Clinical Perspectives on the Role of Tenecteplase in Acute Coronary Syndromes

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Background and Objective of the Survey

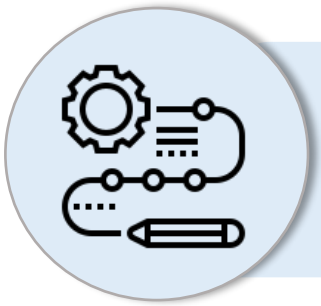
Tenecteplase, a tissue plasminogen activator, is integral in managing acute coronary syndromes (ACS), particularly in restoring blood flow during acute myocardial infarction (AMI). Its mechanism of action involves catalyzing the conversion of plasminogen to plasmin, which subsequently breaks down fibrin clots obstructing coronary arteries, thus promoting reperfusion and salvaging ischemic myocardium. Clinical trials, such as ASSENT-2 and ASSENT-3, have validated its efficacy in achieving timely and sustained coronary reperfusion in patients with AMI.

In clinical practice, tenecteplase is often administered as a bolus injection, making it practical for rapid initiation of reperfusion therapy, especially in settings where immediate access to primary percutaneous coronary intervention (PCI) is not feasible. Patient selection is crucial, with ideal candidates typically presenting with ST-segment elevation myocardial infarction (STEMI) within a specified time window from symptom onset. However, careful consideration of contraindications, such as recent major surgery or prior intracranial hemorrhage, is paramount to mitigate bleeding risks associated with thrombolytic therapy.

Tenecteplase's effectiveness in achieving coronary reperfusion, coupled with its simplified dosing regimen, renders it a valuable therapeutic option in ACS management. Nonetheless, vigilant monitoring for bleeding complications and adherence to appropriate patient selection criteria are essential to optimize outcomes and ensure patient safety during tenecteplase administration.

The objective of the survey is:

To evaluate the clinical perspectives of tenecteplase in acute coronary syndromes



Methodology of the Survey

A survey was conducted to evaluate the clinical perspectives of tenecteplase in acute coronary syndromes. A total of 80 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Clinical Pharmacokinetics and Pharmacodynamics
- Mechanism of Action of Tenecteplase
- Administration
- Clinical Trials on TNK in Ischemic Stroke
- Pharmacokinetic Comparison
- STEMI Clinical Trials
- Tenecteplase (TNKase) in the treatment of acute myocardial infarction

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Tenecteplase (sometimes abbreviated TNK) is a thrombolytic agent manufactured by recombinant DNA technology. Tenecteplase is an FDA-approved medication specifically indicated for reducing mortality in patients with ST-elevation acute myocardial infarction (STEMI). Off-label indications include thrombolysis in treating acute ischemic stroke, pulmonary embolism, and central venous catheter clearance. The most widely used indications are acute myocardial infarction and acute ischemic stroke.

Clinical Pharmacokinetics and Pharmacodynamics[2]

Adequate blood sampling for pharmacokinetic studies of tenecteplase or alteplase in patients with an acute myocardial infarction is subject to considerable practical constraints because these agents are given in an intensive care setting as a single dose only. This greatly restricts the time frame in which sampling may be performed. During myocardial infarction, patients may exhibit fluctuations in cardiac output and hepatic blood flow which increase intra-individual pharmacokinetic variability. The required blood sampling schedule, including the necessary addition of protease inhibitors, often coincides with coronary angiography or other invasive procedures, which may also affect the pharmacokinetic results. In contrast to alteplase, no pharmacokinetic studies were performed with tenecteplase in healthy volunteers because of ethical concerns arising from its increased fibrinolytic potency and longer half-life. The pharmacokinetics of tenecteplase were studied in 179 patients with acute myocardial infarction during clinical development up to regulatory approval. Comparative data with alteplase were obtained concurrently in an additional 53 patients. Two large pharmacokinetic substudies were integrated into the TIMI 10A phase I dose-ranging clinical trial and the TIMI 10B phase II angiographic clinical trial. No pharmacokinetic data were obtained in the phase II safety trial (ASSENT-1) and in the large phase III trial (ASSENT-2) in order not to compromise the clinical objectives of these trials. Post-approval clinical trials have been aimed principally at studying combinations of tenecteplase with antithrombotic agents, for example enoxaparin or abciximab in ASSENT-3, and no further tenecteplase pharmacokinetic data were obtained in those studies.

Pharmacokinetics in Patients, Phase I[2]

In the phase I (TIMI 10A) study, pharmacokinetic parameters were obtained over a wide tenecteplase dose range of 5–50mg, administered as a single intravenous bolus over 5–10 seconds in patients with acute myocardial infarction. The number of patients for whom pharmacokinetic data was obtained in each group varied between 5 and 26. Tenecteplase exhibited biphasic (twocompartment) kinetics in 60 patients, and monophasic kinetics in 20 patients. It is likely that tenecteplase disposition is generally biphasic, but in some patients only a single compartment was detected. Clearance of tenecteplase decreased from 216 ml/min at the 5mg dose to 125 ml/min at 50mg, indicating a moderate pharmacokinetic nonlinearity. However, in the dose range 30–50mg, which was judged to be clinically relevant based on angiographic efficacy, there was no significant difference in clearance (125–143 ml/min). This clearance was 4-fold slower, and the initial half-life of 17–20 min, which corresponded to 55–69% of area under the concentration-time curve (AUC), was 5- fold longer, than reported for alteplase. This study, therefore, provided a clear pharmacokinetic rationale, based on the considerably reduced plasma clearance and prolonged half-life compared with alteplase, to support further clinical development of tenecteplase using a single intravenous bolus rather than an infusion regimen.

Pharmacokinetics in Patients, Phase II[2]

In the phase II (TIMI 10B) pharmacokinetic study, tenecteplase bolus doses of 30, 40 and 50mg were administered and compared with alteplase 100mg given as a 90-minute accelerated infusion regimen.

Tenecteplase exhibited two-compartment kinetics in 90 out of 99 patients, and alteplase pharmacokinetics were evaluated by noncompartmental analysis. In contrast to the phase I (TIMI 10A) study there was no dose dependence of clearance, probably because of the more restricted dose range. The mean initial half-life was 22 minutes and the mean terminal half-life was 115 minutes.

The mean clearance of tenecteplase (105 ml/min) was 4.3-fold slower than that measured for alteplase in TIMI 10B, and the initial (dominant) half-life was 6.3 times longer than that reported for alteplase in the rt-PA-APSAC Patency Study (TAPS), confirming the phase I results. Other pharmacokinetic parameters of alteplase measured in TIMI 10B were similar to those reported in the TAPS study.

Tenecteplase pharmacokinetics were very similar in both the TIMI 10A and TIMI 10B studies. The initial plasma half-life was slightly longer in TIMI 10B (20–24 min) than in TIMI 10A

(17–20 min), but this may be attributable to the more sparse blood sampling in TIMI 10B (reduced from 15 to 8 samples per patient), and the difference is not clinically important. Although tenecteplase clearance was similar at the 40 and 50mg doses, clearance at the 30mg dose was 31% lower in TIMI 10B than in TIMI 10A. This may have been attributable to known minor increases in sialic acid content resulting from manufacturing scale changes and process optimisation of tenecteplase that occurred after TIMI 10A. Increases in sialic acid content will block exposed galactose in oligosaccharide moieties of the tenecteplase molecule and may therefore reduce its clearance by the hepatic asialoglycoprotein receptor.

The initial half-life of tenecteplase was dominant in both studies, accounting for 55–72% of AUC. Overall, V1 (4.2–6.3L) approximated plasma volume, and Vss was 6.1–9.9L, suggesting mainly intravascular distribution. These parameters are consistent with the large molecular mass of tenecteplase (65kD). In contrast to alteplase, little information is available on binding of tenecteplase to plasma proteins in humans. Recently, slow complex formation between tenecteplase and C1 inhibitor was demonstrated in vitro in human plasma.

Sources of Pharmacokinetic Variability[2]

Interindividual variability of tenecteplase pharmacokinetic parameters was relatively high. For example, overall coefficients of variation were 41% for clearance and 58% for V1 in the TIMI 10B study. The intra-individual (residual) variability was not quantitatively assessed, and a combined analysis of the TIMI 10A and TIMI 10 B studies was not performed; both aspects would require further analysis by population mixed effect modelling. In the TIMI 10A and TIMI 10B studies, two-stage data analysis approaches were used to identify patient covariates that contributed to interindividual pharmacokinetic variability. These involved stepwise linear regression of pharmacokinetic parameters on covariates after the former had been computed by model fitting of individual plasma concentration profiles.

n the TIMI 10A study, dose followed by total or lean bodyweight, age and gender were significantly correlated with clearance, whereas none influenced V1. Dose was the most important covariate but only explained 17% of the variability in clearance. On including all covariates in the regression model, still only 30% of the total variability could be accounted for. In TIMI 10B, total or lean bodyweight and age were found significantly to influence both clearance and V1. However, the predictive value of these covariates was again small. Total bodyweight explained 19% of the variability in clearance and 11% of the variability in V1. Age explained a further 11% of the variability in clearance. A 10kg increase in total bodyweight

resulted in a 9.6 ml/min increase in plasma clearance. Conversely, a 10-year increase in patient age resulted in a 16.1 ml/min decrease in plasma clearance.

In both studies, clearance increased with bodyweight and decreased with age. This is not unexpected on consideration of the hepatic elimination route for tenecteplase, because heavier patients might have higher liver weights and therefore increased capacity for tenecteplase clearance. The decrease of clearance with age may reflect reduced expression and/or function of hepatic receptor systems for tenecteplase catabolism. With initial distribution corresponding to plasma volume, the increase of V1 with bodyweight observed in TIMI 10B can also be rationalised, because heavier patients will have higher blood volume. Men had higher mean clearance than women, but the effect was not statistically significant and may have been attributable to the greater bodyweight of male patients. Also, only 28% of the patients with complete demographic data in the pharmacokinetic subset of TIMI 10B were women, which reflected the low female/male ratio in the full trial population and acute myocardial infarction studies in general.

No separate clinical trials were performed to investigate specifically the pharmacokinetics of tenecteplase in special populations such as individuals with hepatic and renal insufficiency. Rat studies showed that tenecteplase is not excreted intact into the urine. Also, the molecular mass of tenecteplase, which is close to that of serum albumin, precludes glomerular filtration in any species. Therefore, it is not expected that renal dysfunction will affect pharmacokinetics. The effect of hepatic dysfunction on the pharmacokinetics of tenecteplase in humans was not studied.

No separate clinical studies were performed to evaluate specifically the potential for pharmacokinetic interaction between tenecteplase and other drugs commonly administered in the treatment of subjects with acute myocardial infarction. All study patients included in the pharmacokinetic analyses received aspirin and heparin as concomitant medication.

Mechanism of Action of Tenecteplase[1]

Tenecteplase is a bioengineered alteplase variant, a recombinant DNA-derived version of naturally occurring tissue plasminogen activator (tPA). The drug is derived from three amino acid substitutions at three sites (T, N, and K represent the three regions changed from the natural tPA protein). Native tPA is a serine protease found in endothelial cells. Tenecteplase binds to the fibrin component of a blood clot (thrombus). It acts within the endogenous fibrinolytic coagulation cascade to selectively catalyze the cleavage of plasminogen to plasmin.

The activated plasmin subsequently degrades fibrin, resulting in clot dissolution and recanalization of blood flow.

Tenecteplase exhibits much higher fibrin specificity, increased resistance to inactivation by endogenous inhibitor plasminogen activator inhibitor (PAI-1), and a longer half-life compared to native tPA. Due to its long half-life, Tenecteplase can be administered as a single intravenous bolus injection.

Administration[1]

Tenecteplase is supplied as a lyophilized powder in a 50 mg vial; it is packaged with a separate 10 mL vial of sterile water for reconstitution to obtain a final 5 mg/mL concentration. The reconstituted solution can be refrigerated at 2 °C to 8 °C (36 °F to 46 °F) and must be used within 8 hours.

Tenecteplase is administered as a single 5-second intravenous bolus at weight-based tiered doses of 0.25 mg/kg or 0.50 mg/kg with a maximum dose of 50 mg. Tenecteplase has a half-life of 20 to 25 minutes.

The STREAM trial demonstrated a lower incidence of intracranial hemorrhage (ICH) in patients over 75 who received half doses of tenecteplase (0.25 mg/kg) compared to the standard dose of 0.5 mg/kg.

Myocardial Infarction[1]

Acute myocardial infarction (MI) is managed with timely thrombolysis or percutaneous coronary intervention (PCI). While PCI is the preferred approach, thrombolysis remains a crucial primary strategy for patients who cannot receive PCI within the preferred treatment window.

The CAPTIM study demonstrated tenecteplase might be as effective as PCI in treating acute ST-elevation myocardial infarction (STEMI) when administered in the prehospital setting. This strategy is desirable for patients who cannot receive PCI within the recommended 90 minutes after first medical contact. Indeed, up to 70% of STEMI patients present to hospitals without PCI capability, thus requiring transfer to a PCI facility or an alternative primary revascularization strategy. This strategy is further supported by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which encourage prehospital thrombolytic therapy within 30 minutes of symptom onset.

Tenecteplase may be used in conjunction with antiplatelet and anticoagulation therapy. The drug can also be used before undergoing PCI. In the case of failed thrombolysis with tenecteplase, rescue PCI should be considered.

The safety and efficacy of tenecteplase before PCI continue to be investigated. The ASSENT-4 trial was prematurely discontinued due to excessive in-hospital mortality in the study group receiving tenecteplase-facilitated PCI. Whereas the WEST and GRACIA-2 studies found comparable efficacy between tenecteplase-facilitated PCI and primary PCI, these studies determined the greatest benefit was achieved when routine PCI is postponed at least 3 to 12 hours after tenecteplase administration.

Acute Ischemic Stroke[1]

Several randomized controlled trials for acute ischemic stroke have compared tenecteplase and alteplase. The EXTEND-1A TNK trial showed better reperfusion versus alteplase in lesions with low clot burden. The NOR-TEST2 trial with 0.4 mg/kg of tenecteplase failed to show non-inferiority to a standard dose of IV alteplase. The ATTEST trial compared 0.25 mg/kg of tenecteplase and the standard dose of IV alteplase and found no differences in the outcomes.

The TAAIS trial compared doses of tenecteplase in computed tomography (CT) confirmed middle cerebral artery (MCA) occlusion. The trial concluded higher recanalization rates and greater neurological improvement, as evidenced by an improvement in the National Institutes of Health Stroke Scale (NIHSS) in the 0.25 mg/kg cohort. Additionally, this dose group demonstrated a better modified Rankin Scale (mRS) score of 0 or 1 at 90-day follow-up. The efficacy of the 0.25 mg/kg dose group is further supported by a meta-analysis of 5 randomized controlled trials, which found greater efficacy and a lower rate of symptomatic intracranial hemorrhage (sICH) with the 0.25 mg/kg dose compared to 0.1 mg/kg and 0.4 mg/kg dose.

The most recently published AcT trial in Canada is a large randomized open-label trial comparing 0.25 mg/kg of tenecteplase and alteplase. This trial demonstrated the non-inferiority of tenecteplase versus alteplase.

From all the available data about tenecteplase in acute ischemic stroke, one can conclude that no clear positive phase 3 trial shows its superiority over alteplase. 0.4 mg/kg of tenecteplase showed no advantage over the 0.25 mg/kg dose. Given its longer half-life so that it can be given as a single bolus dose and its lower cost, tenecteplase is becoming more accepted in most stroke centers in the USA over alteplase.

The 2019 American Heart Association/American Stroke Association (AHA/ASA) Guidelines provide the most current recommendations for tenecteplase use in AIS. The AHA/ASA

guidelines include tenecteplase at 0.25 mg/kg and 0.40 mg/kg doses as an alternative therapy (class IIB recommendation). The guideline stated that it might be reasonable to choose tenecteplase (a single IV bolus of 0.25 mg/kg maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolytic who are also eligible to undergo mechanical thrombectomy. Tenecteplase administered as a 0.4 mg/kg single IV bolus has not been proven to be superior or non-inferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.

Pulmonary Embolism[1]

Although tenecteplase is not FDA-approved for use in pulmonary embolism (PE), several studies have evaluated its efficacy and safety in use for acute PE. Tenecteplase may be considered for high-risk or massive PE. High-risk or massive PE is defined by sustained hypotension or cardiogenic shock and given at the same dose as acute MI.

The PEITHO study and its long-term outcome evaluation represented the largest trial evaluating the use of thrombolytics in the setting of acute PE. The study showed tenecteplase may improve hemodynamics in patients with PE and evidence of right heart strain but at an increased risk of intracranial hemorrhage compared to placebo (6.3% vs 1.2%). In addition, no difference in long-term function was noted with tenecteplase. To date, no study has directly compared the efficacy and safety of tenecteplase to other thrombolytics in acute PE.

Adverse Effects[1]

Adverse effects of tenecteplase, including bleeding, anaphylaxis, thromboembolism, and arrhythmia, are similar to other thrombolytics.

Bleeding is the most common complication of tenecteplase and thrombolytic use. Bleeding can occur anywhere in the body, as well as at puncture and surgical sites. Intracranial hemorrhage poses the most significant concern for increased mortality. The incidence of symptomatic intracranial hemorrhage in patients receiving tenecteplase (2.9%) is comparable to patients receiving alteplase (2.7%), another thrombolytic agent. The risk of bleeding with tenecteplase is increased with concomitant use of anticoagulants and antiplatelet agents.

Thromboembolic events and cholesterol embolization have been reported using thrombolytics, including tenecteplase. In addition, cardiac dysrhythmias have been associated with thrombolytic use in STEMI as an occurrence of tissue reperfusion.

In the ASSENT-4 study, higher incidences of mortality, cardiogenic shock, congestive heart failure, and recurrent myocardial infarction requiring repeat revascularization were observed

in the cohort receiving tenecteplase with PCI versus PCI alone. In such cases of large STEMI, clinicians are advised to choose either thrombolysis or PCI as the primary reperfusion strategy.

Contraindications[1]

Tenecteplase is contraindicated in several conditions. These include the following:

- Active internal bleeding
- Severe uncontrolled hypertension
- History of cerebrovascular accident
- History of aneurysm or arteriovenous malformation
- History of intracranial neoplasm
- Intracranial or intraspinal surgery within the last 2 months
- Head or spinal trauma within the previous 2 months
- Conditions that increase the risk of bleeding

Tenecteplase is an FDA pregnancy category C drug. No well-controlled studies evaluate the risk of adverse maternal or fetal outcomes in tenecteplase. Whether tenecteplase is excreted in breast milk is unknown. Pregnancy is a relative contraindication to tenecteplase and should only be given after carefully considering the risks and benefits to the patient and fetus.

Significant drug-drug interactions that contraindicate tenecteplase use include defibrotide and mifepristone. Concurrent use of tenecteplase with defibrotide may increase bleeding risk due to additive effects and duplicate anticoagulation. Mifepristone and tenecteplase are contraindicated when using mifepristone for pregnancy termination; the combination may increase the risk of severe or prolonged vaginal bleeding due to additive effects.

Monitoring[1]

Patients receiving tenecteplase require routine neurologic and cardiovascular monitoring to assess for bleeding and hypersensitivity reactions.

Nonessential handling and puncture should be avoided in the first few hours after tenecteplase administration. If an arterial puncture cannot be avoided, the preferred site is an upper extremity blood vessel that can be easily compressed. Direct pressure should be applied for 30 minutes following venipuncture.

A neurological exam must be serially performed to assess for deterioration in mental status or any new focal neurological deficits, which may suggest a bleeding event. An urgent brain CT should be performed if there is any sign of neurological deterioration. If the patient is also

receiving concomitant anticoagulation such as heparin, the agent should be stopped, and the appropriate reversal agent should be administered. Other bleeding sites, such as puncture or surgical sites and bruising, should also be monitored.

Vital signs must be frequently evaluated for fever, hypotension, and tachycardia. Assessment of clinical signs of anaphylaxis, including angioedema, rash, and respiratory distress, must also be routinely performed. Supportive medication such as antihistamines and intramuscular epinephrine should be available.

Due to the risk of cardiac arrhythmia in tenecteplase, cardiac monitoring is necessary. In addition, antiarrhythmic therapy for bradycardia and ventricular instability should be available during tenecteplase administration.

Toxicity[1]

Overdose of tenecteplase results in serious bleeding. There is no antidote or reversal agent for tenecteplase. In the event of bleeding, tenecteplase must be immediately discontinued and supportive care provided.

Enhancing Healthcare Team Outcomes[1]

The successful administration of tenecteplase and maximization of health outcomes relies on the effective coordination of the interprofessional healthcare team. Tenecteplase must be administered within a strict time frame, with a thorough review of contraindications to therapy and vigilant clinical monitoring after administration.

The single bolus administration of tenecteplase makes the drug an ideal candidate in the prehospital setting. Prehospital professionals such as emergency medical technicians (EMTs) and first responders are trained and qualified to administer tenecteplase in specific settings. Their ability to evaluate electrocardiogram (ECG) and identify STEMIs is crucial in providing advanced notification to hospital teams.

Open communication among all team members is crucial to therapeutic success when using tenecteplase. Pharmacists conduct thorough medication reconciliation before tenecteplase administration to identify any contraindications to therapy or drug-drug interactions and must immediately alert the clinical team. Additionally, pharmacists will collaborate with nurses for proper drug preparation, dosing, and administration. Nurses are essential in monitoring for potential adverse events during and after the administration of tenecteplase and promptly reporting any concerns to the attending so corrective action can be initiated.

The close communication and collaborative approach among the interprofessional healthcare team members are crucial for achieving maximal therapeutic benefit with the fewest adverse events.

Clinical Trials on TNK in Ischemic Stroke[3]

Several clinical trials were conducted to test the efficacy and safety of TNK in reperfusion therapy for ischemic stroke. The 2019 American Heart Association/American Stroke Association Guidelines recommended 0.4 mg/kg TNK as an alternative to alteplase in patients with mild neurological impairment and no major intracranial occlusion. Moreover, 0.25 mg/kg TNK was recommended in the 2019 American Heart Association/American Stroke Association Guidelines in patients without contraindications for intravenous (IV) fibrinolysis who were also eligible to undergo mechanical thrombectomy. Considering the limited clinical trials on TNK, the class of recommendation and level of evidence are low (IIb, B-R). The 2021 European Stroke Organisation Guidelines recommended 0.25 mg/kg TNK over 0.9 mg/kg alteplase before mechanical thrombectomy within 4.5 h from stroke onset. However, the recommendation of TNK over alteplase was based on expert consensus recommendation with a weak strength of recommendation and low quality of evidence. In the real-world clinic, TNK is still used cautiously to treat ischemic stroke, and more clinical trials on TNK in ischemic stroke are needed.

Table 1: Clinical Trials on TNK in Ischemic Stroke

Name	**EXTEND IA TNK II**	**EXTEND IA TNK**	**NOR-TEST**	**ATTEST**	**TAAIS**	**Haley et al**
Year	**2020**	**2018**	**2017**	**2015**	**2012**	**2010**
Study design	PROBE	PROBE	PROBE	PROBE	PROBE	Multi-center, perspective randomized controlled trial
Dose	0.4 mg/kg 0.25 mg/kg	0.25 mg/kg	0.4 mg/kg	0.25 mg/kg	0.1 mg/kg 0.25 mg/kg	0.1 mg/kg 0.25 mg/kg 0.4 mg/kg
Time window	4.5h	4.5h	4.5h	4.5h	6h	3h
Imaging	ICA/MCA/ BA occlusion	ICA/MCA/ BA occlusion			CTA: intracranial vessel occlusion; CTP: TTP≥core volume 20%, core volume≤20 mL	
Sample size	300	202	1100	96	75	112

Initial NIHSS	16 VS 17	17 VS 17	5.6 VS 5.8	12 VS 11	14.5 VS 14.6 VS 14	8 VS 10 VS 9 VS 13
90d mRS 0–1	49 VS 49%(p=0.69)	51 VS 43%(p=0.20)	64% VS 63%(p=0.52)	28% VS 20%(p=0.28)	54% VS 40%(p=0.25)	45.2% VS 48.4% VS 36.8% VS 41.9%
Symptomatic intracranial hemorrhage	PH2 36h: 1.3VS. 4.7% (p=0.12)	PH2 36h: 1 VS 1% (p=0.99)	ECASS III: 3 VS 2% (p=0.70)	ECASS III: 6% VS 8% (p=0.59) SITS-MOST: 2% VS 4% (p=0.50)	SITS-MOST: 4 VS 12% (p=0.33)	0% VS 6.5% VS 15.8% VS 3.2%
Mortality	15 VS 17% (p=0.35)	10 VS 18% (p=0.049)	5 VS 5% (p=0.68)	17% VS 12% (p=0.51)	8 VS 12% (p=0.68)	6.5% VS 22.6% VS 15.8% VS 25.8%

Pharmacokinetic Comparison[3]

Because fibrin molecules bind to each other and form the skeleton of a thrombus, (Fig 1), it can be lysed through fibrinolysis. Tissue plasminogen activator (tPA) is generated in endothelial cells to convert plasminogen into plasmin. Plasmin breaks down the fibrin skeleton by converting fibrin into fibrinogen degradation products, and the thrombus is eventually dissolved to achieve recanalization of the occluded vessel.

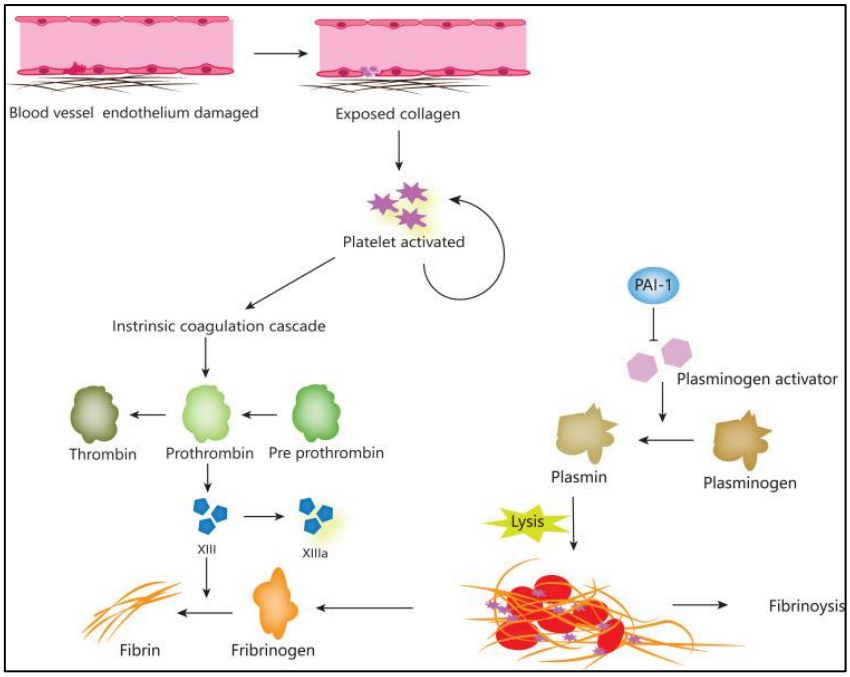


Fig 1: Mechanism of thrombosis.

Similar to alteplase, TNK is also a 527-amino acid-modified human tissue plasminogen activator that contains the fibronectin finger, epidermal growth factor, kringle 1, kringle 2, and serine protease domains. However, three amino acids are substituted in TNK compared to alteplase: the substitution of threonine 103 with asparagine and glutamine 117 with asparagine has increased the half-life of TNK; the amino acid replacement in positions 296–299 has enhanced its resistance to plasminogen activator inhibitor-1 (PAI-1) and potentiated fibrin specificity. The different biomolecular structure of TNK has given it more pharmacological advantages over alteplase (Table 2). The prolonged half-life enables TNK to be administered as a single intravenous bolus rather than a bolus and continuous infusion. The single bolus of TNK is more convenient for “drip and ship” cases. Moreover, poor fibrin selectivity of alteplase results in excessive systematic bleeding events and disintegration of the blood–brain barrier leading to post-stroke cerebral edema and hemorrhagic transformation. Alteplase also causes more damage to the fibrinolytic system than TNK and increases the risk of intracerebral hemorrhage.[9] Further, alteplase inhibits platelet aggregation and influences the coagulation process with an elevated risk of hemorrhagic events.[9] Therefore, theoretically, TNK is a better thrombolytic agent than alteplase with lower risk of side-effects when administrated intravenously in ischemic stroke patients.

Table 2: Pharmacokinetic Comparison Between Alteplase and TNK

	Fibrin Selectivity	PAI-1 Resistance	Half-Life Time	Platelet-Rich Thrombus Activity	BBB Damage	Fibrinogen Depletion	HDL-C Level Lowering	Thrombolytic Potency
Alteplase	Moderate	Low	4–8min	Low	Moderate	Moderate	Moderate	Low
TNK	High	Moderate	11–20min	High	Unknown	Low	Low	High

Abbreviations: PAI-1, plasminogen activator inhibitor-1; BBB, blood-brain barrier; HDL-C, high-density lipoprotein cholesterol.

Optimal Dose in Ischemic Stroke[3]

A pilot dose-escalation safety study was conducted to investigate the safety and efficacy of TNK in ischemic stroke patients (n=88) at four doses (0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.5 mg/kg). The occurrence of symptomatic intracranial hemorrhage (sICH) at TNK doses of 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg were lower than that of alteplase (0% vs 0% vs 0% vs 15%, respectively). A phase IIb, randomized, double-blind trial was conducted in 2010 to compare the three doses of TNK (0.1 mg/kg, 0.25 mg/kg, and 0.4 mg/kg) with alteplase. The trial was terminated prematurely because patient enrolment was very slow, with only 112 patients being finally enrolled. The dose of 0.4 mg/kg TNK was prematurely terminated considering its poor performance in both efficacy and safety; in terms of good outcome (combining major neurological improvement and symptomatic ICH), the 0.25 mg/kg TNK group had the highest proportion (15/31, 48.4%), followed closely by the 0.1 mg/kg TNK group (14/31, 45.2%). By comparison, the rt-PA group had 41.9% (13/31) good outcomes. The difference between the 0.25 mg/kg and 0.1 mg/kg groups was not statistically significant because of the insufficient sample size after patient enrolment was terminated (n=112). Moreover, the study did not show conclusive results for an optimal dose of TNK in ischemic stroke.

The Tenecteplase VERSUS Alteplase for Acute Ischemic Stroke (TAAIS) trial enrolled patients with middle cerebral artery (MCA) occlusion on CTA and reversible penumbra on CTP (n=75) and showed the superiority of 0.25 mg/kg TNK over 0.1 mg/kg TNK among all the efficacy endpoints (mean rates of reperfusion at 24 h: 88.8% vs. 69.3%, P=0.006; complete recanalization at 24 h: 80% vs. 35%, P=0.002; median improvement in National Institutes of Health Stroke Scale score at 24 h: 11 vs. 7, P=0.0059; and mRS 0–1: 72% vs. 36%, P=0.011). However, no significant difference was detected in safety endpoints between the two doses of TNK (sICH: 4% vs. 4%, P=1.000). The TAAIS trial and another meta-analysis both implied that the optimal dosage of TNK in ischemic stroke may be 0.25 mg/kg, and this dosage was utilized in subsequent Phase II and Phase III trials including ATTEST (Alteplase vs.

tenecteplase for thrombolysis after ischaemic stroke), TEMPO-1 (Tenecteplase–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion), and EXTEND-IA TNK (Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke trial). The TEMPO-1 study also found that there were no serious drug-related adverse events in the 0.1 mg/kg TNK group. In the 0.25 mg/kg TNK group, there was one sICH (4%). Comparable risks of sICH were found between the 0.1 mg/kg TNK and 0.25 mg/kg TNK groups. Owing to a small sample size (n=100) and non-randomized study design, it was served as a safety and feasibility trial. The Norwegian tenecteplase stroke trial (NOR-TEST trial), a phase III trial with over 1000 enrolled patients, utilized 0.4 mg/kg TNK and failed to prove the superiority of TNK over alteplase on functional outcomes (mRS score 0–1 at 3 months: 64% vs. 63%, P=0.52). Safety outcomes were also similar between the TNK and alteplase groups (sICH: 3% vs. 2%, P=0.49; death within 3 months: 5% vs. 4%, P=0.49). The limitations of the NOR-TEST trial included a large proportion of TIA and stroke mimics (25%) and mild neurological impairment (median NIHSS score=4) that decreased its external validation. The EXTEND-IA TNK 2 trial failed to prove the superiority of 0.4 mg/kg TNK compared with 0.25 mg/kg TNK. Per another study, 0.25 mg/kg was the optimal dosage for patients undergoing bridge therapy. (intravenous thrombolysis [IVT]+mechanical thrombectomy [MT])

STEMI Clinical Trials[3]

Tenecteplase went into clinical trial comparisons with alteplase as a single bolus thrombolytic. Patients in the tenecteplase randomized trials in acute myocardial infarction also received heparin and aspirin co-administered with either lytic. The definitive Phase 3 double-blinded trial, ASSENT-2 found equivalent 30-day mortality (7%) in 16,949 patients randomized between the two treatments. The tenecteplase group had significantly fewer non-cerebral bleeding complications (26% to 29%; P=0.0003), while showing no difference in the incidence of intracranial hemorrhage (0.9% in both groups). No differences were observed in the rates of reinfarction.

As primary percutaneous coronary intervention (PCI) became first line treatment of STEMI, tenecteplase treatment for STEMI was relegated to cases where PCI was not available in a timely fashion. ASSENT-4, a randomized trial of tenecteplase-facilitated PCI versus primary PCI in 1667 patients, found that rather than enhancing the effects of PCI, tenecteplase prior to PCI was associated with a higher rate of in-hospital major adverse events including in-hospital

death, intracranial hemorrhage (1%), and reinfarction, despite more than twice as many patients in the tenecteplase group having an open infarct artery at the time of the first angiogram. This counterintuitive finding may have been due to the narrow window of potential benefit in STEMI (1–3 hours) which may have negated the restoration of flow effect on the ischemic myocardium. These patients were still exposed to the potential harm of thrombolysis, i.e. cerebral and myocardial hemorrhage, making the net effect unfavorable. The benefit/harm ratio may be different for stroke thrombolysis prior to thrombectomy.

The Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial compared pre-hospital intravenous tenecteplase (with concomitant antiplatelet and anticoagulant medicines) to primary PCI on arrival to a PCI-capable hospital, randomizing 1892 STEMI patients less than 3 hours from symptom onset who were unable to receive PCI within one hour of first medical contact. Eighty percent of the pre-hospital patients were randomized to treatment in the ambulance, the remainder at a referring community hospital. Patients in the tenecteplase group (pharmaco-invasive strategy) that did not have evidence of reperfusion by 90 minutes after fibrinolytic treatment by electrocardiographic or clinical criteria were given rescue PCI, but otherwise had their coronary arteriogram 6–24 hours after randomization. The median time from symptom onset to start treatment was 100 minutes for pre-hospital tenecteplase group and 178 minutes for the primary PCI group. Reperfusion criteria at 90 minutes after treatment were met by 63.7% of the tenecteplase group, in 86% of whom Thrombolysis in Myocardial Infarction (TIMI) grade flow of 2 or 3 was later observed on non-urgent angiogram, indicating complete filling of the distal coronary arterial bed. In the primary PCI group, TIMI 2 or 3 flow on the initial angiogram was found in only 30.6%. The pre-hospital tenecteplase group reported nominally fewer (12.4% to 14.3%) primary clinical composite endpoint events of all-cause death, cardiogenic shock, congestive heart failure, and reinfarction at 30 days, however, there were no significant differences on that outcome or on one-year all-cause mortality. Early in the trial an excess of intracranial hemorrhage was observed in patients 75 years or older treated with the standard 0.5mg/kg dose of tenecteplase. The protocol was amended lowering the dose to 0.25 mg/kg for those 75 and older, and no further intracranial hemorrhages occurred in that age group. The similarly designed STREAM-2 trial is comparing safety and efficacy of the pharmaco-invasive strategy at 0.25 mg/kg of tenecteplase to primary PCI in patients age 60 and greater.

Tenecteplase achieved regulatory approval in the US (TNKase; Genentech) and Europe (Metalyse; Boehringer Ingelheim) in the year 2000 as a tiered weight-based dose of 0.5 mg/kg to a maximum of 50 mg given as a 5–10 second bolus for the treatment of STEMI. Clinical

trials of tenecteplase for pulmonary embolism, for catheter clearance,' and for ischemic stroke (see below) have also been reported, but these are not currently FDA approved indications. A version of tenecteplase is marketed as a biosimilar in India for both STEMI and stroke indications under different commercial names and different doses, but in vitro studies from Boehringer Ingelheim reported less purity and reduced thrombolysis with that version, questioning its status as a biosimilar.

Tenecteplase (TNKase) in the treatment of acute myocardial infarction

Thrombolytic therapy versus primary angioplasty[4]

Acute myocardial infarction presenting with ST-segment elevation (STEMI) is usually precipitated by plaque disruption with coronary thrombosis. The quick recanalization by either thrombolysis (TBL) or primary angioplasty (P-PCI) is the most important way to improve the short- and long-term prognosis. Current American and European guidelines "prefer" P-PCI, usually believed to achieve better coronary recanalization rates, prevent re-infarction and, ultimately, improve survival. However, many conceptual and practical items dispute this presumed superiority of P-PCI.

Table 3. Reasons for preferring thrombolysis (TBL) to primary angioplasty (P-PCI)

TBL is immediately available everywhere
The time-delay to perform P-PCI exceeds 90 minutes in a large fraction of patients
P-PCI does not reduce mortality consistently, particularly vs pre-hospital TBL
TBL can be improved by new adjunctive treatments (clopidogrel and enoxaparin)

The claim that P-PCI leads to a mortality reduction has never been shown in any single trial and is only suggested by an overview of 23 small trials, with only 2 trials enrolling more than 1000 patients. Furthermore, this small advantage is no longer significant when the comparison is made with the accelerated infusion of alteplase. Too many times have we observed the failure of such positive small meta-analyses, such as those evaluating the effects of nitrates or magnesium in acute myocardial infarction, or the efficacy of angiotensin-II blockers to prevent atrial fibrillation, or the efficacy of aspirin to prevent eclampsia.

The frequently quoted mortality reduction observed in patients treated with P-PCI in registries is largely biased both by the incapacity of statistical methods, such as the propensity score, to take into account important, intangible confounders, and by the entry in the P-PCI cohort of only those patients actually being treated and not those patients intended to treat.

Currently, only 25% of American hospitals provide primary angioplasty and the majority of patients must be transferred to receive the mechanical intervention. As a consequence, only approximately 4% of transferred patients receive P-PCI within 90 minutes from first medical contact. Attempts to improve this situation so far have required "huge" efforts, with a negligible mortality yield. An increase in the number of catheterization laboratories has been proposed to cope with these shortcomings. However, such a proliferation dilutes the number of patients treated in each catheteriztion laboratory, endangering quality, not to say the costs of increasing population-based coronary angiograms in patients without myocardial infarction. Further difficulties arise during weekends and at night, again jeopardizing quality.

Pre-hospital thrombolytic therapy[4]

On the other hand, TBL can be delivered everywhere and particularly when used in the pre-hospital setting is extremely competitive with P-PCI, as demonstrated by the CAPTIM study. In the recent, important MINAP registry the pre-hospital use of TBL (nearly always TNKase) ranked among the strongest independent predictors of in-hospital survival in the United Kingdom.

The American College of Cardiology/American Heart Association guidelines encourage the recording of the 12-lead electrocardiogram "on-scene" and performing pre-hospital TBL within 30 minutes. Indeed, the STEMI picture is dominated by time, with the small incremental benefit of P-PCI rapidly vanishing after 90 minutes after first medical contact, particularly among young patients with large myocardial infarction, for whom the equivalence of TBL and P-PCI may already be achieved by a delay of only 45 minutes. Since time is so important, it is believed that most benefit may be achieved by treating as many patients as possible in the first 3 hours from the onset of symptoms, regardless of whether TBL or P-PCI is used. It is now estimated that an efficient network can offer pre-hospital TBL in the first 3 hours in approximately 50% to 60% of STEMI patients.

TBL can be further improved by reducing the re-infarction rate by adjunctive use of clopidogrel and enoxaparin as soon as possible, ideally pre-hospital.

Pharmacologic properties of TNKase in acute myocardial infarction[4]

TNKase consists of the alteplase molecule (with the exception of three point mutations) and has a molecular weight of 65,000 kD. Thr^{103} substitution by Asn and the mutation of the sequence Lys^{296} – His-Arg-Arg to Ala-Ala-Ala-Ala prolong the half-life and increase the resistance to plasminogen activator inhibitor-1 (PAI-1). Additional substitution of Asn^{117} by Gln results in an 8-fold decrease in clearance and in a 200-fold increase in resistance to PAI-1.

Compared with other molecules used in clinical practice, TNKase has the highest degree of fibrin specificity and binding. Fibrin specificity, in turn, implies a reduced propensity for causing major non-cerebral bleeds, because lytic activity is restricted to plasmin on the fibrin surface, thus avoiding the

breakdown of fibrinogen, factor V, factor VIII and α2-antiplasmin. The TNKase conformational change reduces its elimination and prolongs its plasma half-life (α-half-life 11–20 minutes, β-half-life 41–138 minutes). Nitrates do not appear to affect TNKase levels, as opposed to what happens with alteplase levels. Moreover, the inhibition by PAI-1 is reduced 80 times compared with alteplase.

The above properties are interesting in the treatment of patients with STEMI, allowing single bolus infusion and preventing drug inactivation at the site of platelet-rich coronary thrombosis. In addition, TNKase has more intense anti-platelet properties both in vitro and in vivo compared with those of alteplase. In experimental models the thrombolytic potency of TNKase is 3-fold higher than that of alteplase.

Clinical use of TNKase in acute myocardial infarction[4]

The first experience of dose-testing TNKase in STEMI began in the TIMI-10A trial, showing a dose-dependent increase in TIMI-3 flow rates in the 5 to 50 mg dose range ($p = 0.032$).

In the dose-escalating pilot TIMI 10B patency trial, involving 886 patients 18 to 80 years old, bolus TNKase injection achieved coronary TIMI grade-3 flow rates of 55%, 63% and 66% at 90 minutes after 30, 40 and 50 mg bolus injection. The TIMI-3 flow rate was similar to that observed in the control group, receiving front-loaded alteplase.

The safety of TNKase in STEMI was investigated in ASSENT-1; 3235 patients received either 30 or 40 or 50 mg TNKase as a bolus injection. The total stroke rate at 30 days was 1.5% and the intracranial hemorrhage (ICH) rate was 0.8%, without significant differences between groups. Serious bleeding, requiring blood transfusion, occurred in 1.4% of patients in the TNKase group and in 7% of those treated with front-loaded alteplase. Importantly, TIMI-10B and ASSENT-1 showed the importance of reducing the heparin dose in conjunction with TNKase, to minimize the risk of ICH.

Survival data with TNKase have been tested in comparison with those achieved using front-loaded alteplase in the large, multicenter, confirmation ASSENT-2 trial. A total of 16,949 patients with STEMI in the first 6 hours from the onset of symptoms received either weight-adjusted TNKase over 5 to 10 seconds (less than 60 kg: 30 mg; 60–69.9 kg: 35 mg; 70–79.9 kg: 40 mg; 80–89.9 kg: 45 mg; and more than 90 kg: 50 mg) or front-loaded alteplase, along with aspirin and reduced-dose unfractionated heparin. This was an equivalence trial and all-cause mortality at 30 days was the primary end-point. There was no difference between TNKase and alteplase in mortality (6.18% vs 6.15%) and stroke rate, including ICH (0.93% vs 0.94%, respectively). Moreover, in the TNKase group there was a decreased rate in non-cerebral bleeds (26.43% vs 28.95%, $p = 0.0003$), in major bleeds (4.68% vs 5.94%, $p = 0.0002$) and in the need for blood transfusion (4.25% vs 5.49%, $p = 0.0002$). There was also a tendency for ICH to be decreased by TNKase among the high-risk population of females of more than 75 years old who weighed <67 kg (1.14% vs 3.02%). The general ASSENT-2 trial results were confirmed in all major subgroups, including those related to age, gender, infarct location, Killip class and diabetes status. Interestingly, mortality was significantly lower in the TNKase group when treatment was given more

than 4 hours after the onset of symptoms (7.0% vs 9.2%, p = 0.018), a finding that could be attributed to the drug's fibrin specificity leading to better dissolution of older coronary clots and confirms from a clinical standpoint the improved pharmacologic profile of this molecule.

Table 4. Clinical studies with TNKase in STEMI

Trial (year)	Patients	Comparison	Main findings
ASSENT-2 (1999)	16,949	TNKase vs rt-PA	TNKase and rt-PA equivalent, ↓ major bleeding with TNKase
ASSENT-3 (2001)	6,095	ENOX vs ABX vs UFH[a]	ENOX and ABX better than UFH
ENTIRE-TIMI 23 (2002)	483	ENOX vs ABX vs UFH[a]	ENOX and ABX better than UFH, ↑ bleeding with ABX
ASSENT-3-PLUS (2003)	1,639	ENOX vs UFH[a], pre-hospital delivery	↓ reinfarction with ENOX, ↑ stroke/intracranial bleed
CAPITAL-AMI (2005)	170	F-PCI[c] vs TNKase[a]	↓ residual ischemia with F-PCI
ASSENT-4 (2006)	1,667	F-PCI[c] vs P-PCI[b]	↑ death/ischemia/bleeding in the F-PCI group
WEST (2006)	304	TNKase vs F-PCI[c] vs P-PCI	TNKase and F-PCI comparable to P-PCI
GRACIA-2 (2007)	212	TNKase[d] vs P-PCI	↑ reperfusion with TNKase Similar ventricular damage

Among other in-hospital outcomes, TNKase also reduced the rate of congestive heart failure (ie, Killip class >1: 6.1% vs 7.0%, p = 0.025).

Thus, the ASSENT-2 trial indicates that single-bolus TNKase is equivalent to the more complex accelerated alteplase infusion, in terms of mortality and mortality/stroke combination, with the further advantage of a decrease in major bleeding rate. These positive results were persisting after 1 year.

TNKase and the adjunctive use of antithrombotic therapy and of mechanical intervention

The possibility of further improving the effects of TNKase by means of new adjunctive treatments has been explored in ASSENT-3 and ENTIRE-TIMI 23 studies. In ASSENT-3 a total of 6095 patients with STEMI in the first 6 hours from the onset of symptoms were treated with either full-dose TNKase plus unfractionated heparin (UFH), full-dose TNKase plus enoxaparin (ENOX), or half-dose TNKase plus UFH and the GPIIB-IIIA inhibitor abciximab (ABX). Compared with UFH, the primary end-point (30-day mortality plus in-hospital reinfarction and in-hospital refractory ischemia) was reduced by ENOX

(11.4% vs 15.4%, p = 0.0002) and by the combination of UFH plus ABX (11.1%, p = 0.0001). When in-hospital ICH or major bleeds were added to the primary end-point (so called efficacy plus safety end-point), again, a significant reduction was observed both in the ENOX group (13.7% vs 17.0%, p = 0.0037) and in the UFH plus ABX group (14.2%, p = 0.01416). ABX increased the rate of thrombocytopenia compared to both ENOX and UFH (3.2% vs 1.2% and 1.3% respectively, p = 0.0001) and it also increased the cost of treatment.

Similar results were observed in the smaller ENTIRE-TIMI 23 trial. This trial had a design very similar to that of ASSENT-3, although there was a further group receiving ENOX in combination with ABX and half-dose TNKase. Overall, the adjunctive use of ENOX with TNKase, compared with UFH, reduced the combined incidence of death/myocardial infarction at 30 days (4.4% vs 15.9%, p = 0.005). ABX did not further decrease the end-point; rather, ABX increased the risk of major bleeding (5.2% vs 2.4% compared with UFH alone and 8.5% vs 1.9% compared with ENOX alone). Major bleeding was also increased when half-dose TNKase was combined with eptifibatide, a small-molecule GP IIB-IIIA inhibitor in the INTEGRITI study. In conjunction with the GUSTO-V data, ASSENT-3, ENTIRE-TIMI-23 and INTEGRITI indicate that GPIIB-IIIA agents should not be associated with thrombolytic drugs. In conclusion, ASSENT-3 and ENTIRE-TIMI 23 showed that a much simpler thrombolytic regimen is feasible, permitting bolus administration of both TNKase and of adjunctive low-molecular-weight heparin.

This new regimen was tested in the pre-hospital phase of STEMI treatment in the ASSENT-3-PLUS study. In this trial, after electrocardiographic confirmation was obtained in the field, 1639 patients were treated with TNKase and randomly allocated to ENOX or UFH adjunctive treatment. Of interest, 53% of patients could be treated in the first 2 hours, a much higher proportion compared with that observed in previous studies. In the pre-hospital setting ENOX tended to reduce the composite of 30-day mortality or in-hospital reinfarction or in-hospital refractory ischemia (14.2% vs 17.4%, p = 0.08), but there was no difference in the efficacy plus safety end-point, also including the rate of ICH or major bleeding (18.3% vs 20.3%, p = NS). ENOX reduced the reinfarction rate (3.5% vs 5.8%, p = 0.028), but increased the rate of total stroke (2.9% vs 1.3%, p = 0.026) and of ICH (2.20% vs 0.97%, p = 0.047). The increase in ICH occurred in the group of patients more than 75 years old. A pre-specified pooled analysis of data from ASSENT-3 and ASSENT-3-PLUS trials largely confirmed the utility of using ENOX instead of UFH in conjunction with TNKase, reducing the primary efficacy end-point (composite of death, reinfarction and refractory ischemia) from 16.0% to 12.2%, p < 0.001 and the primary efficacy plus safety (ICH or major bleeding) end-point from 18.0% to 15.0%, p = 0.003. Among the 1049 patients who required urgent revascularization the ENOX beneficial effect was even larger (15.4% vs 10.1%, p = 0.013). The excess in stroke rates observed with ENOX (1.3% vs 0.9%), although not significant, was mainly due to an excess in ICH among women of more than 75 years old in ASSENT-3-PLUS.

Following these observations, the intravenous bolus of ENOX was omitted and the maintenance dose was reduced by 25% in patients of more than 75 years old in the large definitive confirmation EXTRACT-TIMI 25 trial.

The role of the routine, immediate use of coronary angioplasty (so called "facilitated" angioplasty, F-PCI) after treatment with TNKase was first explored in CAPITAL-AMI. This was a small study randomizing 170 high-risk STEMI patients treated with TNKase toward immediate revascularization by PCI or to conservative management. The primary end-point was the composite of death, reinfarction, recurrent unstable ischemia, or stroke at 6 months. The median time from the onset of symptoms to TNKase administration was 120 minutes and the median time from symptoms to balloon inflation 204 minutes. Overall, the primary end-point was reduced by immediate PCI from 24.4% to 11.6% ($p = 0.04$), a result driven mainly by the reduction in the rate of recurrent unstable ischemia ($p = 0.03$). There were no differences in death, reinfarction, stroke or major bleeding.

These encouraging results stimulated the planning of the larger ASSENT-4 PCI trial, a trial designed to investigate whether TNKase facilitation would improve the prognosis of patients for whom a time-delay of 1 to 3 hours before P-PCI was anticipated. The trial design was open-label and the primary end-point was the composite of death or congestive heart failure or shock within 90 days. Only 1667 of the originally planned 4000 patients were enrolled, because the trial was prematurely interrupted by the data and safety monitoring board for an excess of in-hospital mortality in the group where P-PCI was facilitated by TNKase (6% vs 3%, $p = 0.0105$). The median time from TNKase injection to first balloon inflation was 104 minutes. A TIMI-3 flow was achieved before P-PCI in 43% of TNKase-treated patients and in 15% of patients in the control group ($p < 0.0001$). The primary end-point at 90 days was increased in the facilitated group (19% vs 13%, $p = 0.0045$), along with the stroke rate (1.8% vs 0%, $p < 0.0001$). These disappointing results have been attributed, in retrospect, to an alleged pro-thrombotic effect of TBL and, more convincingly, to the risk of creating an intra-plaque hemorrhage by inflating the balloon in the first 2 hours after TBL (ie, in a lytic state). In retrospect, the risk of death at 90 days was reduced by TNKase facilitation when patients were randomized in ambulance (relative risk 0.74, 95% CI 0.24–2.30) and mostly increased when patients were recruited in P-PCI capable hospitals (relative risk 1.62, 95% CI 0.94–2.81). These observation raise important methodological issues about ASSENT-4 PCI, since 45% patients were actually enrolled in P-PCI capable hospital, a design not exactly germane as to define what is the best strategy for the treatment of patients at the earliest point of care, particularly in the pre-hospital setting. This holds true particularly when considering that the trial was open-label.

More pertinent to investigating the role of TNKase facilitation is the WEST study, a randomized, open-label, feasibility study of 304 STEMI patients enrolled in the community (40% enrolled pre-hospital). All patients received aspirin and ENOX and were randomized to either TNKase, or to TNKase followed by PCI within 24 hours (including rescue PCI for reperfusion failure) or to P-PCI. The time from the onset of symptoms to randomization was 113, 130 and 176 minutes respectively. There were no

differences between the three groups in the primary composite of death or reinfarction, refractory ischemia, congestive heart failure, cardiogenic shock or major ventricular arrhythmia (25% vs 24% vs 23%, p = NS). In the group receiving plain TNKase there was a higher rate of the death/reinfarction combination (13.0% vs 6.7% vs 4.0%, p = 0.021), but not of death (4.0% vs 1.0% vs 1.0%, p = NS).

Thus, the WEST trial confirms the data from CAPTIM: when delivered very rapidly, possibly in the pre-hospital phase, TNKase is very competitive with P-PCI and may offer a very simple and effective treatment, particularly if subsequent PCI is offered to those patients with recurrent ischemia or deemed at high clinical risk.

TNKase followed by early routine PCI (within 3–12 hours, so called "pharmaco-invasive" approach) has been compared with P-PCI in 212 patients enrolled in the GRACIA-2 study. This is a non-inferiority trial designed to evaluate whether a lytic strategy represents a reasonable option for STEMI patients, irrespective of geographic or logistic barriers, when compared with P-PCI. The primary end-points were epicardial and myocardial reperfusion and the extent of left ventricular damage (as assessed by infarct size and left ventricular function). Complete ST-segment resolution at the electrocardiogram was observed more frequently in the TNKase group (61% vs 43%, p = 0.01), implying an improved myocardial perfusion (as measured by the TIMI myocardial perfusion grade at 60 minutes). Infarct size and left ventricular ejection fraction were similar in the two groups.

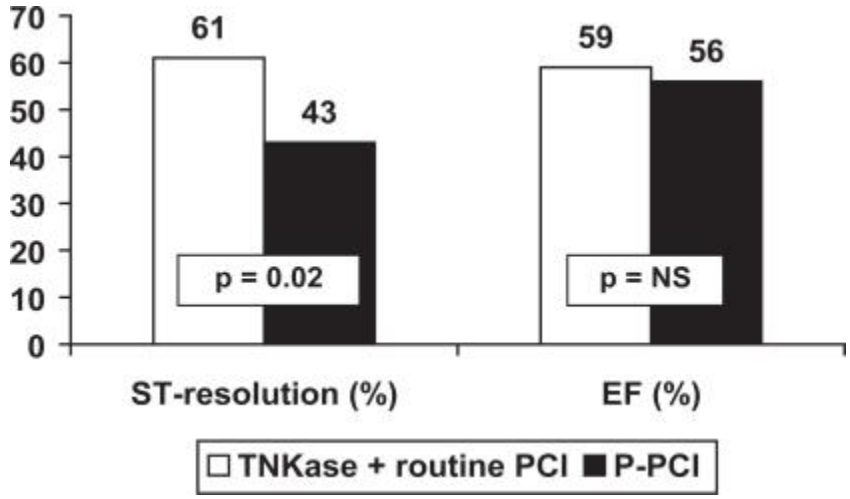


Fig 2: ST-segment complete resolution after PCI and left ventricular ejection fraction in GRACIA-2.[4]

Table 5. Reasons for using TNKase in STEMI patients[4]

TNKase is the most fibrin-specific thrombolytic agent available
TNKase may be injected by single intravenous bolus in 5–10 seconds
TNKase is as effective as accelerated rt-PA, but with less major bleeding
Pre-hospital TNKase (with rescue/routine PCI) seems as effective as primary angioplasty

Table 6. How to use TNKase in STEMI patients[4]

Bolus intravenous injection of TNKase over 5–10 seconds
TNKase dose according to body weight (BW)
30 mg if BW <60.0 kg
35 mg if BW between 60.0 and 69.9 kg
40 mg if BW between 70.0 and 79.9 kg
45 mg if BW between 80.0 and 89.9 kg
50 mg if BW ≥90.0 kg
Adjunctive anti-platelet therapy
Aspirin: 160–325 mg, followed by 75–162 mg per day, indefinitely
Clopidogrel: 75 mg per day (for at least 28 days if no stenting, 1 month
if using a bare metal stent, 1 year if using a drug eluting stent)
Initial clopidogrel dose: 300 mg if age ≤75 or if a stent is implanted
Adjunctive unfractionated heparin
Intravenous bolus: 60 U per kg (maximum 4000 U)
Intravenous infusion: 12 U per kg per hour (maximum 1000 U per hour)
Target activated partial thromboplastin time: 1.5–2.0 control
Treatment duration: minimum 48 hours
Adjunctive enoxaparin (only if serum creatinine <2.5 mg/dL in men, <2.0 in women):
Less than 75 years old: Intravenous bolus of 30 mg
Less than 75 years old: Subcutaneous injection of 1 mg/kg every 12 hours
At least 75 years old: No intravenous bolus
At least 75 years old: Subcutaneous injection of 0.75 mg/kg every 12 hours
If the creatinine clearance is <30 mL/min: subcutaneous injection every 24 hours
Treatment duration: for the duration of index hospitalization, up to 8 days
For patients undergoing PCI after TNKase
If on unfractionated heparin: additional boluses as needed
If on enoxaparin: no further anticoagulant if <8 hours from the subcutaneous injection
If on enoxaparin: additional intravenous bolus of 0.3 mg/kg if 8–12 hours
after the subcutaneous injection

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Survey Form

1. How often do you prescribe Tenecteplase for patients with acute coronary syndromes (ACS)?

a) Always

b) Often

c) Sometimes

d) Rarely

2. In your experience, what is the primary indication for using Tenecteplase in ACS?

a) STEMI (ST-Elevation Myocardial Infarction)

b) NSTEMI (Non-ST-Elevation Myocardial Infarction)

c) Unstable Angina

d) Cardiogenic Shock

3. Which diagnostic tool do you find most reliable in assessing the success of Tenecteplase therapy in ACS?

a) Cardiac biomarkers (e.g., Troponin)

b) ECG

c) Echocardiogram

d) Angiography

4. What is your primary goal in treating ACS with Tenecteplase?

a) Rapid reperfusion

b) Symptom relief

c) Preventing complications

d) Improving long-term survival

5. How often do you encounter bleeding complications with Tenecteplase therapy in ACS?

a) Never

b) Rarely

c) Occasionally

d) Frequently

6. In your experience, what is the average time to reperfusion with Tenecteplase in ACS patients?

a) Less than 30 minutes

b) 30-60 minutes

c) 60-90 minutes

d) More than 90 minutes

7. What is the typical duration of hospitalization for ACS patients treated with Tenecteplase?

a) Less than 3 days

b) 3-5 days

c) 5-7 days

d) More than 7 days

8. How do you monitor the effectiveness of Tenecteplase in your patients?

a) ECG changes

b) Clinical symptoms

c) Biomarkers (e.g., Troponin)

d) All of the above

9. What do you consider the most significant advantage of Tenecteplase over other thrombolytics?

a) Single bolus administration

b) Faster action

c) Lower cost

d) Fewer side effects

10. In your practice, what percentage of ACS patients receive Tenecteplase?

a) Less than 25%

b) 25-50%

c) 51-75%

d) More than 75%

11. How do you decide between Tenecteplase and percutaneous coronary intervention (PCI) for ACS?

a) Patient's clinical stability

b) Time since symptom onset

c) Availability of PCI facilities

d) All of the above

12. How often do you use Tenecteplase in combination with antiplatelet therapy for ACS?

a) Always

b) Often

c) Sometimes

d) Rarely

13. What is your preferred antiplatelet therapy to combine with Tenecteplase?

a) Aspirin

b) Clopidogrel

c) Prasugrel

d) Ticagrelor

14. How do you assess the risk of re-thrombosis in patients treated with Tenecteplase?

a) Regular follow-up ECGs

b) Biomarker monitoring

c) Clinical symptom assessment

d) All of the above

15. How frequently do you recommend follow-up echocardiograms for patients treated with Tenecteplase?

a) Within 24 hours

b) Within one week

c) Within one month

d) Only if symptoms persist

Survey Findings

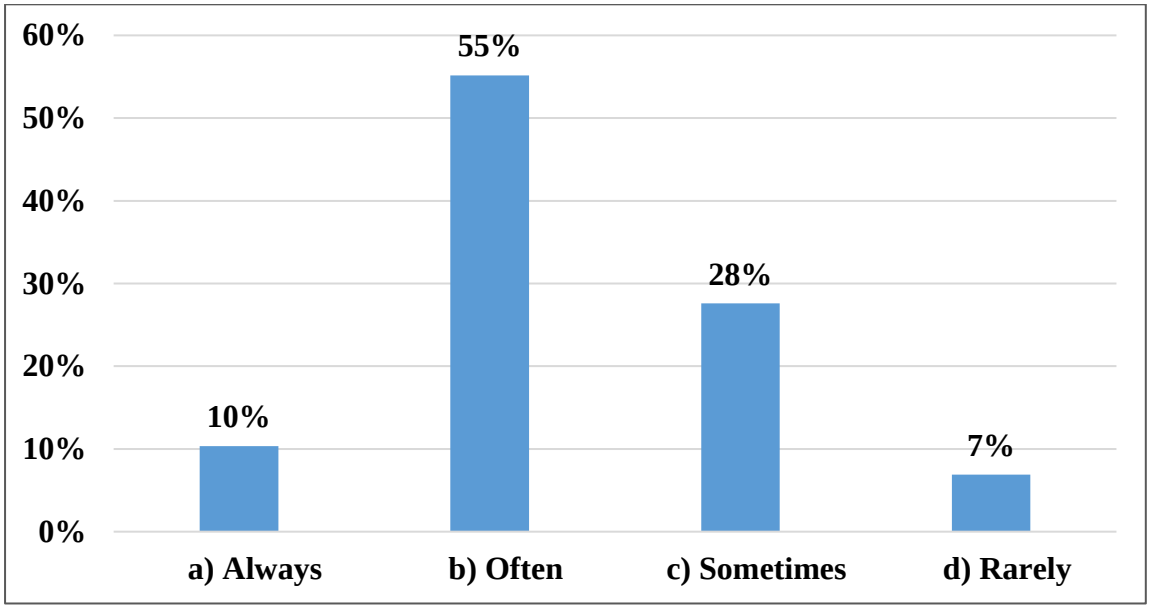
1. How often do you prescribe Tenecteplase for patients with acute coronary syndromes (ACS)?

a) Always

b) Often

c) Sometimes

d) Rarely



55% of doctors often prescribe Tenecteplase for patients with acute coronary syndromes (ACS).

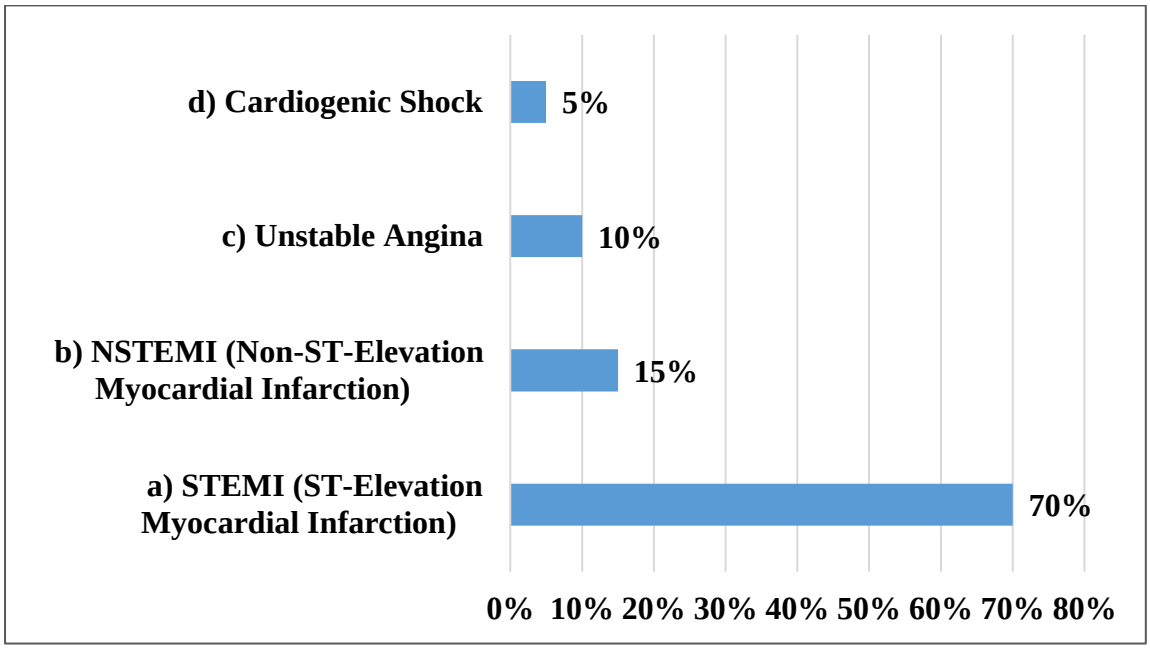
2. In your experience, what is the primary indication for using Tenecteplase in ACS?

a) STEMI (ST-Elevation Myocardial Infarction)

b) NSTEMI (Non-ST-Elevation Myocardial Infarction)

c) Unstable Angina

d) Cardiogenic Shock



According to majority of doctors, 70%, STEMI (ST-Elevation Myocardial Infarction) is the primary indication for using Tenecteplase in ACS.

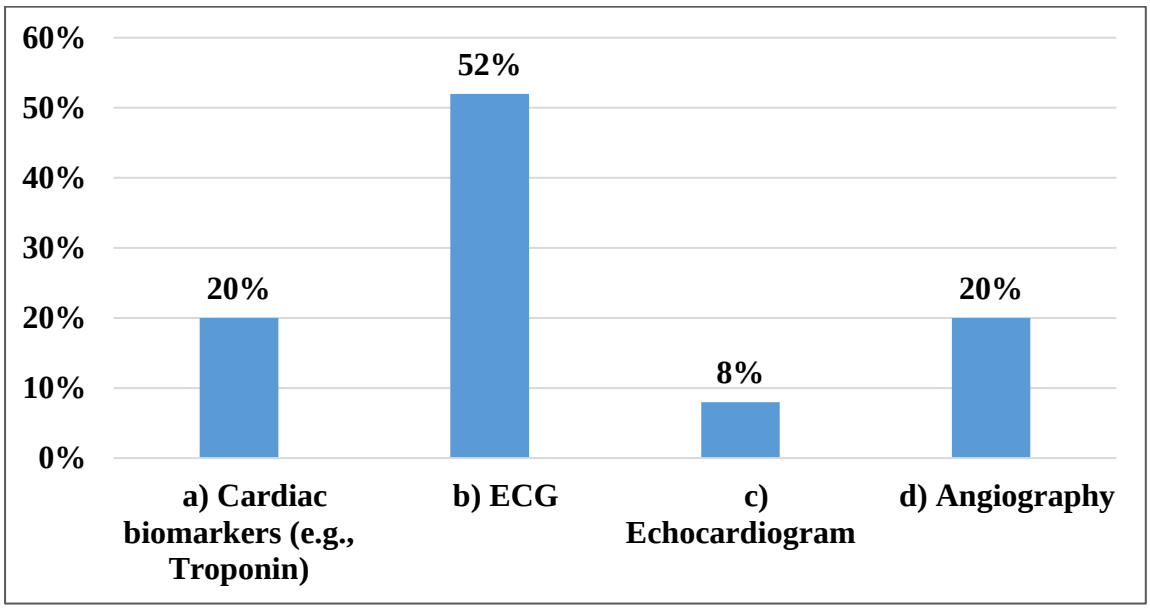
3. Which diagnostic tool do you find most reliable in assessing the success of Tenecteplase therapy in ACS?

a) Cardiac biomarkers (e.g., Troponin)

b) ECG

c) Echocardiogram

d) Angiography



As per 52% of doctors, they find ECG the most reliable diagnostic tool in assessing the success of Tenecteplase therapy in ACS.

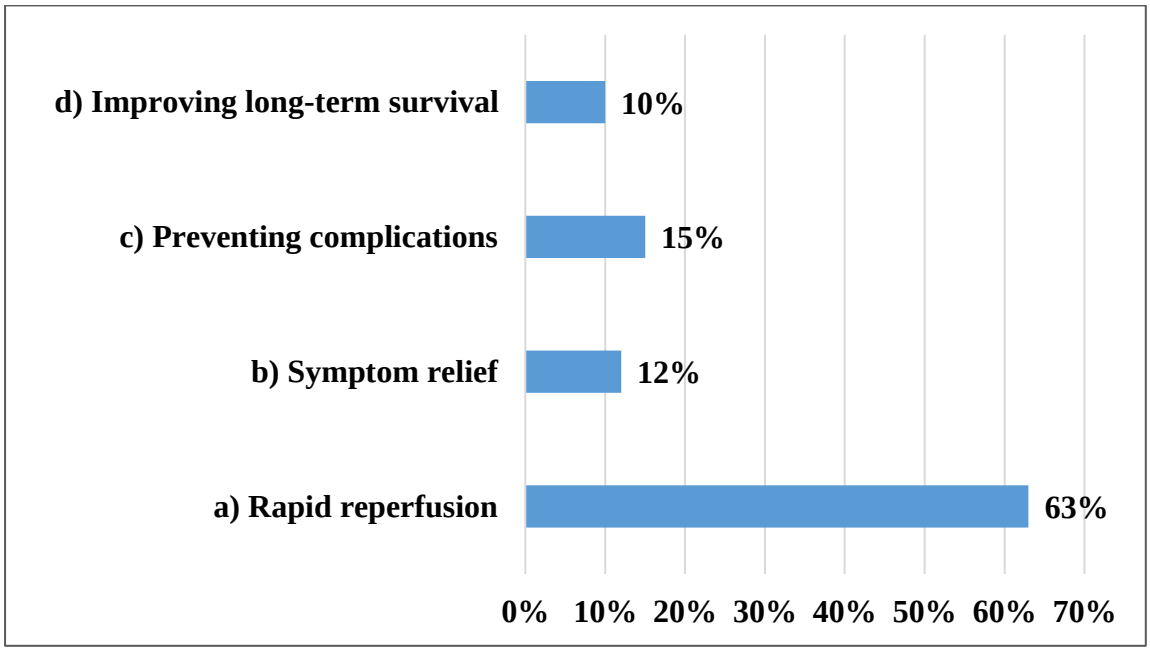
4. What is your primary goal in treating ACS with Tenecteplase?

a) Rapid reperfusion

b) Symptom relief

c) Preventing complications

d) Improving long-term survival



As per 63% of doctors, their primary goal in treating ACS with Tenecteplase is rapid reperfusion.

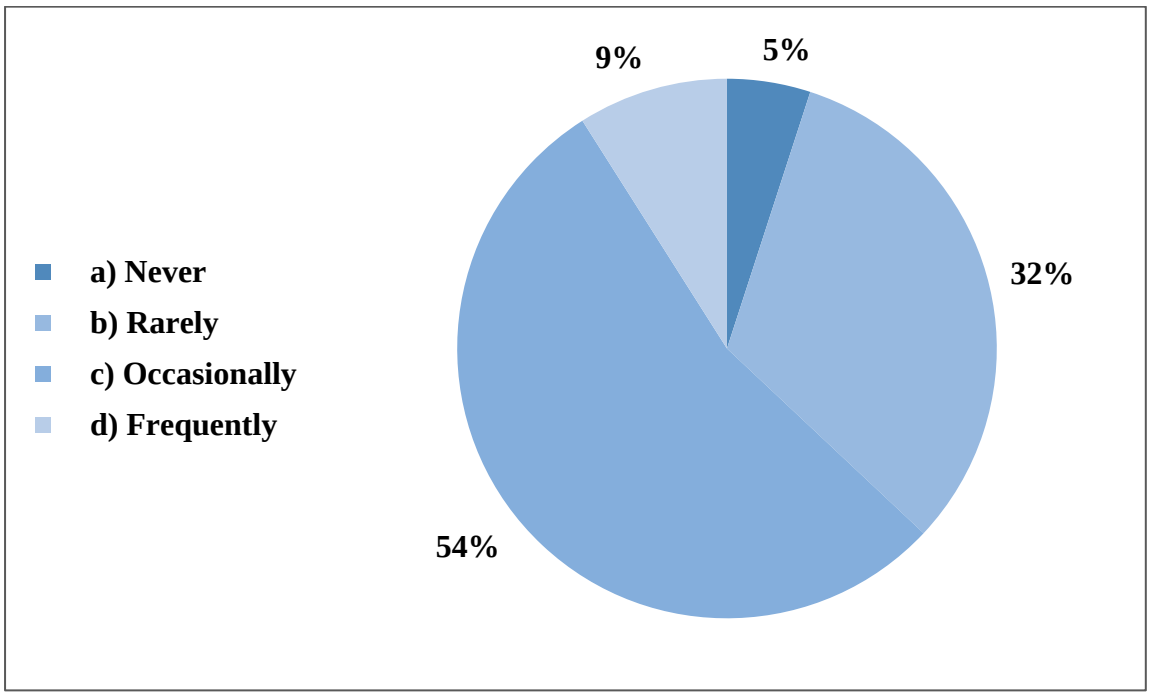
5. How often do you encounter bleeding complications with Tenecteplase therapy in ACS?

a) Never

b) Rarely

c) Occasionally

d) Frequently



54% of doctors occasionally encounter bleeding complications with Tenecteplase therapy in ACS.

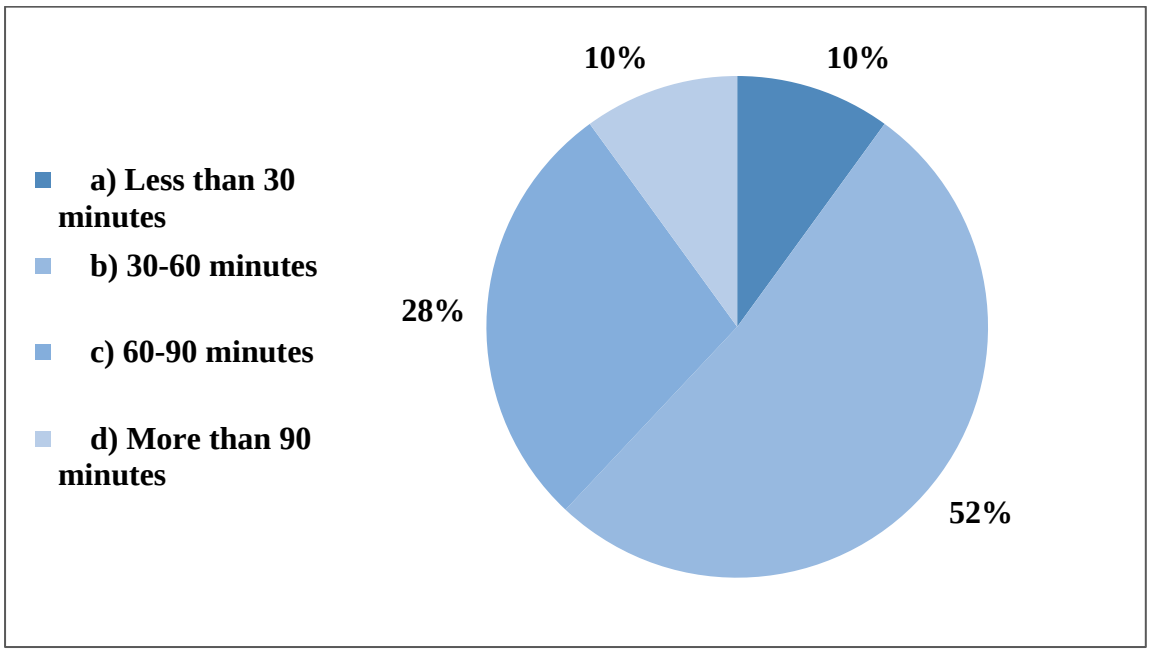
6. In your experience, what is the average time to reperfusion with Tenecteplase in ACS patients?

a) Less than 30 minutes

b) 30-60 minutes

c) 60-90 minutes

d) More than 90 minutes



According to 52% of doctors, the average time to reperfusion with Tenecteplase in ACS patients is 30-60 minutes.

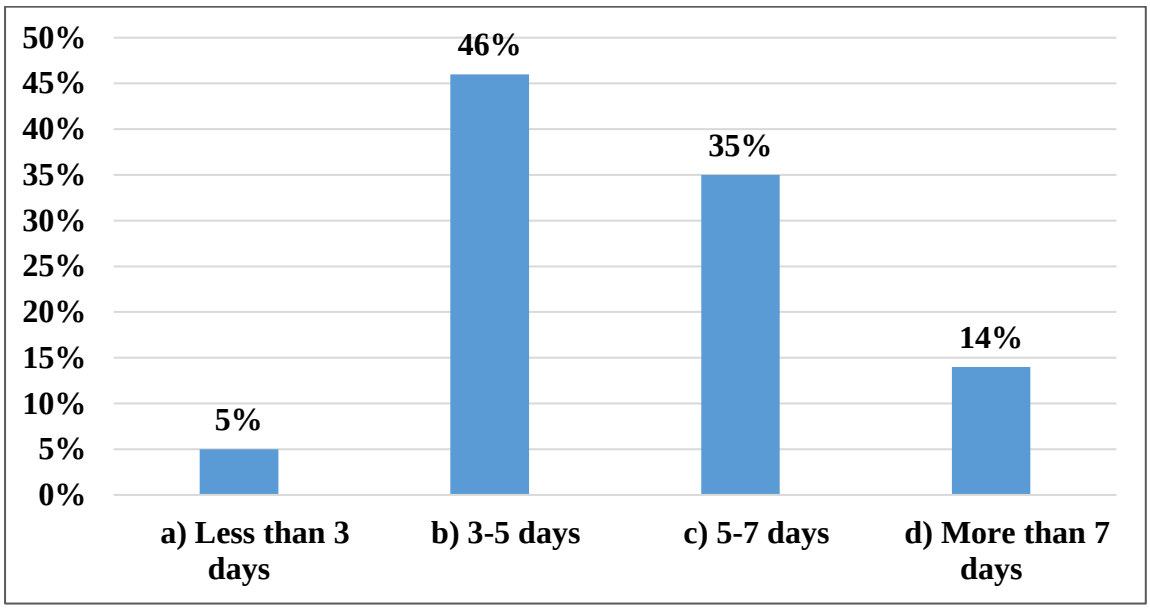
7. What is the typical duration of hospitalization for ACS patients treated with Tenecteplase?

a) Less than 3 days

b) 3-5 days

c) 5-7 days

d) More than 7 days



As per 46% of doctors, the typical duration of hospitalization for ACS patients treated with Tenecteplase is 3-5 days.

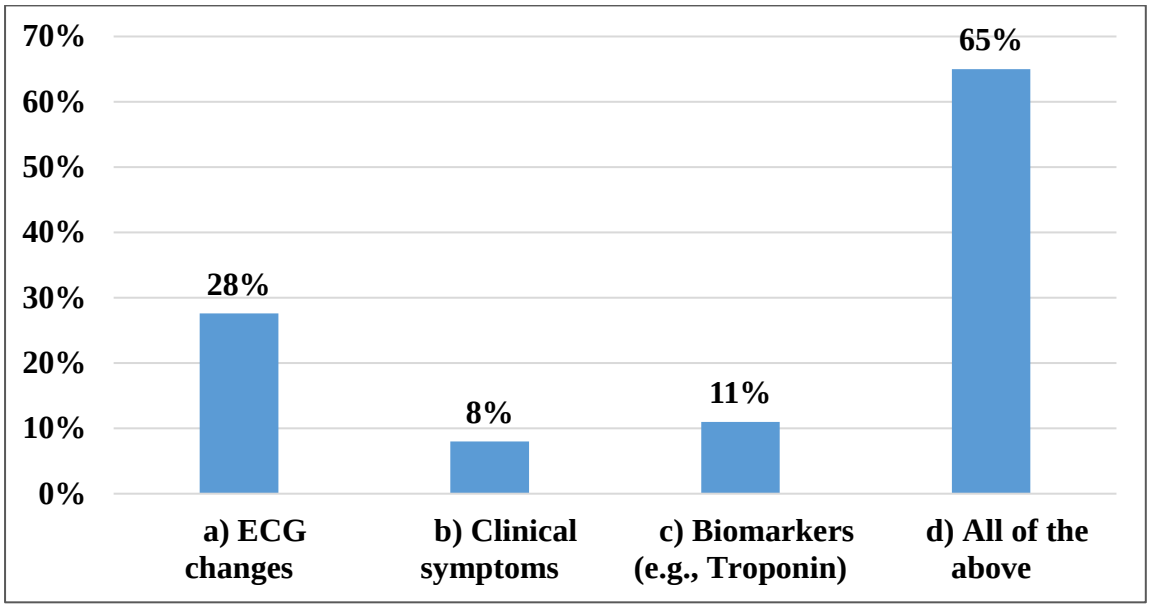
8. How do you monitor the effectiveness of Tenecteplase in your patients?

a) ECG changes

b) Clinical symptoms

c) Biomarkers (e.g., Troponin)

d) All of the above



Majority of doctors, 65%, monitor the effectiveness of Tenecteplase in their patients through ECG changes, clinical symptoms and biomarkers (e.g., Troponin).

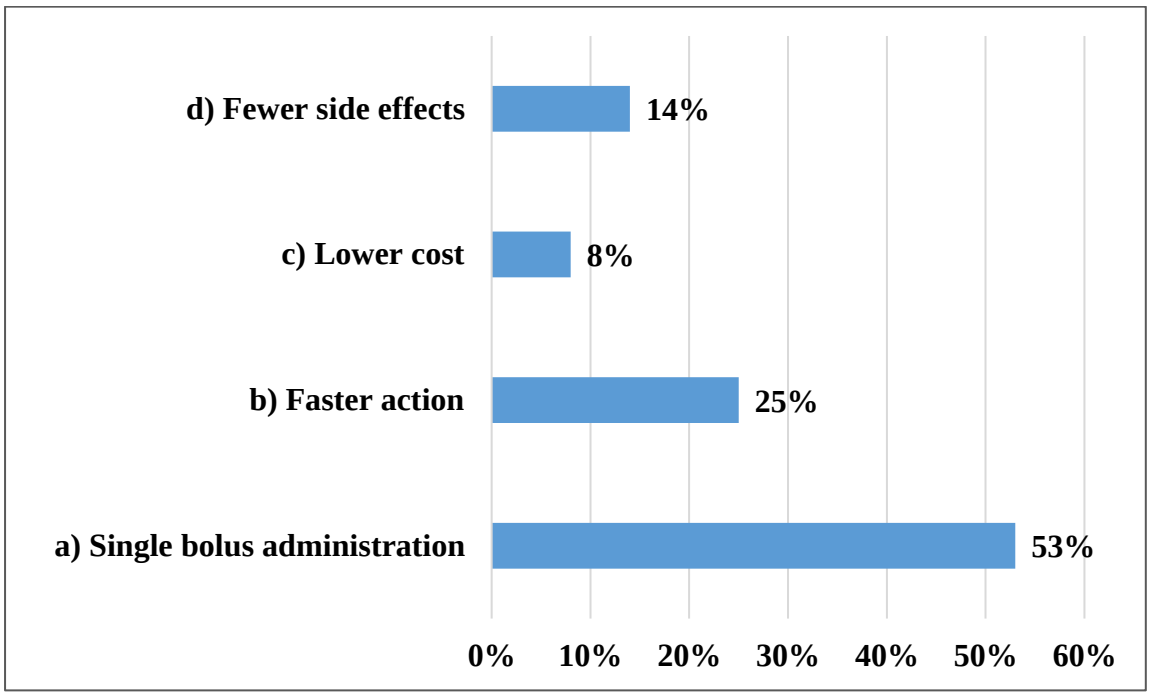
9. What do you consider the most significant advantage of Tenecteplase over other thrombolytics?

a) Single bolus administration

b) Faster action

c) Lower cost

d) Fewer side effects



5#% of doctors consider single bolus administration to be the most significant advantage of Tenecteplase over other thrombolytics.

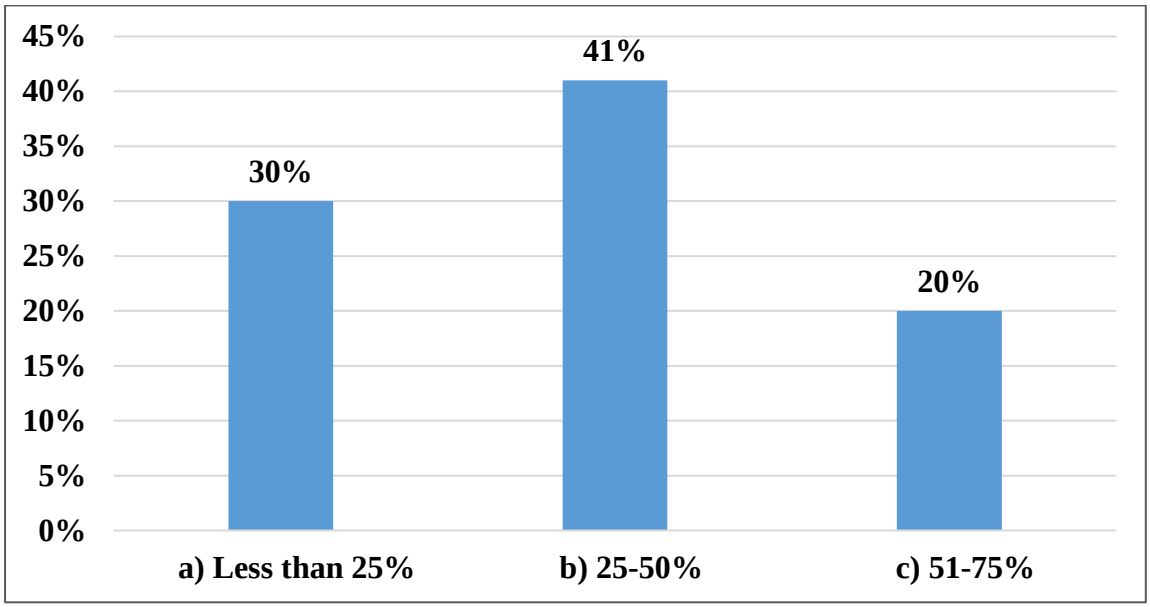
10. In your practice, what percentage of ACS patients receive Tenecteplase?

a) Less than 25%

b) 25-50%

c) 51-75%

d) More than 75%



In the practice of 41% of doctors, 25-50% of ACS patients receive Tenecteplase.

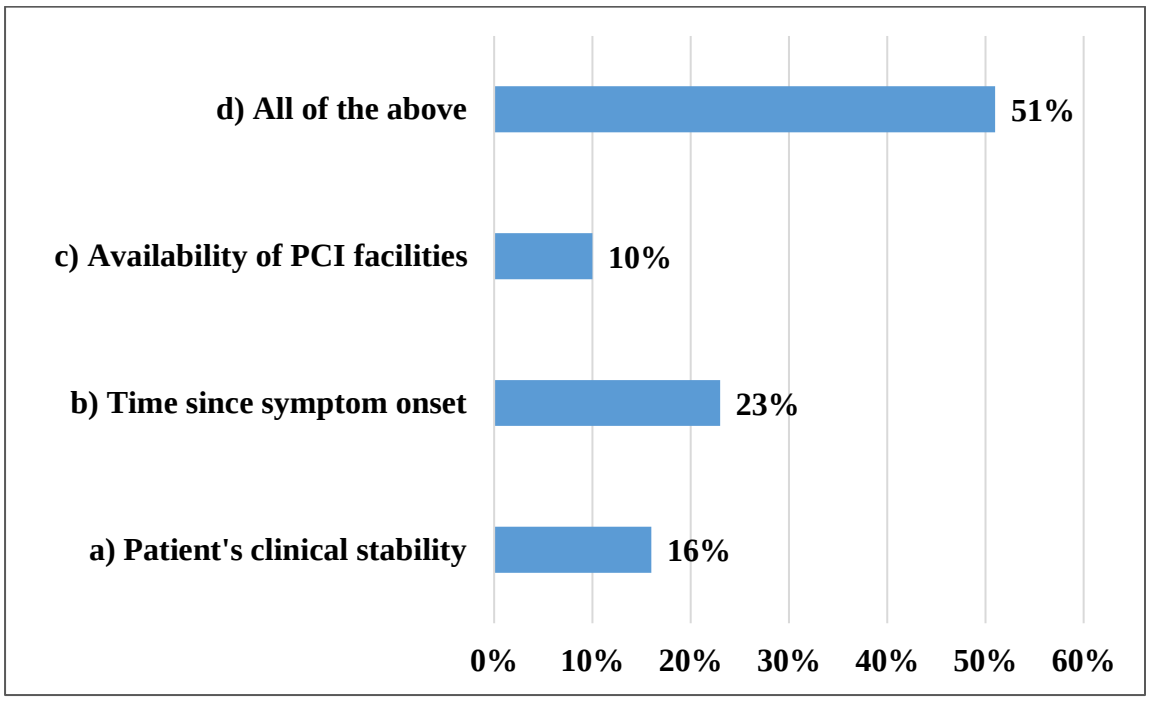
11. How do you decide between Tenecteplase and percutaneous coronary intervention (PCI) for ACS?

a) Patient's clinical stability

b) Time since symptom onset

c) Availability of PCI facilities

d) All of the above



51% of doctors decide between Tenecteplase and percutaneous coronary intervention (PCI) for ACS based on patient's clinical stability, time since symptom onset and availability of PCI facilities.

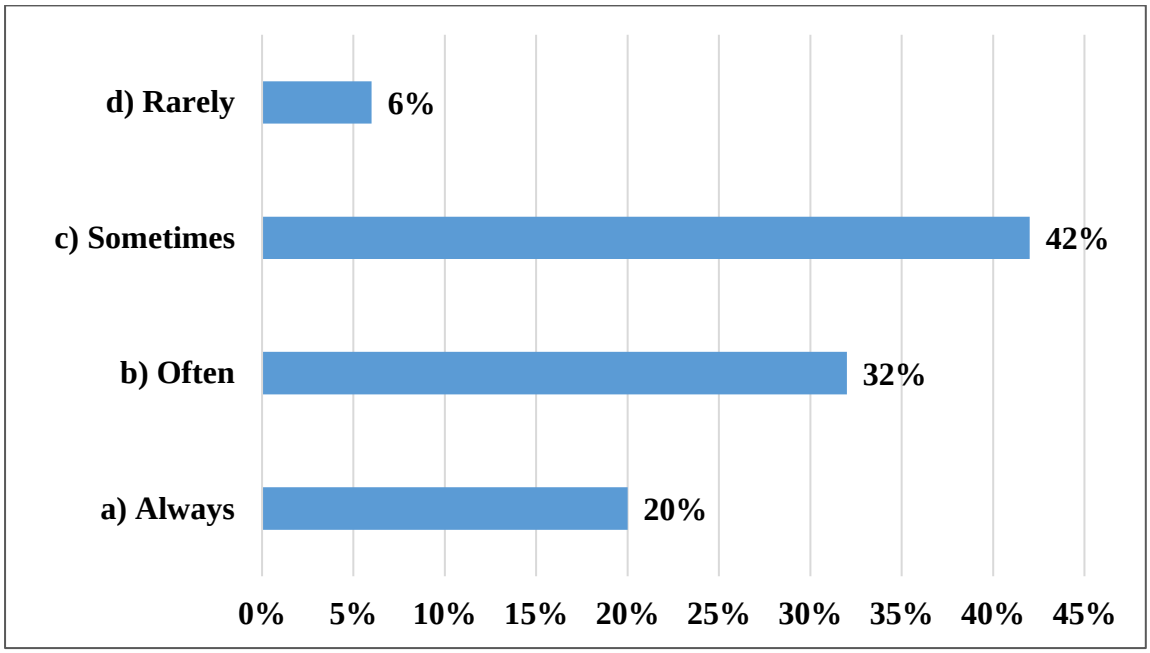
12. How often do you use Tenecteplase in combination with antiplatelet therapy for ACS?

a) Always

b) Often

c) Sometimes

d) Rarely



42% of doctors sometimes use Tenecteplase in combination with antiplatelet therapy for ACS.

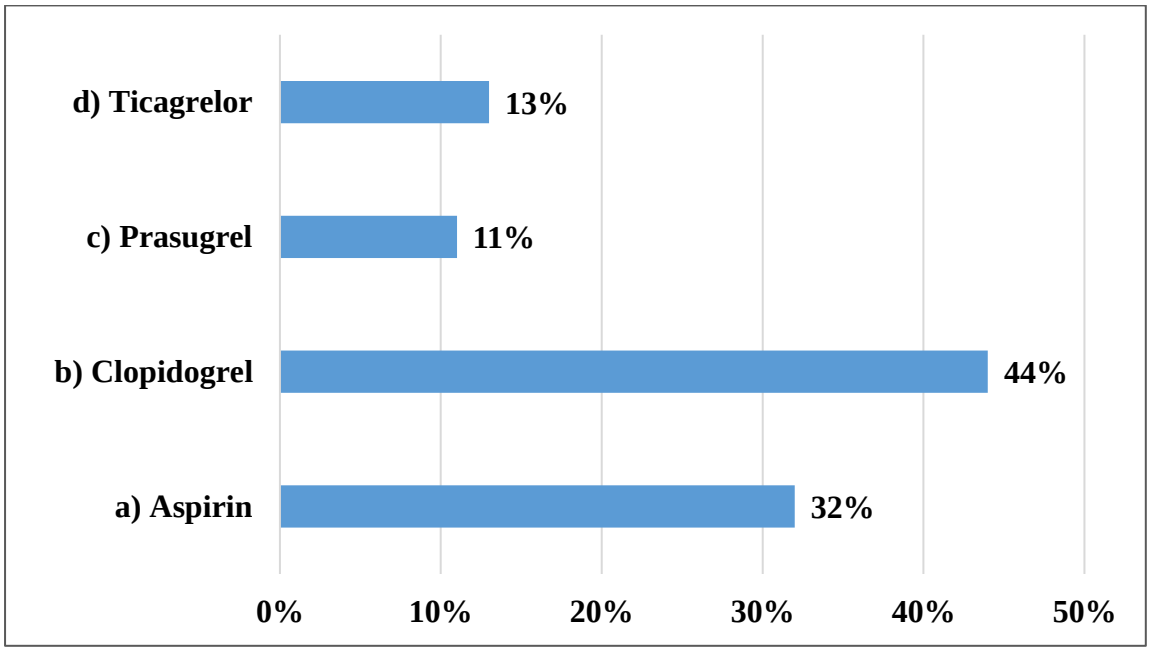
13. What is your preferred antiplatelet therapy to combine with Tenecteplase?

a) Aspirin

b) Clopidogrel

c) Prasugrel

d) Ticagrelor



According to 44% of doctors, their preferred antiplatelet therapy to combine with Tenecteplase is Clopidogrel.

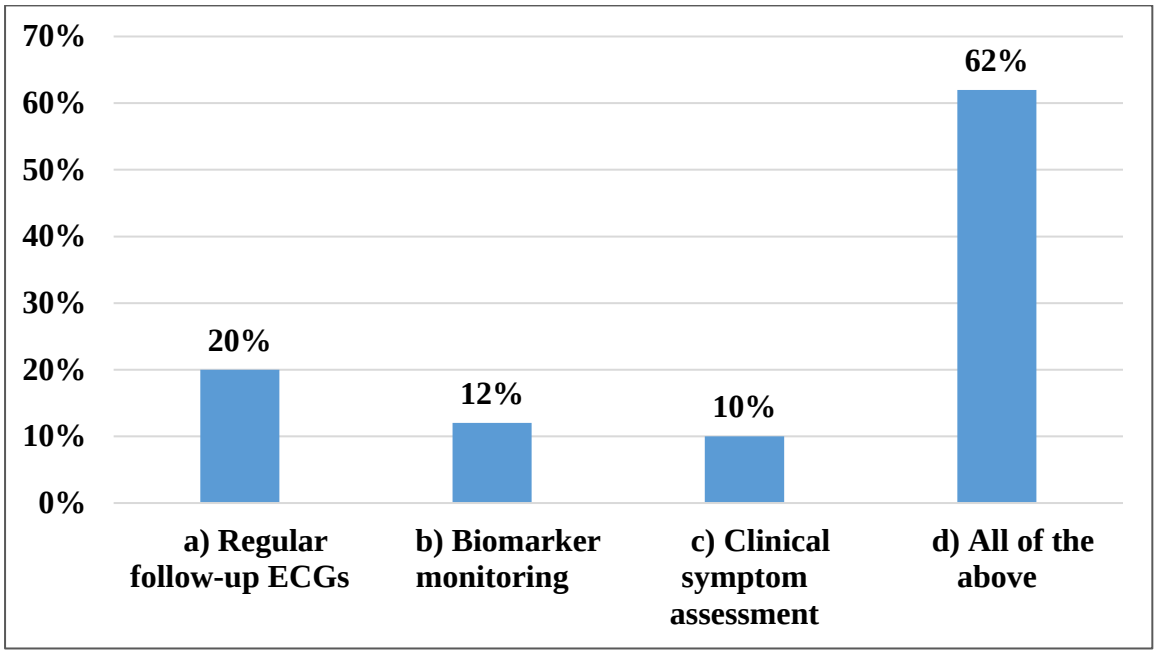
14. How do you assess the risk of re-thrombosis in patients treated with Tenecteplase?

a) Regular follow-up ECGs

b) Biomarker monitoring

c) Clinical symptom assessment

d) All of the above



According to 62% of doctors, they assess the risk of re-thrombosis in patients treated with Tenecteplase by regular follow-up ECGs, biomarker monitoring, clinical symptom assessment.

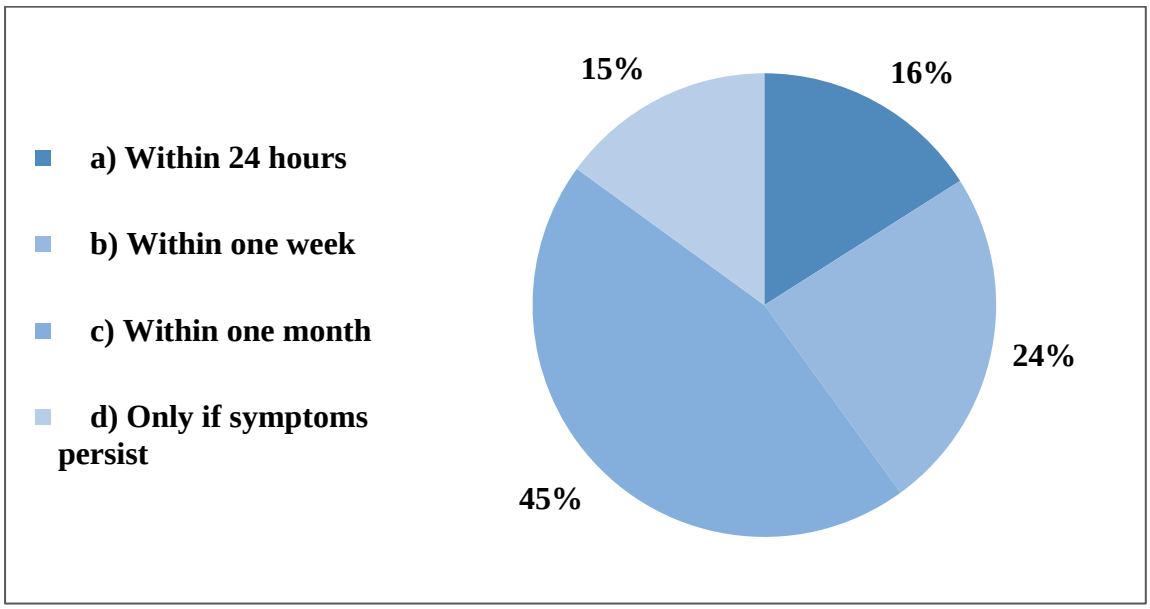
15. How frequently do you recommend follow-up echocardiograms for patients treated with Tenecteplase?

a) Within 24 hours

b) Within one week

c) Within one month

d) Only if symptoms persist



As per 45% of doctors, they recommend follow-up echocardiograms for patients treated with Tenecteplase within one month.

Summary

- 55% of doctors often prescribe Tenecteplase for patients with acute coronary syndromes (ACS).
- According to majority of doctors, 70%, STEMI (ST-Elevation Myocardial Infarction) is the primary indication for using Tenecteplase in ACS.
- As per 52% of doctors, they find ECG the most reliable diagnostic tool in assessing the success of Tenecteplase therapy in ACS.
- As per 63% of doctors, their primary goal in treating ACS with Tenecteplase is rapid reperfusion.
- 54% of doctors occasionally encounter bleeding complications with Tenecteplase therapy in ACS.
- According to 52% of doctors, the average time to reperfusion with Tenecteplase in ACS patients is 30-60 minutes
- As per 46% of doctors, the typical duration of hospitalization for ACS patients treated with Tenecteplase is 3-5 days.
- Majority of doctors, 65%, monitor the effectiveness of Tenecteplase in their patients through ECG changes, clinical symptoms and biomarkers (e.g., Troponin).
- 5#% of doctors consider single bolus administration to be the most significant advantage of Tenecteplase over other thrombolytics.
- In the practice of 41% of doctors, 25-50% of ACS patients receive Tenecteplase.
- 51% of doctors decide between Tenecteplase and percutaneous coronary intervention (PCI) for ACS based on patient's clinical stability, time since symptom onset and availability of PCI facilities.
- 42% of doctors sometimes use Tenecteplase in combination with antiplatelet therapy for ACS.
- According to 44% of doctors, their preferred antiplatelet therapy to combine with Tenecteplase is Clopidogrel.

- According to 62% of doctors, they assess the risk of re-thrombosis in patients treated with Tenecteplase by regular follow-up ECGs, biomarker monitoring, clinical symptom assessment.
- As per 45% of doctors, they recommend follow-up echocardiograms for patients treated with Tenecteplase within one month.

Consultant Opinion

Market Opportunities:

With 55% of doctors frequently prescribing Tenecteplase for ACS, there is a growing market opportunity for pharmaceutical companies to meet the demand for this thrombolytic agent and potentially expand its usage further.

Value for Healthcare Professionals:

As 52% of doctors rely on ECG as the most reliable diagnostic tool for assessing Tenecteplase therapy's success, there is a need for continuous innovation in diagnostic technologies to improve the accuracy and efficiency of treatment monitoring.

Adverse Effect Management:

Since 54% of doctors occasionally encounter bleeding complications with Tenecteplase therapy, pharmaceutical companies can develop targeted education and training programs to help healthcare professionals effectively manage and mitigate these adverse effects.

Market Positioning:

Pharma companies should emphasize the advantages of Tenecteplase, such as its rapid reperfusion capabilities and single bolus administration, in their marketing strategies to position it as a preferred choice over other thrombolytics in ACS management.

Personalized Treatment Decisions:

Developing and promoting risk assessment tools that integrate patient-specific factors can assist healthcare professionals in making personalized treatment decisions between Tenecteplase and PCI based on clinical stability, time since symptom onset, and availability of facilities.

Improving Patient Outcomes:

Pharma companies can collaborate with healthcare professionals to establish standardized protocols for regular monitoring of patients treated with Tenecteplase, including ECG changes, biomarker monitoring, and follow-up echocardiograms, as recommended by 65% of doctors. This can help optimize patient outcomes and ensure timely intervention when necessary.

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

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