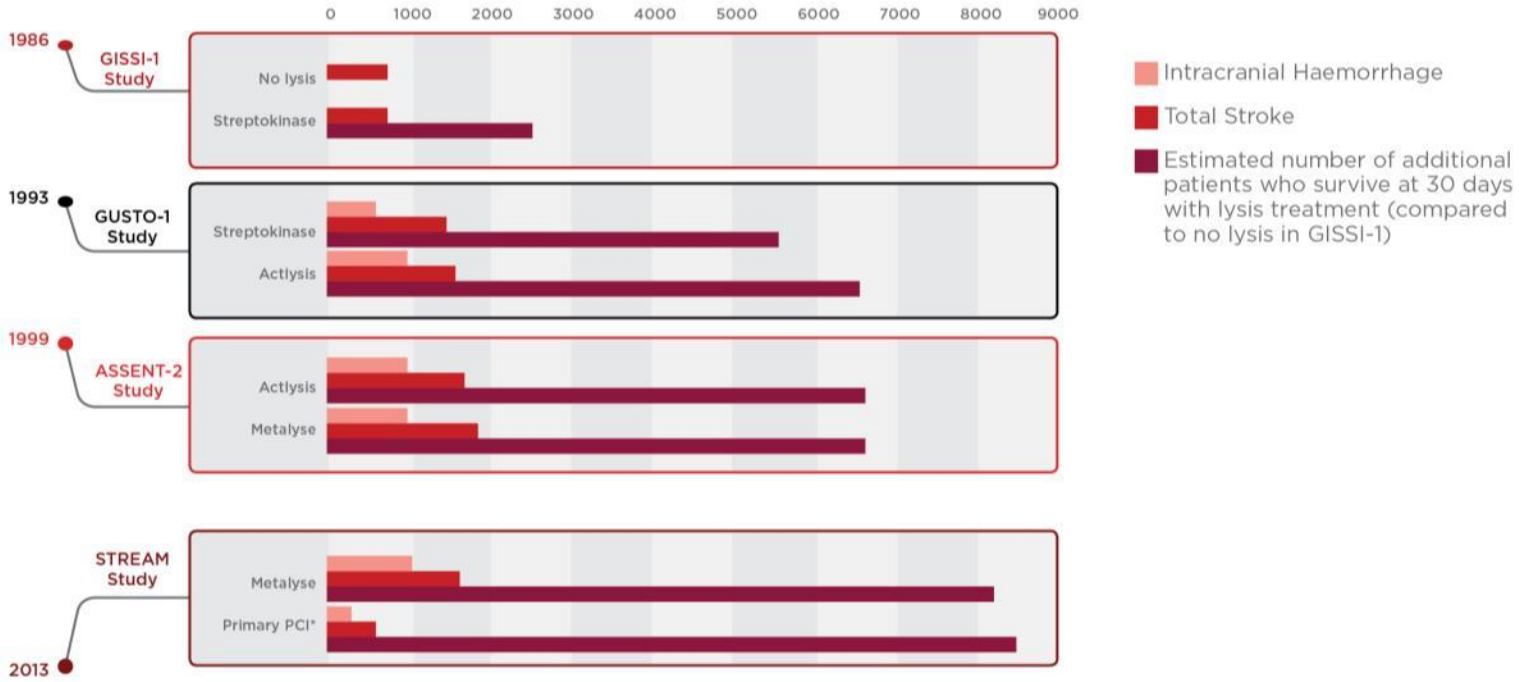
Conversion: 1 ml = 5 mg = 1 ,000 units

METALYSE® Approved package insert. Date of publication. 5 March 2009

guardian guard your heart

WEALTH OF EVIDENCE TO SUPPORT TNK EFFICACY

ESTIMATE NUMBER OF EVENTS PER 100,000 PATIENT YEARS IN PATIENTS SUFFERING FROM ACUTE MYOCARDIAL INFARCTION**



* primary percutaneous coronary intervention; **treatment within 6 hours after onset of symptoms

1. Della GI, Miocardico SN. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet. 1986;1:397.
2. Gusto Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. New England Journal of Medicine. 1993 Sep 2;329(10):673-82.
3. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC.Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. New England Journal of Medicine. 2013 Apr 11;368(15):1379-87.
4. 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 Aug 28;354(9180):716-22.

guardian
guard your heart

METALYSE
DOSAGE

DOSAGE AND ADMINISTRATION

Patients' Body Weight Category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding Volume of re-constituted solution (ml)
<60	6,000	30	60
≥60 to 70	7,000	35	7
≥70 to 80	8,000	40	8
≥80 to 90	9,000	45	9
≥90	10,000	50	10

PLEASE NOTE: The required dose should be administered as a single intravenous bolus over 5 to 10 seconds. A pre-existing intravenous lline, which has beeen used for administration of 0.9% sodium chloride only, may be used for administration of METALYSE. If a line should be flushed after METALYSE injection for proper delivery, METALYSSE is incompatible with dextrose solution. METALYSE should not be mixed with other drugs, neither in the same infusion-vial nor the same venous line not even with heparin).

METALYSE® Approved package insert. Date of publication. 5 March 2009

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

TENECTEPLASE TNK T-PA

Indication	Metalyse is indicated in adults for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.
Patient population	Patients between the ages of 18 and 80 years old
Route of administration	Intravenous

METALYSE® Approved package insert. Date of publication. 5 March 2009

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

TENECTEPLASE TNK T-PA

Pharmaceutical Formulation	Lyophilized powder in 8,000 &10,000 unit (40 & 50 mg) vials
Dosing Regimen	Single 5-second bolus dose based on weight delivered in 5 dosing regimens
Packaging	Each pack contains: A 20 ml glass vial containing a lyophilised cake for preparation of a solution for injection. The cake contains either 8 000 U or 10 000 U of tenecteplase. The vial is fitted with a grey rubber stopper and a flip-off vial cap.

METALYSE® Approved package insert. Date of publication. 5 March 2009

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

TENECTEPLASE TNK T-PA

Safety	Summary of the safety profile • Haemorrhage is a very common undesirable effect associated with the use of tenecteplase. • The type of hemorrhage is predominantly superficial at the injection site. • Ecchymoses are observed commonly but usually do not require any specific action. • Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.
Contra-Indications	See next slide

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

GENERAL CONTRAINDICATIONS?

- The following contraindications apply in general: As with all thrombolytic agents, Metalyse should not be used in cases where there is a high risk of haernorrhage such as:

1. Significant bleeding disorder at present or within the past 6 months, known haermorrhagic diathesis
2. Patients receiving oral anticoagulants, e.g. Warfarin sodium (INR> 1.3)
3. Any history of central nervous system damage (i.E. Neoplasm, aneurysm, intracranial or spinal surgery); - History of stroke
4. History or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
5. Severe uncontrolled arterial hypertension
6. Major surgery or significant trauma in the past 10 days (this includes any trauma associated with the current acute myocardial infarction), recent trauma to head or cranium

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

GENERAL CONTRAINDICATIONS…

7. Prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes), obstetrical delivery, within the past 10 days, recent puncture of a non-compressible blood-vessel (e.g. Subclavian or jugular vein puncture)
8. Severe hepatic dysfunction including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
9. Haemorrhagic retinopathy, e.g. In diabetes (vision disturbances may indicate haemorrhagic retinopathy) or other haemorrhagic ophthalmic conditions
10. Bacterial endocarditis, pericarditis
11. Acute pancreatitis
12. Documented ulcerative gastro-intestinal disease during the last 3 months
13. Arterial aneurysms, arterial/venous malformations
14. Neoplasm with increased bleeding risk
15. Hypersensitivity to the active substance tenecteplase or to any of the excipients

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

DRUG INTERACTIONS?

- Formal interaction studies of Metalyse® with other drugs have not been performed.
- Patients studied in clinical trials of Metalyse® were routinely treated with heparin and aspirin.
- Anticoagulants (such as heparin and vitamin K antagonists) and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole, and abciximab) may increase the risk of bleeding if administered prior to, during, or after Metalyse® therapy.

guardian
guard your heart

METALYSE® Approved package insert. Date of publication. 5 March 2009

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

POSSIBLE SIDE EFFECTS?

The side effects described below have been experienced by people given Metalyse:

VERY COMMON (MAY AFFECT MORE THAN 1 IN 10 PEOPLE):

- bleeding

COMMON (MAY AFFECT UP TO 1 IN 10 PEOPLE):

- bleeding at the injection or puncture site
- nosebleeds
- genitourinary bleeding (you may notice blood in your urine)
- bruising
- gastro-intestinal bleeding (e.g. bleeding from the stomach or bowel)

UNCOMMON (MAY AFFECT UP TO 1 IN 100 PEOPLE):

- irregular heart beat (reperfusion arrhythmias) sometimes leading to cardiac arrest. Cardiac arrest can be life threatening.
- internal bleeding in the abdomen (retroperitoneal bleeding)
- bleeding in the brain (cerebral haemorrhage). Death or permanent disability may occur following bleeding in the brain or other serious bleeding events
- bleeding in the eyes (eye haemorrhage)

RARE (MAY AFFECT UP TO 1 IN 1,000 PEOPLE):

- low blood pressure (hypotension)
- bleeding in the lungs (pulmonary haemorrhage)
- hypersensitivity (anaphylactoid reactions) e.g. rash, hives (urticaria), difficulty breathing (bronchospasm)
- bleeding into the area surrounding the heart (haemopericardium)
- blood clot in the lung (pulmonary embolism) and in the vessels of other organ systems (thrombotic embolisation)

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

POSSIBLE SIDE EFFECTS:

NOT KNOWN (FREQUENCY CANNOT BE ESTIMATED FROM THE AVAILABLE DATA):

- fat embolism (clots consisting of fat)
- nausea
- vomiting
- body temperature increased (fever)
- blood transfusions as consequence of bleedings

AS WITH OTHER THROMBOLYTIC AGENTS, THE FOLLOWING EVENTS HAVE BEEN REPORTED AS SEGUELAE MYOCARDIAL INFARCTION AND/OR THROMBOLYTIC ADMINISTRATOR:

VERY COMMON (MAY AFFECT MORE THAN 1 IN 10 PEOPLE):

- Low blood pressure (hypotension)
- Irregular heart beat
- Chest pain (angina pectoris)

COMMON (MAY AFFECT UP TO 1 IN 10 PEOPLE):

- Further chest pain/angina (recurrent ischaemia)
- Heart attack
- Heart failure
- Shock due to heart failure
- Inflammation of the lining around the heart
- Fluid in the lungs (pulmonary oedema)

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

POSSIBLE SIDE EFFECTS:

AS WITH OTHER THROMBOLYTIC AGENTS, THE FOLLOWING EVENTS HAVE BEEN REPORTED AS SEQUELAE OF MYOCARDIAL INFARCTION AND/OR THROMBOLYTIC ADMINISTRATION...:

UNCOMMON MAY AFFECT UP TO 1 IN 100 PEOPLE):

- Heart arrest
- Problem with the heart valve or heart lining (mitral valve incompetence, pericardial effusion
- Rlood clot in the veins (venous thrombosis)
- Fluid between the heart lining and the heart (cardiac tamponade)
- Rupture of the heart muscle (myocardial rupture)

RARE (MAY AFFECT UP TO 1 IN 1,000 PEOPLE):

- Blood clot in the lung (pulmonary embolism)

These cardiovascular events can be life-threatening and may lead to death. In case of bleeding in the brain events related to the nervous system have been reported e.g. drowsiness (somnolence), speech disorders, palsy of parts of the body (hemiparesis) and fits (convulsions).

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart

WHAT TO LOOK OUT FOR IN THE PACKAGE INSERT

SUMMARY:

- Metalyse®, is for intravenous single bolus administration only.
- The recommended total dose is based upon patient weight, not to exceed 10,000 units (50 mg).
- A single bolus dose should be administered over 5-10 seconds based on patient weight in the next table.

guardian
guard your heart

METALYSE® Approved package insert. Date of publication. 5 March 2009

DOSAGE AND ADMINISTRATION

Patients' Body Weight Category (kg)	Tenecteplase (U)	Tenecteplase (mg)	Corresponding Volume of re-constituted solution (ml)
<60	6,000	30	60
≥60 to 70	7,000	35	7
≥70 to 80	8,000	40	8
≥80 to 90	9,000	45	9
≥90	10,000	50	10

PLEASE NOTE: The required dose should be administered as a single intravenous bolus over 5 to 10 seconds. A pre-existing intravenous lline, which has beeen used for administration of 0.9% sodium chloride only, may be used for administration of METALYSE. If a line should be flushed after METALYSE injection for proper delivery, METALYSSE is incompatible with dextrose solution. METALYSE should not be mixed with other drugs, neither in the same infusion-vial nor the same venous line not even with heparin).

METALYSE® Approved package insert. Date of publication. 5 March 2009

guardian
guard your heart

PRESENTATION ON THE SUMMARY OF PRODUCT CHARACTERISTICS

HOW IS METALYSE ADMINISTERED?

- Precipitation may occur when Metalyse is administered in a dextrose line. Dextrose containing line should be flushed with non-dextrose, saline containing solutions prior to single bolus administration of Metalyse.

- **How supplied:**
  Metalyse is supplied as a sterile, lyophilized powder in a 10,000/ 8 000 unit (50/40 mg) vial under partial vacuum.

  Each 10,000/8 000 unit vial of Metalyse is packaged with one 10 ml vial of Sterile Water for Injection.

WHAT IS THE ADJUNCTIVE THERAPY GIVEN?

- Antithrombotic adjunctive therapy with platelet inhibitors and anticoagulants should be administered according to the current relevant treatment guidelines for the management of patients with ST-elevation myocardial infarction.

- Unfractionated heparin and enoxaparin have been used as antithrombotic adjunctive therapy in clinical studies with Metalyse.

- Acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued with lifelong treatment unless it is contraindicated.

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart

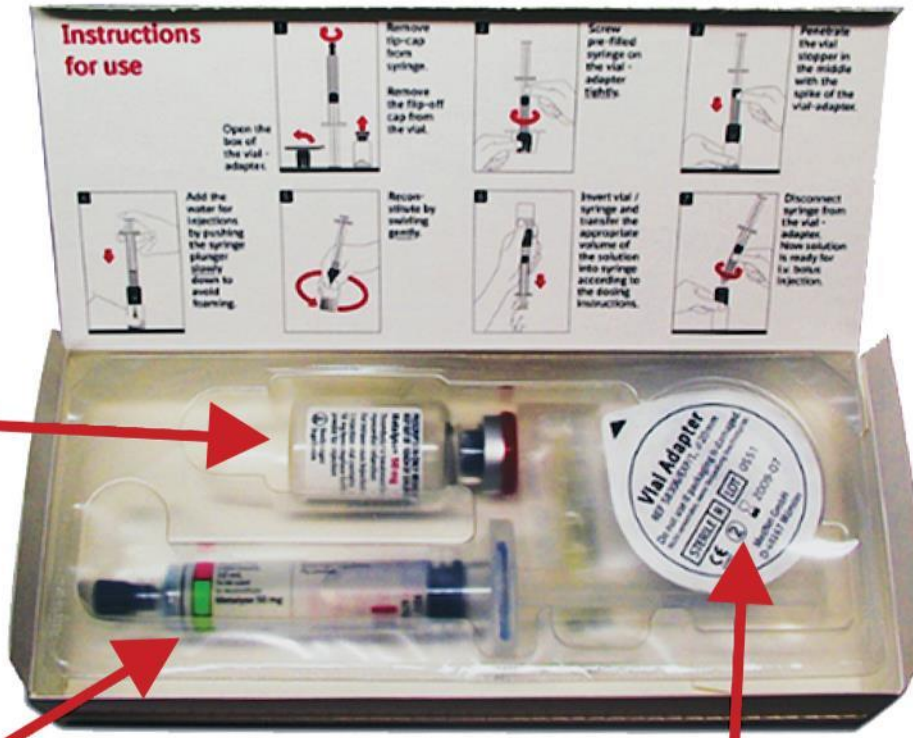
METALYSE®

Please add photo of South African Pack

guardian
guard your heart

HOW IS METALYSE SUPPLIED?

Metalyse is supplied in a 40/50mg glass vial type I, with a coated grey rubber stopper and a flip-off cap filled with powder for solution for injection



Each vial of Metalyse is packaged with a 10mL plastic syringe pre-filled with 40/50ml of sterile water for injections for reconstitution & a sterile vial adapter.

REFERENCE

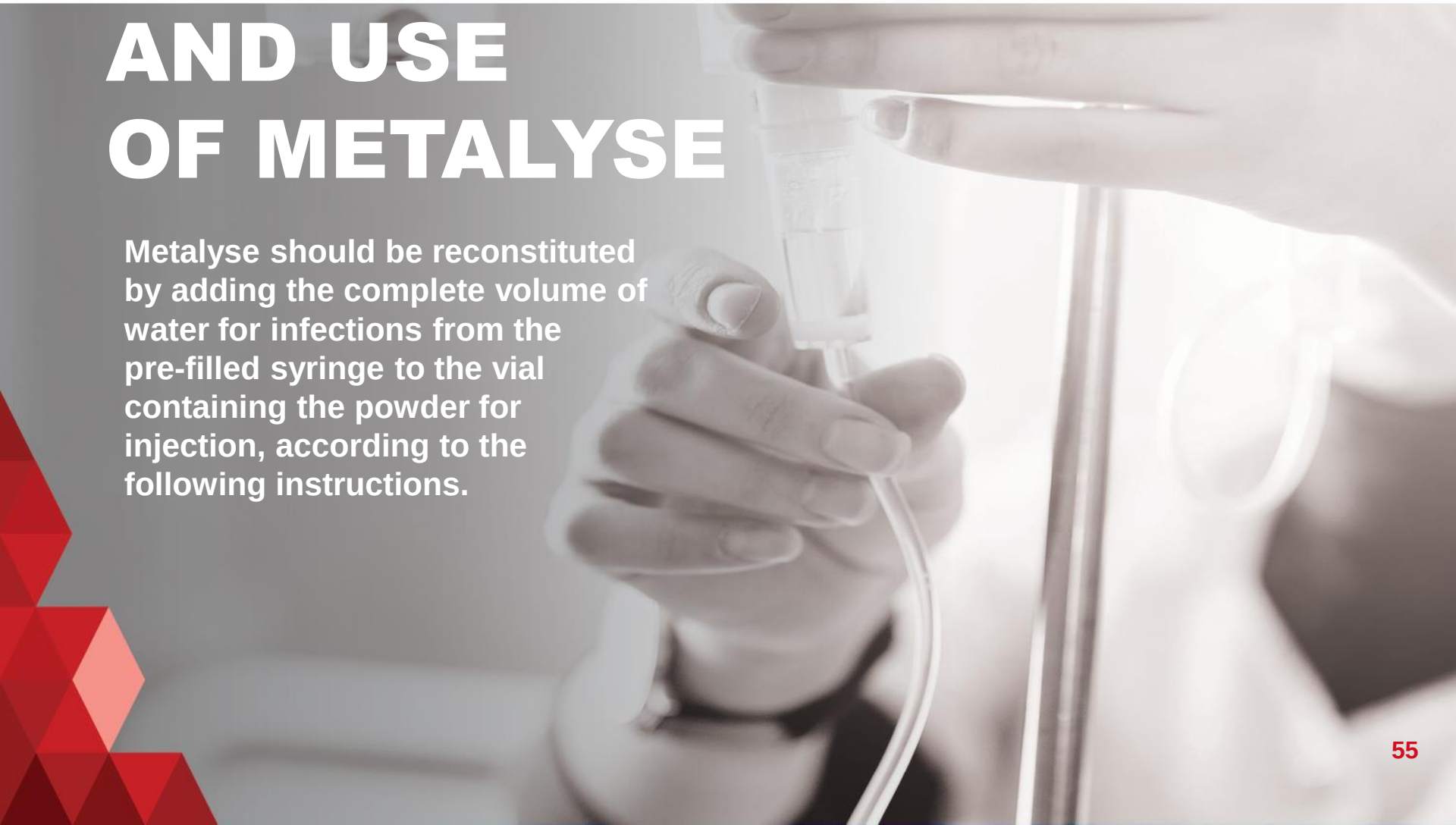
HOW IS METALYSE STORED?

- Metalyse should not be stored above 30^{o}C.
- The container should be kept in the outer carton.
- Each pack has a shelf life of 2 years from production.

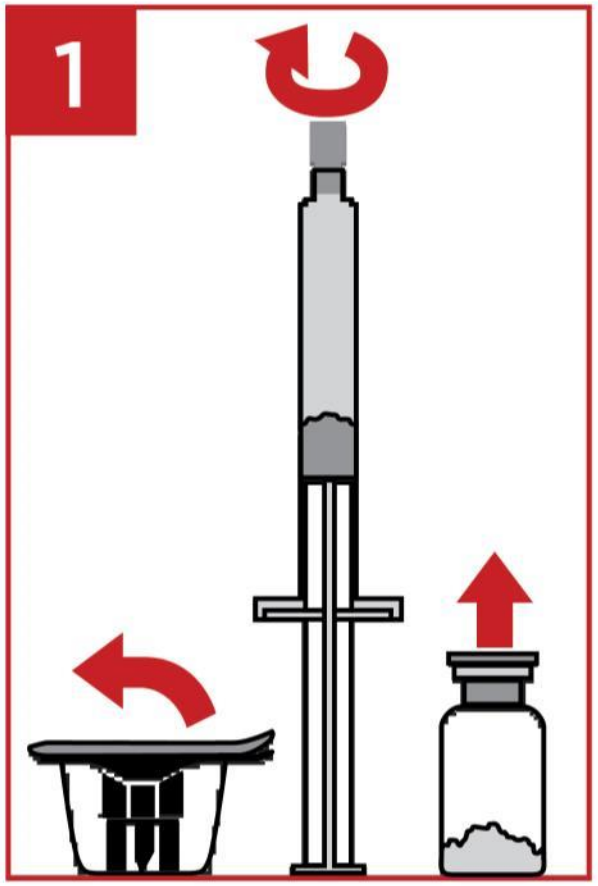
METALYSE® Approved package insert. Date of publication. 5 March 2009

guardian
guard your heart

RECONSTITUTION AND USE OF METALYSE

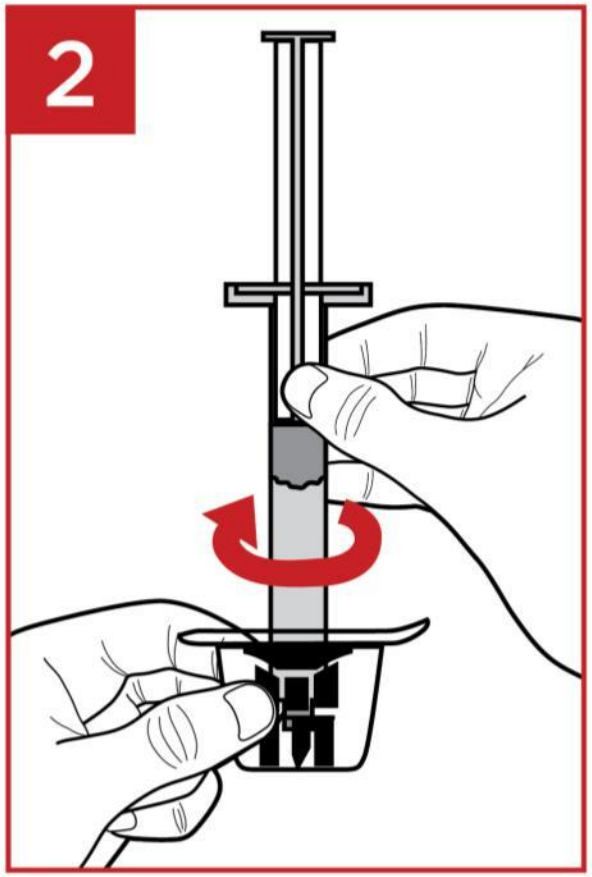


Metalyse should be reconstituted by adding the complete volume of water for infections from the pre-filled syringe to the vial containing the powder for injection, according to the following instructions.



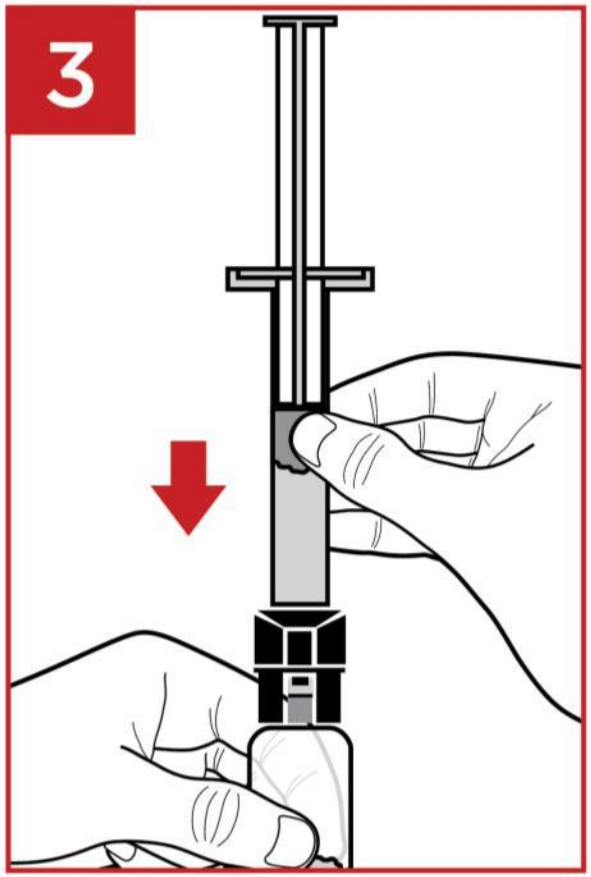
- Open the box of the vial-adapter.
- Remove tip-cap from syringe.
- Remove the flip-off cap from the vial.

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf



- Screw pre-filled syringe on the vial adapter tightly.

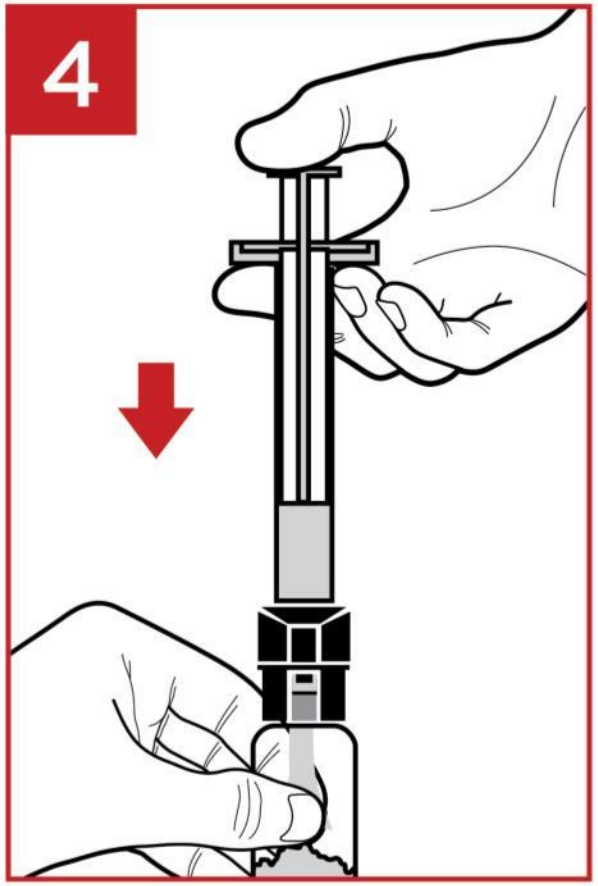
Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf



- Penetrate the vial stopper in the middle with the spike of the vial-adapter.

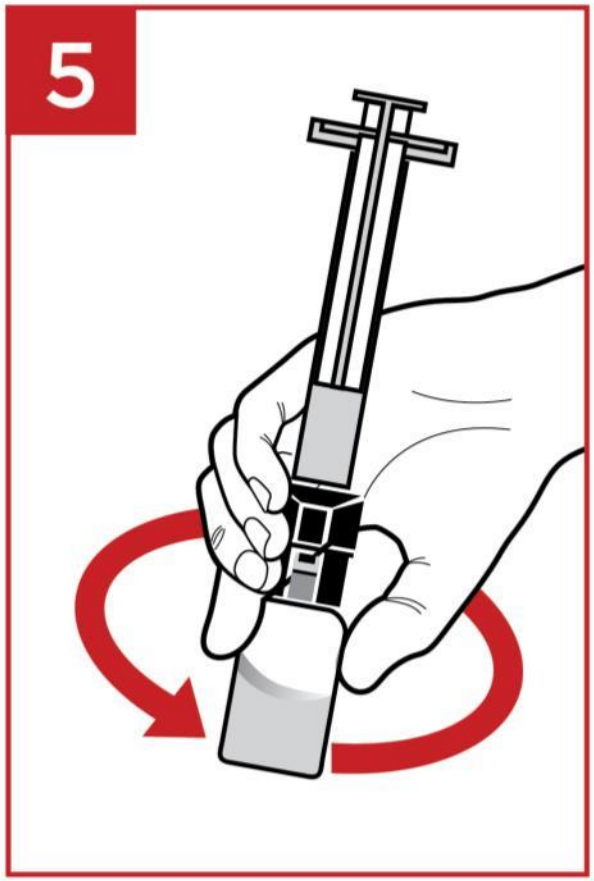
Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

guardian
guard your heart



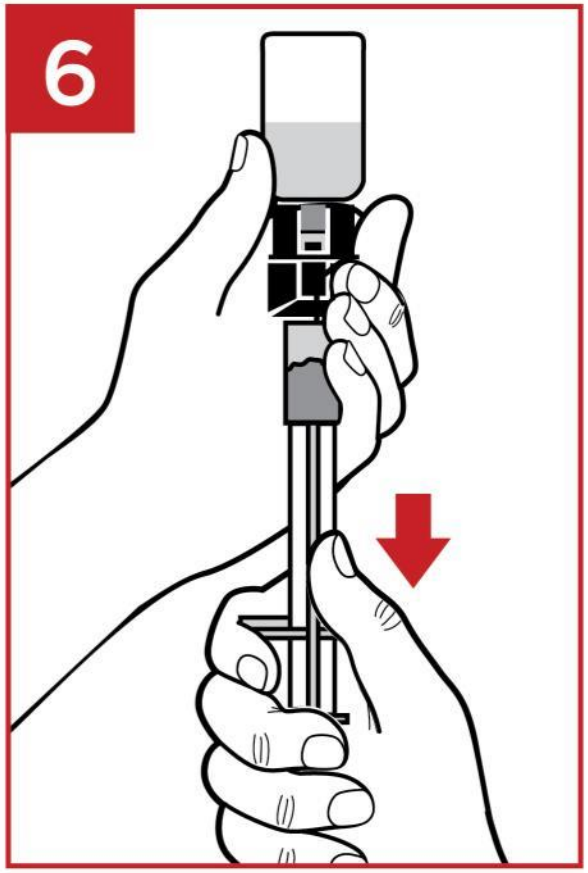
- Add the water for injection by pushing the syringe plunger slowly down to avoid foaming.

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf



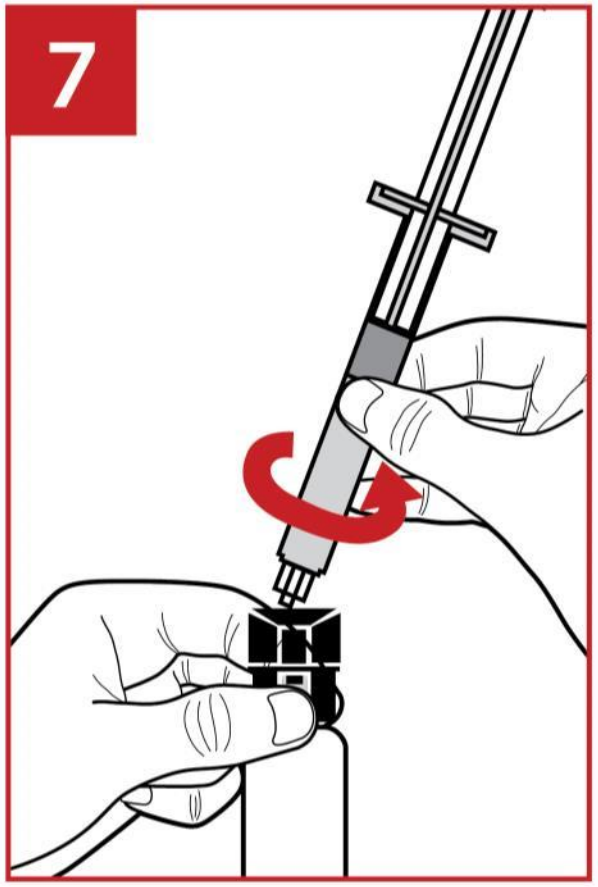
- Reconstitute by swirling gently.

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf



- Invert vial/syringe and transfer the appropriate volume of solution into syringe according to the dosing instructions.

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf



- Disconnect syringe from the vial adapter. Now solution is ready for I.V. bolus injection.

8 Metalyse is to be administered to the patient intravenously over about 10 seconds. It should not be administered in a line containing dextrose.

9 Any unused solution should be discarded.

10 Flush a dextrose containing line with a saline containing solution prior to and following administration.

Metalyse: Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/documents/productinformation/metalyse-epar-product-information_en.pdf

11 ANY UNUSED SOLUTION SHOULD BE DISCARDED.

1. The reconstituted product has been shown to remain chemically and physically stable for up to 24 hours at 30°C.

2. However, from a microbiological point of view, the product should be used immediately after reconstitution.

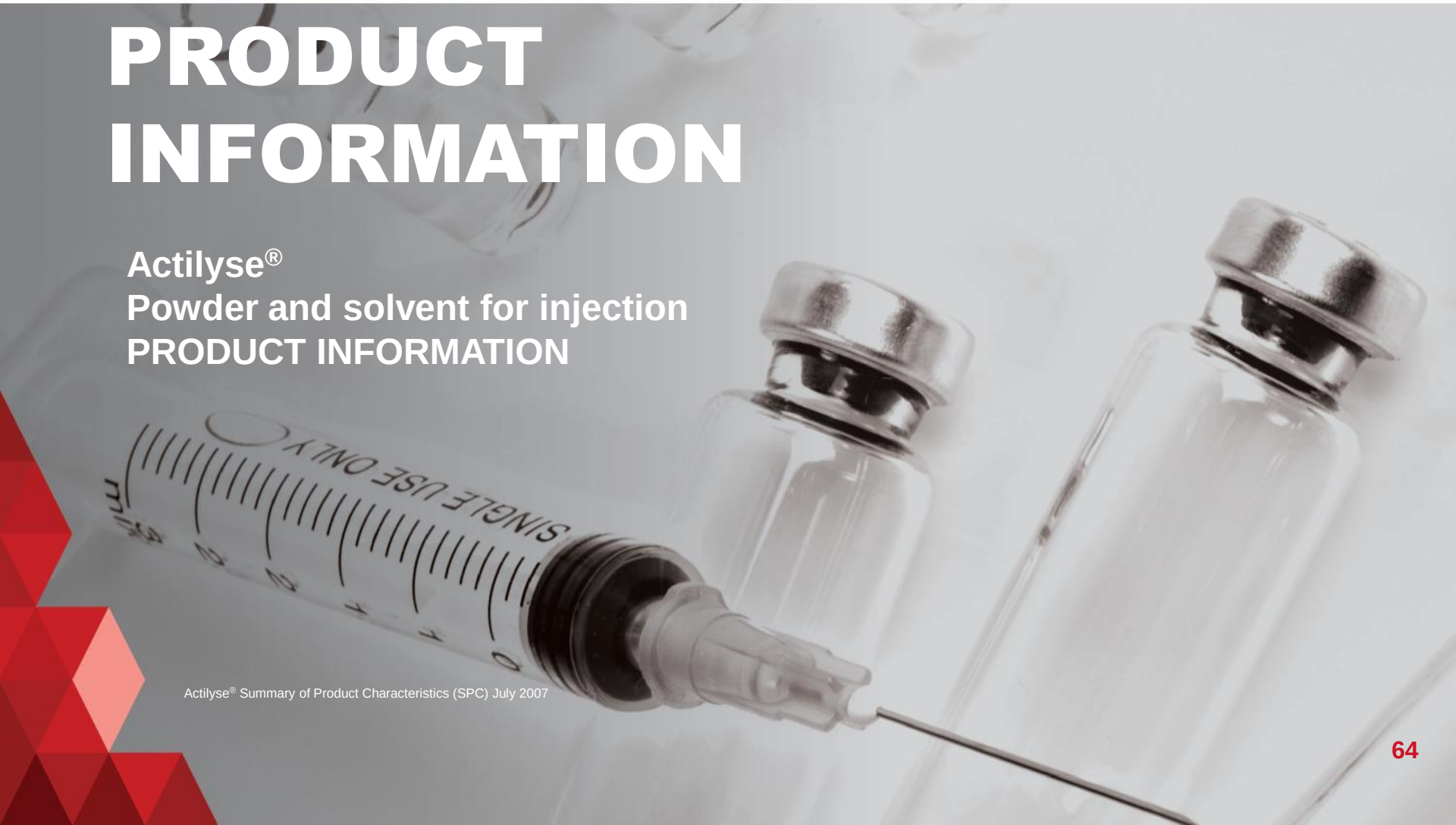
3. If it is not used immediately, in-use storage times would normally not be longer than 24 hours at 2-8°C.

METALYSE® Approved package insert. Date of publication. 5 March 2009

guardian guard your heart

ACTILYSE: PRODUCT INFORMATION

Actilyse®
Powder and solvent for injection
PRODUCT INFORMATION

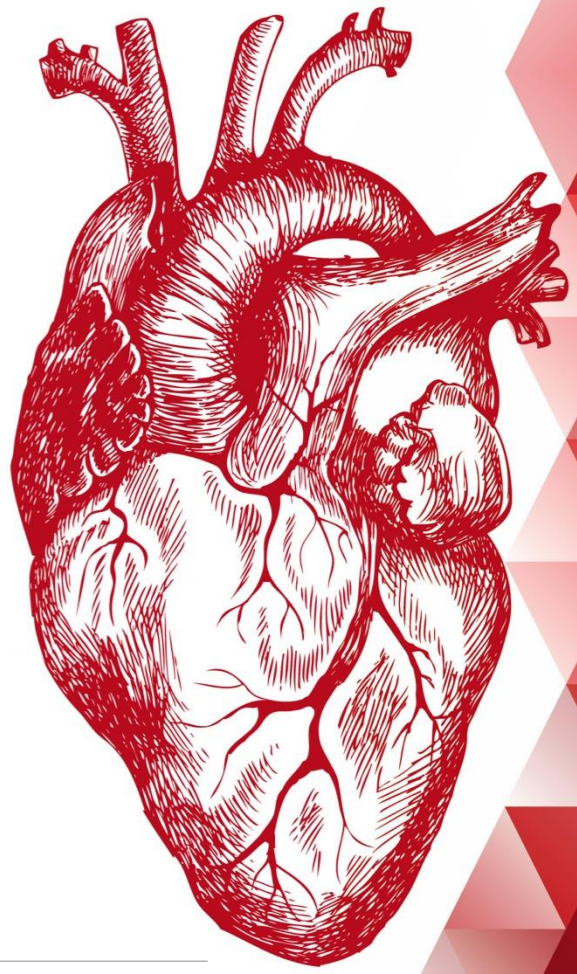


Actilyse® Summary of Product Characteristics (SPC) July 2007

ACUTE MYOCARDIAL INFARCTION

THROMBOLYTICS TREATMENT IN ACUTE MYOCARDIAL INFARCTION:

- 90 minutes (accelerated) dose regimen for patients in whom treatment can be started within 6hrs of symptom onset;
- ACTILYSE® has proven to reduce 30 day mortality in patients with acute myocardial infarction.



Boehringer Ingelheim. Alteplase Summary of Product Characteristics [Internet]. 2018. Available from:http://www.actilyse.com/sites/default/files/downloads/pdf/Actilyse-SPC.pdf

guardian
guard your heart

GENERAL CONTRAINDICATIONS

THE FOLLOWING CONTRAINDICATIONS APPLY IN GENERAL:

As with all thrombolytic agents, ACTILYSE® should not be used in cases where there is a high risk of haemorrhage such as:

1. Significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis
2. Patients receiving oral anticoagulants, e.G. Warfarin sodium (INR> 1.3)
3. Any history of central nervous system damage (i.e. Neoplasm, aneurysm, intracranial or spinal surgery)
4. History or evidence or suspicion of intracranial haemorrhage including sub-arachnoid haemorrhage
5. Severe uncontrolled arterial hypertension
6. Major surgery or significant trauma in the past 3 months

Boehringer Ingelheim. Alteplase Summary of Product Characteristics [Internet]. 2018. Available from: http://www.actilyse.com/sites/default/files/downloads/pdf/Actilyse-SPC.pdf

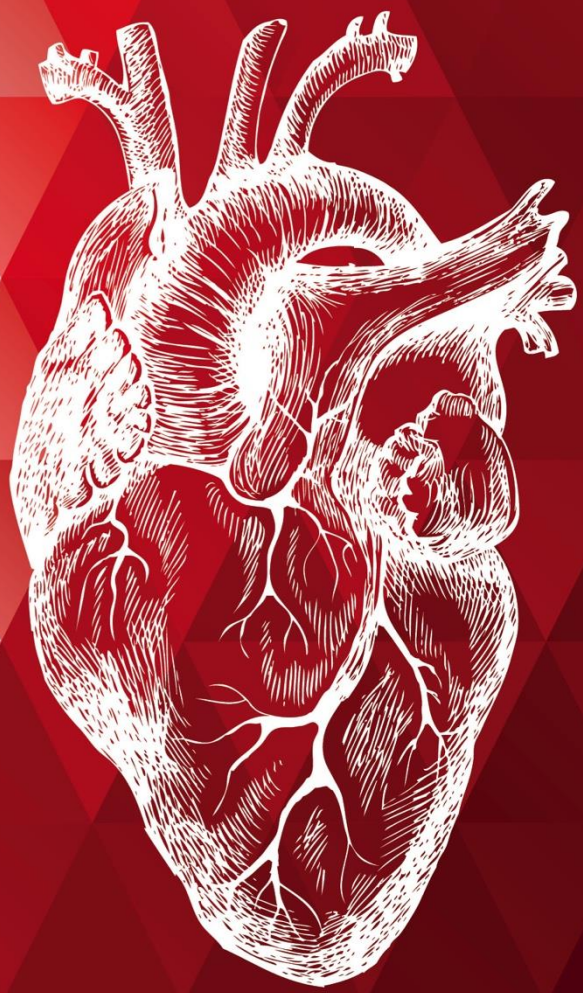
GENERAL CONTRAINDICATIONS

7. Obstetrical delivery, within the past 10 days, recent puncture of a non-compressible bloodvessel (e.g. Subclavian or jugular vein puncture)
8. Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
9. Bacterial endocarditis, pericarditis
10. Acute pancreatitis
11. Documented ulcerative gastro-intestinal disease during the last 3 months
12. Arterial aneurysms, arterial/venous malformations
13. Neoplasm with increased bleeding risk
14. Hypersensitivity to the active substance alteplase or to any of the excipients

Boehringer Ingelheim. Alteplase Summary of Product Characteristics [Internet]. 2018. Available from: http://www.actilyse.com/sites/default/files/downloads/pdf/Actilyse-SPC.pdf

guardian
guard your heart

ACTILYSE DOSAGE



guardian
guard your heart

WEIGHT ADJUSTED DOSING CHART IN STEMI

Body Weight (kg)	IV Bolus 15 mg = 15 ml	30 Min Infusion 0.75 mg/kg (max 50mg)	60 Min Infusion 0.50 mg/kg (max 35mg)	Total Dosage (max100mg)
42 kg	15 ml	32 mg	21 mg	68 mg
44 kg	15 ml	32 mg	22 mg	70 mg
46 kg	15 ml	35 mg	23 mg	73 mg
48 kg	15 ml	36 mg	24 mg	75 mg
50 kg	15 ml	38 mg	25 mg	78 mg
52 kg	15 ml	39 mg	26 mg	80 mg
54 kg	15 ml	41 mg	27 mg	83 mg
56 kg	15 ml	42 mg	28 mg	85 mg
58 kg	15 ml	44 mg	29 mg	88 mg
60 kg	15 ml	45 mg	30 mg	90 mg
62 kg	15 ml	47 mg	31 mg	93 mg
64 kg	15 ml	48 mg	32 mg	95 mg
65 kg & above	15 ml	50 mg	35 mg	100 mg

ACTILYSE® Approved package insert. Date of publication 12 June 2015.

guardian
guard your heart

DOSAGE & ADMINISTRATION - MYOCARDIAL INFARCTION

<6 HOURS AFTER PAIN ONSET; 90 MINUTE ACCELERATED DOSE REGIMEN:

- 15 mg as an intravenous bolus,
- 50 mg as an infusion over the first 30 minutes,
- followed by an infusion of 35 mg over 60 minutes, until the maximal dose of 100 mg

IN PATIENTS WITH A BODY WEIGHT BELOW 65KG THE TOTAL DOSE SHOULD BE WEIGHT ADJUSTED WITH:

- 15 mg as an intravenous bolus,
- and 0.75 mg/kg body weight over 30 minutes (maximum 50 mg),
- followed by an infusion of 0.5 mg/kg over 60 minutes (maximum 35 mg).

ACTILYSE® Approved package insert. Date of publication 12 June 2015.

guardian
guard your heart

RECONSTITUTION OF ACTILYSE INJECTION - 1

1. **Please do not use vial if vacuum Is not present.**

2. **ACTILYSE should be reconstituted to a concentration of 1 mg alteplase per ml by aseptically adding the approprlate volume of sterilized Water for Injections into the ACTILYSE dry powder vial:**

    a. Reconstitute each of the ACTILYSE 50 mg vials with 50 ml sterilized water for injection in the accompanying vial by use of the transfer cannula (provided with the pack).
    b. The transfer cannula must always be introduced vertically into the stopper and through the mark at Its center.
    c. When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution.
    d. Any vigorous agitation should be avoided to prevent foam formation.
    e. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

3. **It Is important that ACTILYSE be reconstituted only with sterilized water for injection without preservatives.**

ACTILYSE® Approved package insert. Date of publication 12 June 2015.

guardian
guard your heart

RECONSTITUTION OF ACTILYSE INJECTION - 2

4. **The reconstituted lyoptilized preparation results in a colourless to pale yellow transparent solution**

5. **The reconstituted solution (1 mg alteplase per ml) may be diluted further,** immediately before administration, with sterilized physiological saline solution (0.9% Sodium Chloride for Injection) up to a minimal concentration of 0.2 mg alteplase per ml

6. **ACTILYSE should not be mixed with other drugs,** neither in the same infusion vial nor the same venous line (not even with heparin).

7. **Before dilution or administration, parenteral drug products should be visually inspected** for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTILYSE® Approved package insert. Date of publication 12 June 2015.

guardian
guard your heart

PRESENTATION AND STORAGE CONDITIONS OF A ACTILYSE 50 MG VIAL

1. Box contaIning 1 vial of ACTILYSE 50 mg in 2333 mg dry powder, 1 vial of sterilized Water for Injections, 50 ml, and 1 transfer cannula for preparing a sterile solution of ACTILYSE.

2. Lyophilized ACT1LYSE is stable up to the expiration date stamped on the vial. Store at or below 25°C.

3. The shelf life In 3 years.

4. The reconstituted solution may be stored in a refrigerator (2 - 8°C) for up to 24 hours and for up to 8 hours at temperatures not over 25°C.

5. The reconstituted solution is for single use only.

6. Any unused solution should be discarded.

7. Protect the lyophilized material during storage from light.

8. During the period of reconstitution and Infusion, protection from light is not necessary.

ACTILYSE® Approved package insert. Date of publication 12 June 2015.

guardian
guard your heart

ACTILYSE® (ALTEPLASE 50 MG) ADMINISTRATION

Helen – please add dosage for AMI and not stroke as per the below

Remove Actilyse® vial, sterile water for injection and transfer device from box, Remark: two treatment packs are required in most cases.

Remove cap from one end of transfer device. Insert piercing pin into upright vial of sterile water for injection. KEEP WATER VIAL UPRIGHT

Remove cap from other end of transfer device. Push inverted Actilyse® vial down so that piercing pin passes through centre of Actilyse® vial stopper.

INVERT BOTH VIALS so Actilyse® is on bottom. Allow ALL water to flow into Actilyse® vial. Remove transfer device.

Swirl gently to dissolve Actilyse® DO NOT SHAKE.

INSPECT SOLUTION for particulate matter and discolouration.

Withdraw BOLUS DOSE (10% of total dose) using a syringe and needle.

Administer INTRAVENOUS BOLUS dose over 1 minute.

Withdraw remaining 90% of dose. DISCARD EXCESS quantity of medicine over that required for treatment.

INFUSE remaining 90% of dose over 60 minutes using infusion pump. At end of treatment FLUSH tubing with 15-20ml of Normal Saline.

REFERENCE

guardian
guard your heart

CLINICAL STUDIES

ASSENT TRIAL SERIES SUMMARY: ASSENT-2, ASSENT-3/ASSENT-3 PLUS, ASSENT-4 PCI

ASSENT-2: Tenecteplase is equivalent to alteplase in the treatment of AMI with respect to:

- 30-day mortality1 and 1-year mortality outcomes[2]
- Combined outcomes for mortality and non-fatal stroke[1]
- Significantly fewer bleeding complications occurred with tenecteplase, reducing the need for blood transfusions.

ASSENT-3 / ASSENT-3 PLUS:

- Low-molecular-weight heparins (LMWHs), e.g. enoxaparin, were viable alternatives to unfractionated heparin (UFH) as concomitant anticoagulation[3,4]

ASSENT-4 PCI: Investigated whether full-dose tenecteplase administered prior to PCI (facilitated PCI) could mitigate negative effect of delay to PCI[5]

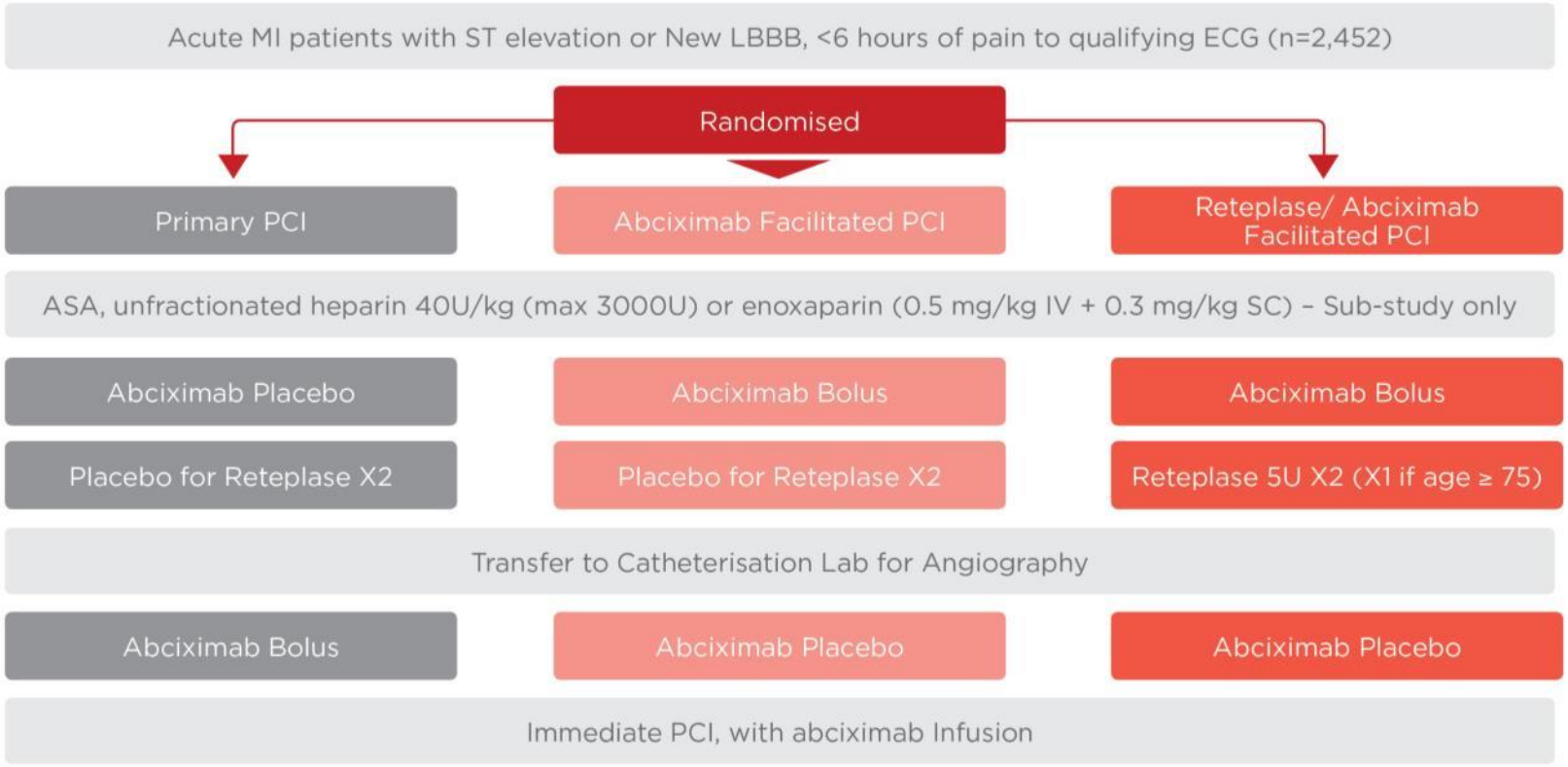
- Study was stopped prematurely due to higher mortality in facilitated PCI group vs. standard PCI[5]
- Facilitated PCI as performed in the trial was associated with more major adverse events than primary PCI alone and cannot be recommended[5]

PCI = percutaneous coronary intervention

1. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. New England Journal of Medicine. 2013 Apr 11;368(15):1379-87.
2. Sinnaeve P, Alexander J, Belmans A, Bogaerts K, Langer A, Diaz R, Ardissino D, Vahanian A, Pehrsson K, Armstrong P, Van de Werf F. One-year follow-up of the ASSENT-2 trial: a double-blind, randomized comparison of single-bolus tenecteplase and front-loaded alteplase in 16,949 patients with ST-elevation acute myocardial infarction. American heart journal. 2003 Jul 1;146(1):27-32.
3. Van de Werf F, Armstrong PW, Granger C, Wallentin L. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet. 2001;358(9282):605-13
4. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F. 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. Circulation. 2003 Jul 15;108(2):135-42.
5. Van de Werf F, Ross A, Armstrong P, Granger C. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet. 2006 Feb 18;367(9510):569-78

guardian
guard your heart

FINESSE: STUDY DESIGN



Primary Endpoint: Composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomisation, cardiogenic shock, and congestive heart failure at 90 days

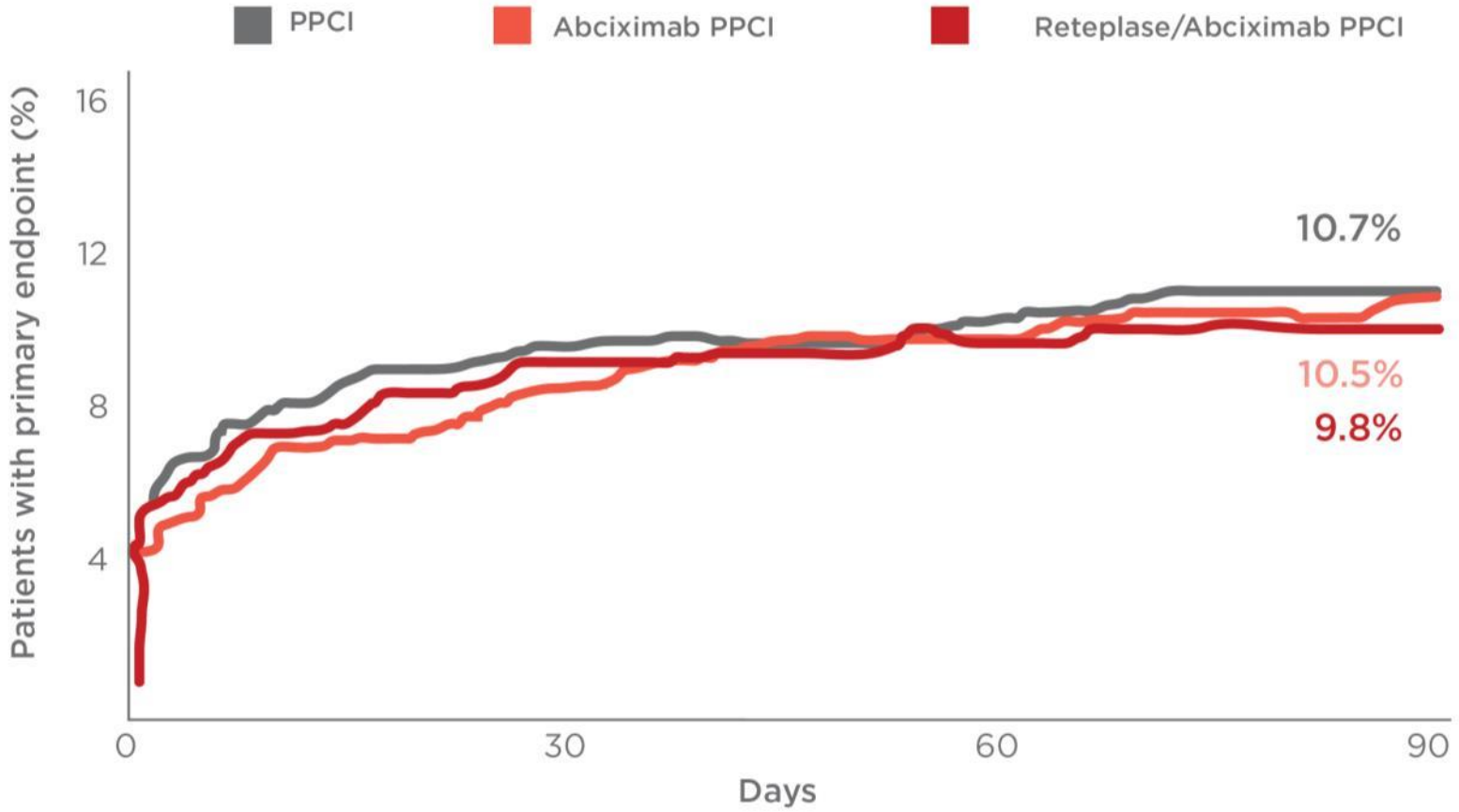
PCI = percutaneous coronary intervention

Adapted from:

Ellis SG, Armstrong P, Betriu A, Brodie B, Herrmann H, Montalescot G, Neumann FJ, Smith JJ, Topol E, FINESSE investigators. Facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention: design and rationale of the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial. American heart journal. 2004 Apr 1;147(4):684.

guardian
guard your heart

FINESSE: KAPLAN-MEIER CURVES FOR THE PRIMARY ENDPOINT AT 90 DAYS



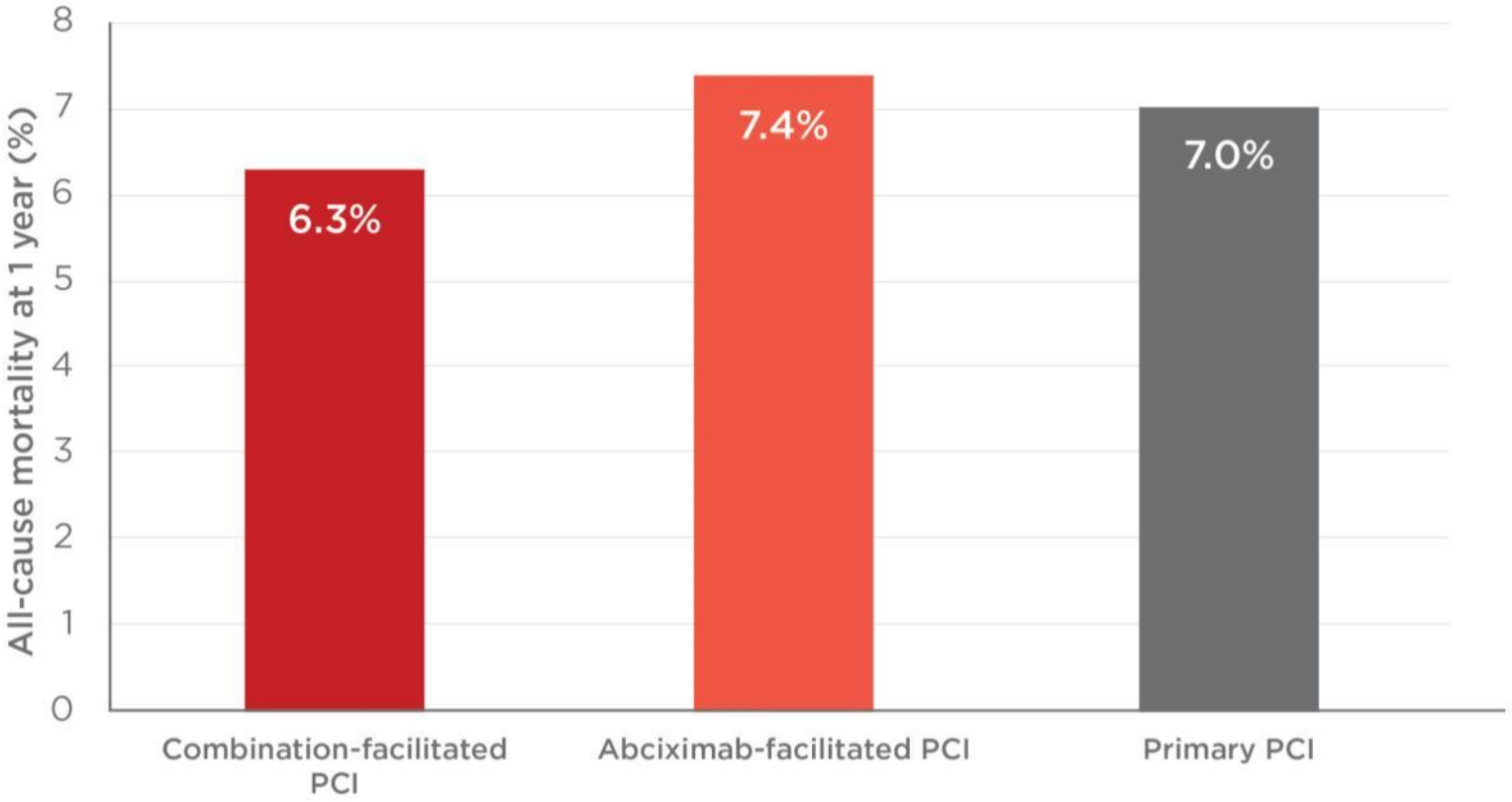
PPCI: Primary percutaneous coronary intervention

Adapted from:

Ellis SG, Tendera M, De Belder MA, Van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ. Facilitated PCI in patients with ST-elevation myocardial infarction. New England Journal of Medicine. 2008 May 22;358(21):2205-17.

guardian
guard your heart

FINESSE:
ALL-CAUSE MORTALITY AT 1 YEAR



PCI: Percutaneous coronary intervention

Adapted from:

Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Hamankiewicz M. 1-year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial. JACC: Cardiovascular Interventions. 2009 Oct 1;2(10):909-16.

guardian
guard your heart

FINESSE: CONCLUSIONS

- Primary endpoint: similar between treatment groups[1]
- PPCI with in-lab abciximab provides better benefit-to-risk ratio vs. two facilitated strategies in STEMI patients who can undergo PCI within 4h of 1st medical contact[1]
- No facilitated PCI strategy provided clinical benefit vs. PPCI with in-lab abciximab[1]
- 1-year follow-up survival data confirms overall lack of clinical benefit with either treatment regimens tested for non-high-risk patients[2]
- Reteplase/abciximab facilitation, and abciximab facilitation, increased bleeding vs. in-lab administration of abciximab[1]
- Combination-facilitated PCI significantly reduced 1-year mortality vs. PPCI[3]
- In high risk patients* presenting to a site without PCI capability, facilitated PCI with early administration of a combination of abciximab + half-dose reteplase or abciximab alone may reduce 90-day clinical outcomes vs. abciximab given just before PCI[3]

PPCI: Primary percutaneous coronary intervention * based on modified TIMI risk score ≥3; with a symptom-to-randomisation time ≤4 h

1. Ellis SG, Tendera M, De Belder MA, Van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ. Facilitated PCI in patients with ST-elevation myocardial infarction. New England Journal of Medicine. 2008 May 22;358(21):2205-17.
2. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Hamankiewicz M. 1-year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial. JACC: Cardiovascular Interventions. 2009 Oct 1;2(10):909-16.
3. Herrmann HC, Lu J, Brodie BR, Armstrong PW, Montalescot G, Betriu A, Neuman FJ, Effron MB, Barnathan ES, Topol EJ, Ellis SG. Benefit of facilitated percutaneous coronary intervention in high-risk ST-segment elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention hospitals. JACC: Cardiovascular Interventions. 2009 Oct 1;2(10):917-24.

guardian
guard your heart

DANAMI-2 (DANISH ACUTE MYOCARDIAL INFARCTION 2 STUDY)

Compared fibrinolysis within hospitals with transfer to invasive-treatment centres for PCI

Average distance between referring hospitals and invasive-treatment centres was 50 km

Study design

1,572 patients with acute STEMI (symptoms present for ≥30 min but <12 h) randomly assigned to either:
- treatment with primary PCI, or
- thrombolysis (accelerated treatment with intravenous alteplase)

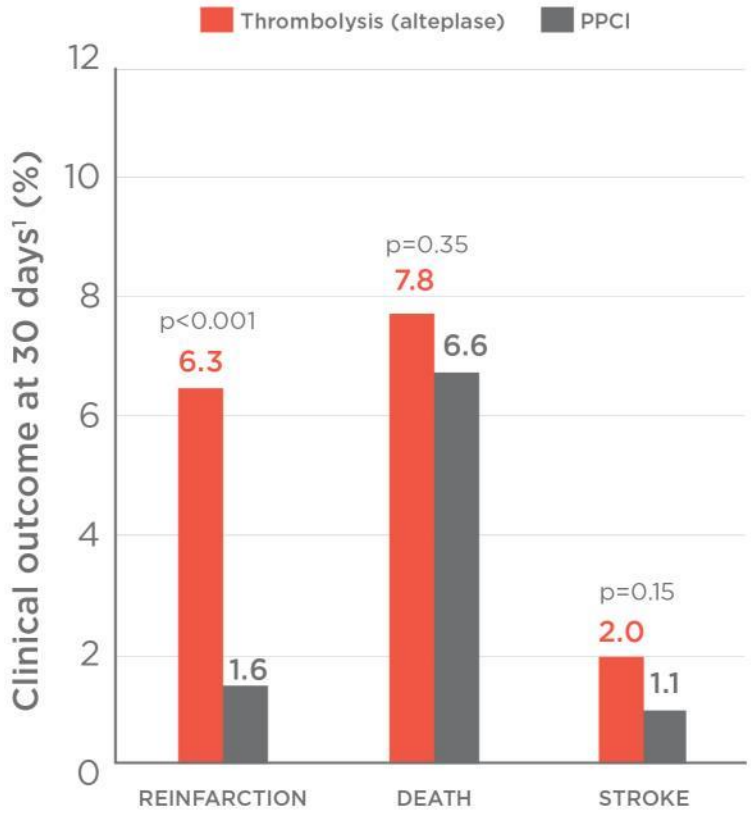
Patients were enrolled at either:
- 1 of 24 referral hospitals (n=1,129), or
- 1 of 5 invasive-treatment centres (n=443)

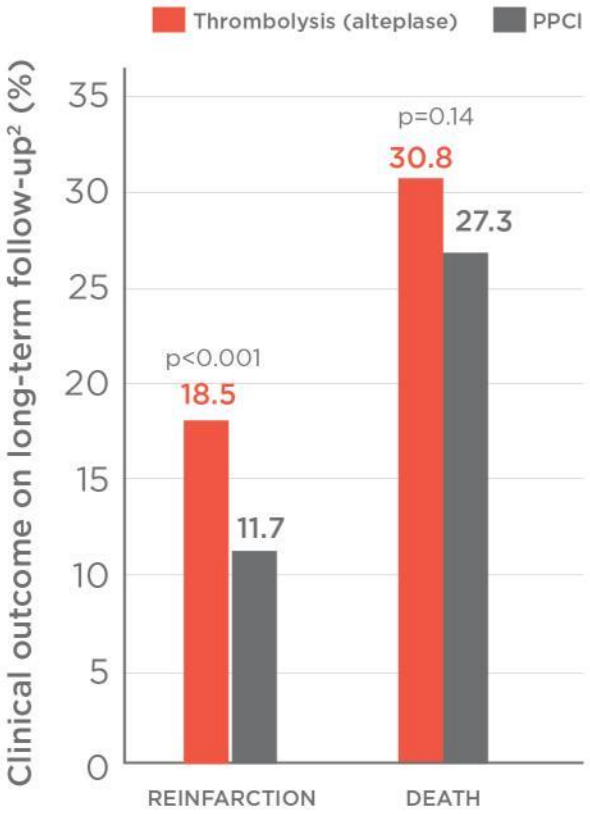
Primary endpoint: Composite of death from any cause, clinical evidence of re-infarction or disabling stroke within 30 days of follow-up.

PCI: Percutaneous coronary intervention

Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. New England Journal of Medicine. 2003 Aug 21;349(8):733-42.

DANAMI-2: CLINICAL OUTCOME





PPCI: Primary percutaneous coronary intervention

1. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. New England Journal of Medicine. 2003 Aug 21;349(8):733-42.
2. Nielsen PH, Maeng M, Busk M, Mortensen LS, Kristensen SD, Nielsen TT, Andersen HR, DANAMI-2 Investigators. Primary angioplastyversus fibrinolysis in acute myocardial infarction: long-term follow-up in the Danish acute myocardial infarction 2 trial. Circulation. 2010 Apr 6;121(13):1484.

guardian
guard your heart

DANAMI-2: CONCLUSIONS

Clinical benefit of PPCI over fibrinolysis was seen at 30 days and at long-term follow-up, largely due to a reduction in the risk of re-infarction

If transfer of patient to an invasive-treatment centre can be completed within 2 h, PPCI is superior to on-site fibrinolysis

PPCI: Primary percutaneous coronary intervention

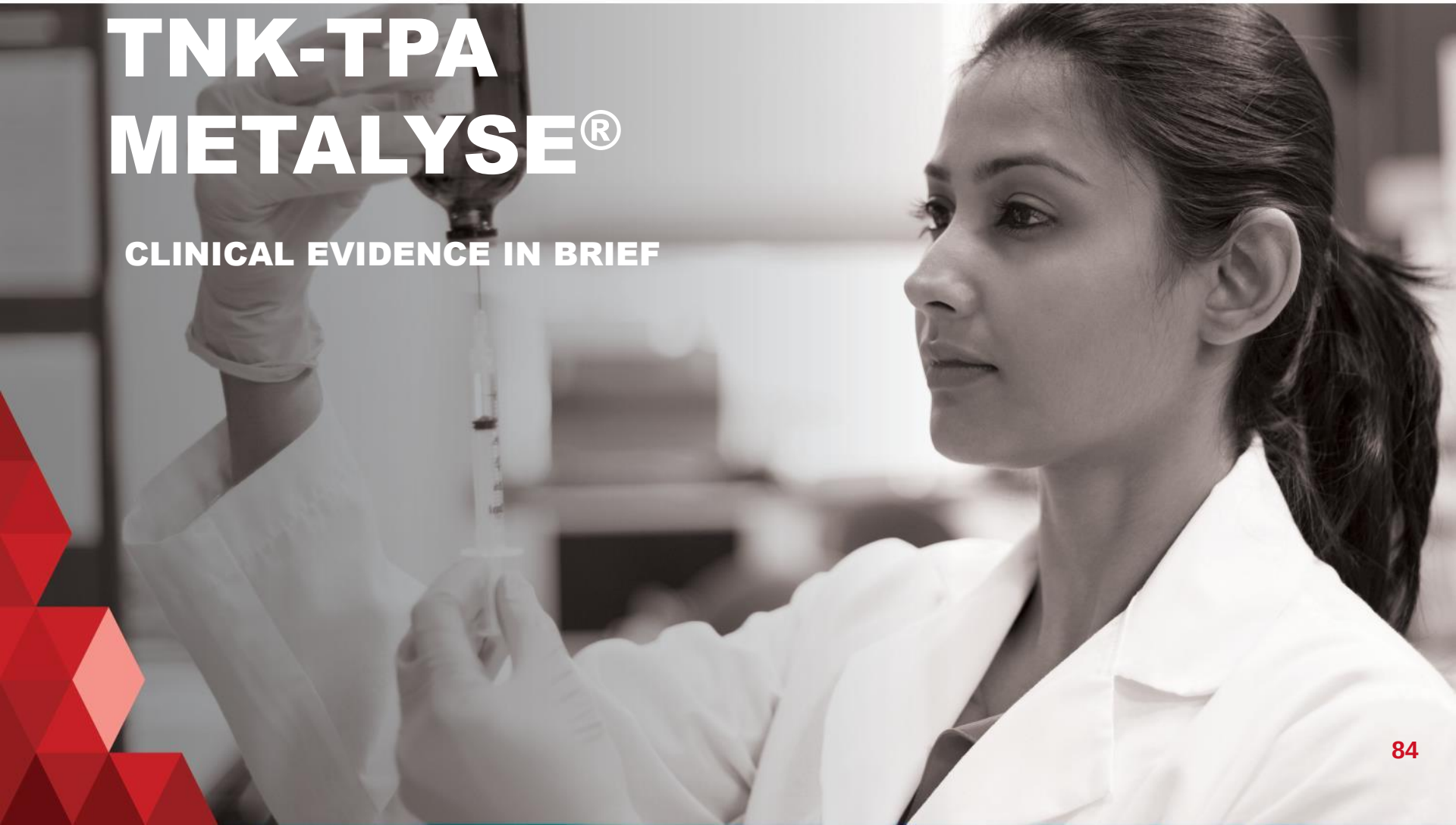
Nielsen PH, Maeng M, Busk M, Mortensen LS, Kristensen SD, Nielsen TT, Andersen HR, DANAMI-2 Investigators. Primary angioplasty versus fibrinolysis in acute myocardial infarction: long-term follow-up in the Danish acute myocardial infarction 2 trial. Circulation. 2010 Apr 6;121(13):1484

guardian
guard your heart

TENECTEPLASE

TNK-TPA METALYSE®

CLINICAL EVIDENCE IN BRIEF



TIMI 10A TRIAL

WHAT DID WE LEARN?

- Prolonged half-life of Metayse allows effective clot lysis as single bolus dosing.
- Metalyse is highly fibrin specific.
- Good initial safety and efficacy profiles.

Cannon CP, McCabe CH, Gibson CM, Ghali M, Sequeira RF, McKendall GR, Breed J, Modi NB, Fox NL, Tracy RP, Love TW. TNK-tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 10A dose-ranging trial. Circulation. 1997 Jan 21;95(2):351-6.

TIMI 10B TRIAL

WHAT DID WE LEARN?

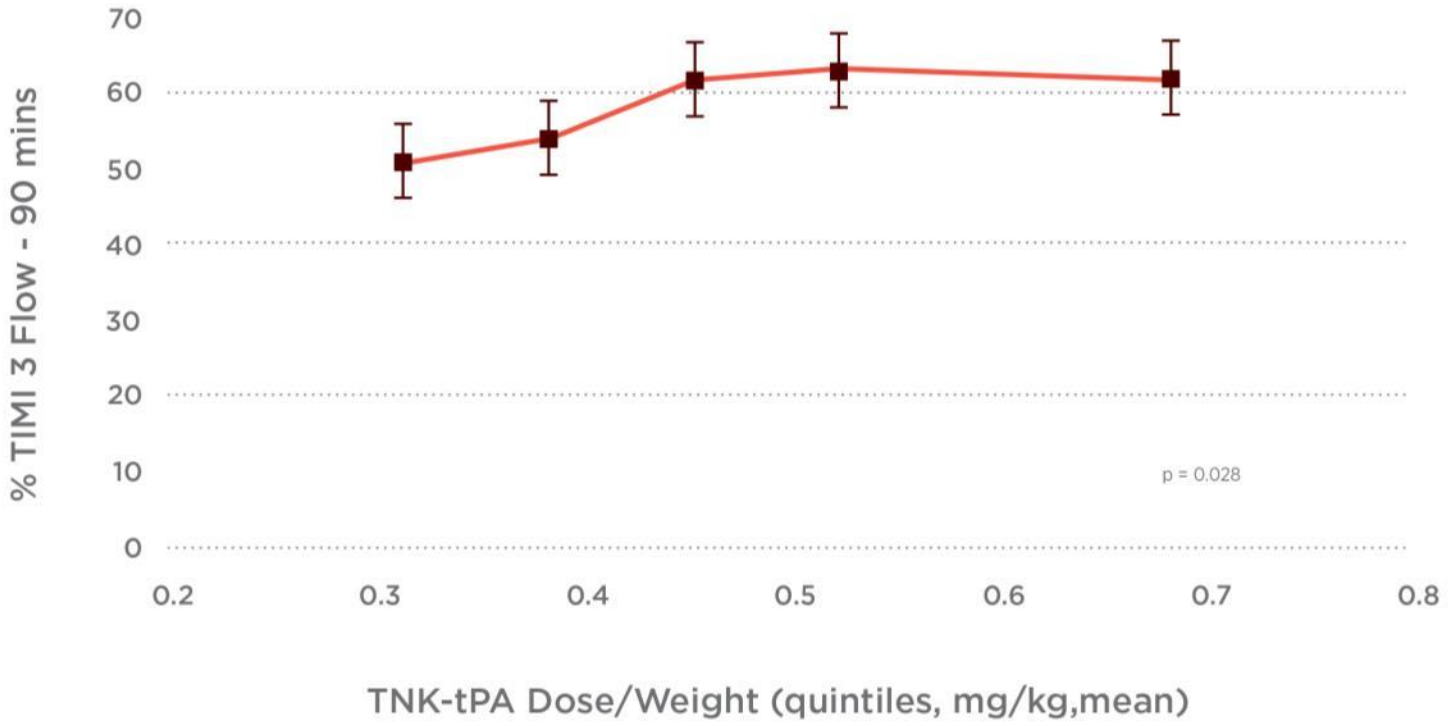
- Weight adjustment was found important in achieving optimal re-perfusion.
- Reduced heparin dose appeared to improve safety of Tenecteplase and alteplase.

Cannon CP, Gibson CM, McCabe CH, Adgey AA, Schweiger MJ, Sequeira RF, Grollier G, Giugliano RP, Frey M, Mueller HS, Steingart RM. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. Circulation. 1998;98(25):2805.

TIMI 10B TRIAL: EFFICACY FOR CLOT LYSIS:

OPTIMUM EFFECTIVE DOSE OF TENECTEPLASE = 0.5MG/KG

Based on TIMI 3 flow at 90 minutes. P-value for trend =0.028 across quintiles



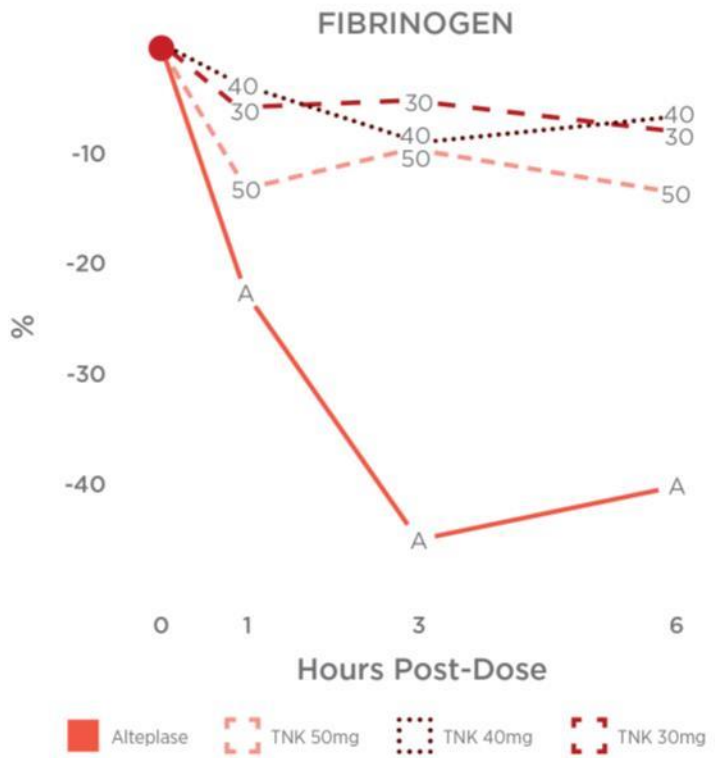
Adapted from:

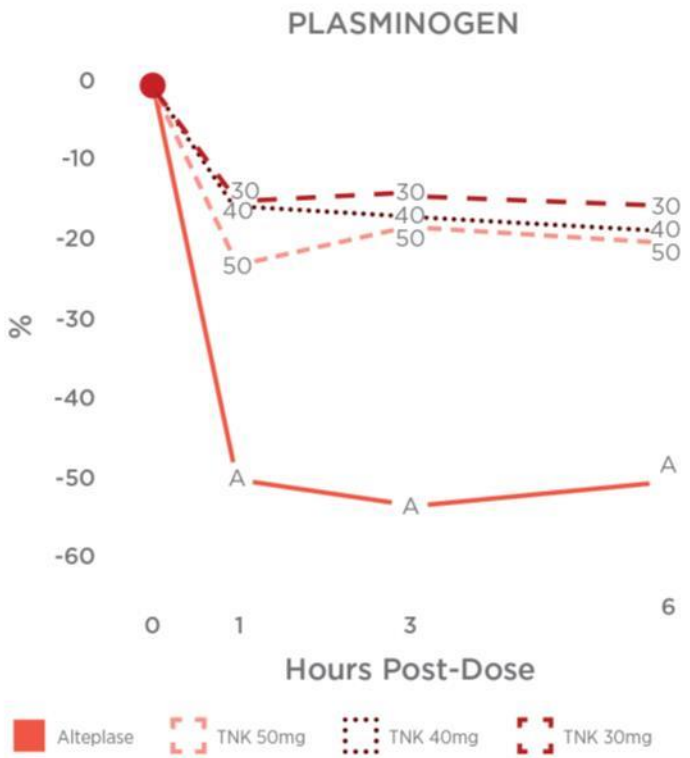
Cannon CP, Gibson CM, McCabe CH, Adgey AA, Schweiger MJ, Sequeira RF, Grollier G, Giugliano RP, Frey M, Mueller HS, Steingart RM. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. Circulation. 1998;98(25):2805.

guardian
guard your heart

TIMI 10B TRIAL : TENECTEPLASE FIBRIN SPECIFICITY EVIDENCE

WITH A HIGHLY FIBRIN SPECIFIC AGENT THERE IS LESS CONSUMPTION OF FIBRINOGEN AND PLASMINOGEN THUS LEADING TO LESS WASTAGE OF THESE IMPORTANT PROTEINS





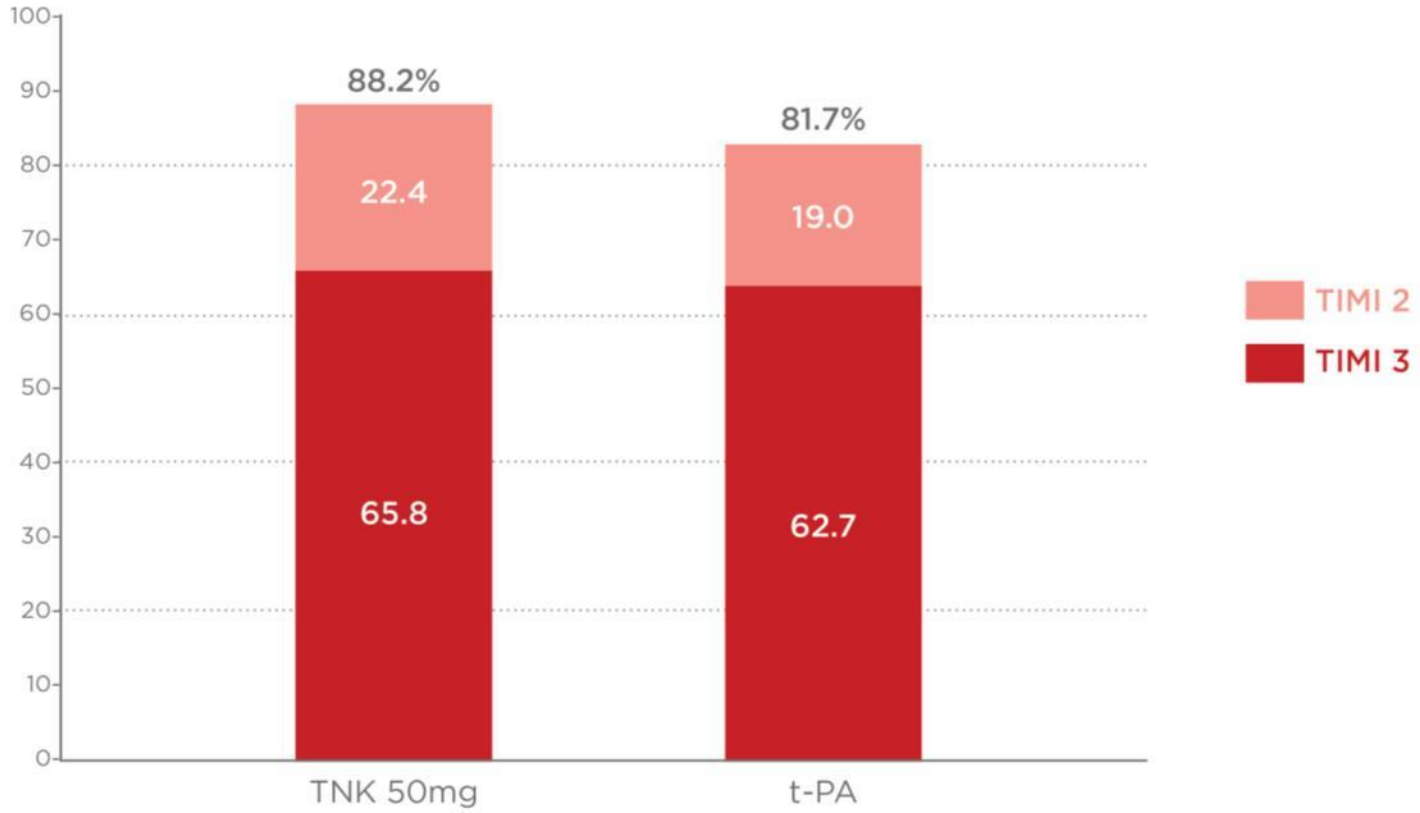
TNK: tenecteplase

Cannon CP, Gibson CM, McCabe CH, Adgey AA, Schweiger MJ, Sequeira RF, Grollier G, Giugliano RP, Frey M, Mueller HS, Steingart RM. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. Circulation. 1998;98(25):2805.

guardian
guard your heart

TIMI 10 B TRIAL: PATENCY RATES

MEASURES AT 90 MINUTES AFTER START OF THROMBOLYSIS



Cannon CP, Gibson CM, McCabe CH, Adgey AA, Schweiger MJ, Sequeira RF, Grollier G, Giugliano RP, Frey M, Mueller HS, Steingart RM. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. Circulation. 1998;98(25):2805.

guardian
guard your heart