

**THE USE OF THROMBOLYTIC AGENTS IN ACUTE MYOCARDIAL INFARCTION (AMI) PATIENTS****E KUMOLASASI<sup>1\*</sup>, WONG SIN WEI<sup>1</sup>, CHUA ENG WEE<sup>1</sup>**<sup>1</sup>Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur. Email: e\_kumolasaki@yahoo.co.id*Received: 24 Aug 2012, Revised and Accepted: 16 Jan 2013***ABSTRACT**

What is known: Rapid restoration of patency of the infarct-related artery is the key to preserving myocardium and improving survival in acute myocardial infarction (AMI). Controversy surrounding the efficacy and cost of thrombolytic agents has lent uncertainty to the choice of thrombolytic agents.

Objective: The primary objective of this study was to assess the use of thrombolytic agents in AMI, including time to treatment, and types, efficacy, and adverse effects of thrombolytic agents employed.

Methods: Patients who were hospitalised with AMI over the past two years from January 2007 to December 2008 were involved. Medical records were retrospectively reviewed.

Results: The thrombolytic agents were most commonly given within two to four hours (42.85%) of symptom onset and were rarely given after 12 hours (11.43%). A negative correlation was found between time to treatment and creatine kinase (CK) reduction [ $r(33) = -0.27, p > 0.05$ ]. The majority of the patients were given streptokinase. No significant differences were found between streptokinase and alteplase in CK reduction, duration of hospitalisation, and post-infarct residual heart function. Bleeding was the predominant adverse drug event reported in the alteplase treatment group. Streptokinase was associated with cardiovascular side effects and allergic reactions.

What is New: The study included Malaysian patients.

Conclusion: streptokinase and alteplase had similar efficacy in AMI patients. Other factors such as adverse effects should be considered when selecting a thrombolytic agent.

**Keywords:** Acute Myocardial Infarction; Thrombolytic agents; Streptokinase; Alteplase; Creatine kinase

**INTRODUCTION**

Acute myocardial infarction (AMI) is one of the clinical presentations of ischemic heart disease[1]. It is defined as myocardial cell death due to prolonged ischemia[2]. This is usually the result of rupture of an atherosclerotic plaque within the artery. The heart muscle supplied by that artery is damaged or dies because of a lack of oxygen[3]. Myocardial infarction (MI) can be classified based on size and location, or more commonly, on electrocardiographic findings, into ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI)[2,4].

MI is a major cause of morbidity and mortality worldwide. More than three million people each year are estimated to have an acute STEMI, and more than four million have a NSTEMI[5]. In Malaysia, ischaemic heart disease alone accounts for 12.9% of medically certified deaths in 2008. Prevalence of MI increases with age and is higher in men (14.4%) than in women (10.6%)[6].

Rapid restoration of patency of the infarct-related artery is the key to preserving myocardium and improving survival[7]. The efficacy of thrombolysis is measured by the level of reperfusion achieved by the involved myocardium. The Thrombolysis in Myocardial Infarction trial (TIMI) grading system was developed to evaluate the angiographic patency of coronary arteries after myocardial infarction[8]. Thrombolytic agents available to treat AMI include streptokinase (SK), urokinase (u-PA), alteplase (rt-PA), anistreplase (APSAC), saruplase, reteplase (r-PA), tenecteplase (TNK-tPA), lanoteplase and staphylokinase[9]. Controversy surrounding the efficacy and cost of thrombolytic agents has led to uncertainty as to which thrombolytic agent to use[10].

Successful thrombolytic therapy not only improves survival and left ventricular function but also reduces the risk of post-infarct arrhythmias[11]. Early patency of the infarct-related artery is a major determinant of survival after thrombolysis for AMI. Early and prompt reperfusion is crucial as 'time lost' is equivalent to 'myocardium lost'. Studies suggest that time to treatment influences the efficacy of thrombolytic agents in restoring early patency of the

infarct-related vessel[12-13]. Despite overwhelming data showing that prompt reperfusion therapy improves survival, it is still widely underutilized and delayed[14].

Thrombolytic treatment is not without adverse effects. Minor bleeding, hypotension, and allergic reactions are common in patients treated with SK[15]. Besides that, some studies also found that the risk of intracranial haemorrhage (ICH) is increased with thrombolytic therapy especially rt-PA[16-17]. This study was conducted with two primary objectives: (i) to assess the use of thrombolytic agents, i.e. usage, type, efficacy, and side effects in patients with AMI, and (ii) to determine the relationship between time to treatment and thrombolysis efficacy.

**MATERIALS AND METHODS****Methods**

This retrospective study involved in-patients who presented with AMI and received thrombolytic therapy at our institution over the past two years from January 2007 to December 2008. The patients were recruited via universal sampling. Medical records of all patients were reviewed and those with incomplete data were excluded. Important data that were collected include patient demographics, the time of first AMI symptoms, details of thrombolytic treatment (time of administration, name of the agent, and dose), past medical history, duration of hospitalisation, list of current medications, laboratory investigations, adverse drug events, and disease complications. The time interval from symptom onset to treatment was calculated by deducting the time when the first symptoms appeared from the time when treatment was given. CK reduction, which was the difference between the peak CK value (usually between 16-30 hours following an episode of MI) and the ensuing CK level, duration of hospitalisation, and post-infarct ejection fraction (an indicator of residual heart function) were chosen as three important measures of thrombolysis efficacy. An elevated creatine kinase (CK) concentration was defined as a CK level two or more times the upper limit of the normal range used by the local laboratory.

### Statistical Analysis

Analysis was performed by using Statistical Package for Social Sciences (SPSS) version 17.0 and the results were presented in the form of graphs using Microsoft Office Excel™ 2007. Continuous data were presented as means  $\pm$  standard deviations while categorical variables were presented as frequencies and percentages. The data were tested for normality before being analysed. Where the scores were normally distributed, independent group *t*-test was used to compare the two treatment groups i.e. SK and rt-PA. When this was not the case Mann-Whitney U test would be used instead. Head-to-head comparison was not feasible when the patients were treated with more than one thrombolytic agent. In bivariate analysis, relationship between time to treatment and CK reduction was determined using Spearman's rank correlation test. Probability values of (*P*) less than 0.05 (two-tailed) were considered statistically significant.

### RESULTS

The study included a total of 35 patients. As shown in Table 1, the majority of AMI patients treated with thrombolytic agents were male (94.29%), aged less than 45 years old (31.43%), and had more than one risk factor for coronary heart disease. Dyslipidaemia (100%) was the most prevalent risk factor, followed by hypertension (94.29%), smoking (74.29%), diabetes (42.86%), family history (34.29%), and a history of previous MI (8.57%). Despite drug therapy, many patients were still unable to attain desired lipid control, as evidenced by 52.94% of the patients who reported abnormal total cholesterol and high-density lipoprotein (HDL) cholesterol levels; half with abnormal low-density lipoprotein (LDL) cholesterol levels, and 44.12% not achieving target triglyceride levels (Table 2).

**Table 1: Demographic data of AMI patients treated with thrombolytic agents**

Variables		Number of patient (%) n=35
Gender	Male	33 (94.29)
	Female	2 (5.71)
Age	<45	11 (31.43)
	45-54	10 (28.57)
	55-64	8 (22.86)
	65-74	5 (14.28)
	>75	1 (2.86)
Risk factor	Smoker	26 (74.29)
	Family history	12 (34.29)
	Diabetes	15 (42.86)
	Hypertension	33 (94.29)
	Dyslipidaemia	35 (100)
	Previous MI	3 (8.57)

**Table 2: Lipid levels of AMI patients**

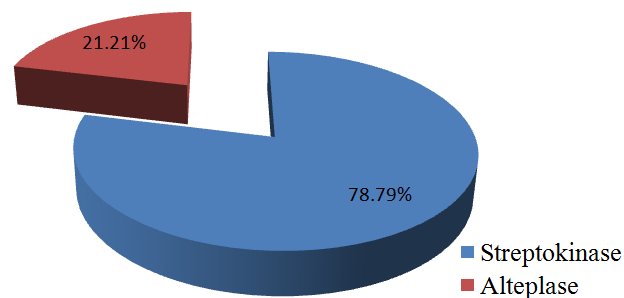
Types of lipid	Mean $\pm$ SD (mmol/L)	Normal		Abnormal	
		No. patient	%	No. patient	%
T.chol	5.76 $\pm$ 1.05	16	47.06	18	52.94
HDL	1.25 $\pm$ 0.30	16	47.06	18	52.94
LDL	3.72 $\pm$ 0.93	17	50.00	17	50.00
TG	1.73 $\pm$ 1.00	19	55.88	15	44.12

\*Note: Total patient = 34

Total cholesterol (T.chol), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglyceride (TG).

Two types of thrombolytic agents were used during the study period i.e. SK and rt-PA. The majority of the patients (78.79%) were given SK (Figure 1). Thrombolytic therapy was most commonly administered within two to four hours (42.85%) of symptom onset (Table 3). A delay of more than 12 hours was relatively rare

(11.43%). Prompt thrombolysis enabled greater CK reductions, which signified arrest of myocardial damage. This was substantiated by a weak negative correlation that was found between time to thrombolytic therapy and reduction in CK ( $r(33) = -0.269$ ;  $p > 0.05$ ) (Table 4).



**Fig. 1: Types of thrombolytic agent used in AMI patients (n= 33)**

**Table 3: Number of patients given thrombolytic therapy, stratified with respect to the time of drug administration**

Time (Hours)	Number of patient (n=35)	
	Received thrombolytic therapy(%)	
<2	6 (17.14)	
2-4	15 (42.85)	
4-6	5 (14.29)	
6-12	5 (14.29)	
>12	4 (11.43)	

**Table 4: Spearman's rank correlation test between time to treatment and CK reduction**

Factor	Correlation cofactor (r) for CK reduction	P value
Time from symptoms to treatment	-0.27	>0.05

\*Note: r 0.2-0.5 = medium correlation

The efficacy of thrombolysis may not only be influenced by time to treatment but also the types of thrombolytic agents used. SK and rt-PA were compared with respect to extent of CK reduction, duration of hospitalisation, and post-infarct ejection fraction (Table 5); however no statistically significant differences were reported. Nevertheless, it is still worth pointing out that patients treated with rt-PA had higher

reductions in CK ( $2744.29 \pm 1678.38$  U/L for rt-PA versus  $1605.38 \pm 1225.96$  for SK;  $p > 0.05$ ), and shorter lengths of hospitalisation ( $6.29 \pm 2.06$  days for rt-PA versus  $7.08 \pm 1.52$  days for SK;  $p > 0.05$ ). As regards preservation of heart function there did not seem to be a large difference either, with the reported mean ejection fractions for SK and rt-PA being  $56.51 \pm 14.01\%$  and  $52.24 \pm 11.30\%$  respectively.

**Table 5: Comparison between streptokinase and alteplase**

Parameter	Mean $\pm$ SD		P value
	Streptokinase regimen (n=26)	Alteplase regimen (n=7)	
CK reduction (U/L)	$1605.38 \pm 1225.96$	$2744.29 \pm 1678.38$	>0.05
Length of stay (days)	$7.08 \pm 1.52$	$6.29 \pm 2.06$	>0.05
Ejection fraction (%)	$56.51 \pm 14.01$	$52.24 \pm 11.30$	>0.05
INR	$1.13 \pm 0.43$	$2.13 \pm 1.34$	<0.01*
APTT (sec)	$42.56 \pm 14.95$	$149.34 \pm 39.16$	<0.0001*
PT (sec)	$14.98 \pm 4.23$	$24.06 \pm 12.28$	<0.01*
Reported adverse events	Gum bleeding (2) Maculopapular rash (1) Bradycardia (1)	Haematuria (2) Gum bleeding (1)	-
Major complications	Cardiogenic shock (2): one resulted in death; the other led to transfer of the patient to another institution	Possible reinfarction (1)	-

Note: Streptokinase regimen = Streptokinase, clopidogrel and aspirin; Alteplase regimen = Alteplase, heparin, clopidogrel and aspirin

- : No statistical comparison done; \*means significant difference

Though rt-PA compares favourably with SK in terms of the above-mentioned parameters, it appears to pose a greater risk of bleeding. Significantly higher levels of activated partial thromboplastin time (aPTT;  $z = -3.95$ ,  $p < 0.0001$ ), international normalized ratio (INR;  $z = -3.03$ ,  $p < 0.01$ ), and prothrombin time (PT;  $z = -2.94$ ,  $p < 0.01$ ) were recorded for patients who were given rt-PA. Indeed, minor bleeding was the predominant adverse effect in the rt-PA treatment group, with two cases of haematuria and one case of gum bleeding. Important adverse effects reported in the SK groups include gum bleeding, allergic reactions, and infusion-related bradycardia. We would also like to point out that two patients treated with SK experienced cardiogenic shock: one passed away whereas the other was transferred to another institution for further management. One patient in the rt-PA treatment group suffered reinfarction; however the diagnosis was not conclusive.

## DISCUSSION

In this study, most of the patients enrolled were male. This can be due to the fact that the incidence of AMI is greater in males than in females because of their higher CHD risk factor levels[18-19]. The use of thrombolytic agents is also age-related and the majority of our patients were less than 45 years old. Similar observation was reported by Gurwitz et al.[20]. Thrombolytic therapy is seldom used in elderly patients, those older than 75 years in particular, because it is unlikely to confer survival benefit and may even have a significant survival disadvantage[21]. It was found that dyslipidaemia was the predominant risk factor for CHD. Worryingly, many patients reported abnormal lipid levels despite drug therapy. The Interheart case-control study estimated that 45% of heart attacks in Western Europe and 35% of heart attacks in Central and Eastern Europe were due to abnormal blood lipids, and that abnormal lipids increased the risk for heart attacks by three folds[22]. We recommend that the management of dyslipidaemia should be optimized as per the Clinical Practice Guidelines on Management of Acute Stemi[14].

Time to thrombolytic therapy is an important predictor of MI size and patient outcome[23]. It was found that thrombolytic therapy was often given within two to four hours of symptom onset, and an interval of more than 12 hours was uncommon. A study of Zijlstra et al. reported similar results in which 32% of patients presented in

less than two hours, 39% in two to four hours and 24% more than four hours of symptom onset[24]. A weak negative correlation was also found between time to treatment and CK reduction, suggesting that early thrombolysis produced better outcome. Mortality rates can be lowered by as much as 6.5% if treatment is given within the first hour, falling to 3.7% if within two hours, and 2.6% after six hours[25]. Therefore, prompt initiation of thrombolytic therapy is of notable importance. Clinical trials by Fibrinolytic Therapy Trialists (FTT) Collaborative Group, 1994 reported that beyond 12 hours, treatment benefit was non-significant and minimal[26]. However, this should not become the basis for precluding thrombolytic therapy after a delay of longer than 12 hours. Although the evidence is not convincing, we believe that some of the patients may still benefit from late thrombolytic therapy.

The choice of thrombolytic agents is often a subject of debate especially regarding their efficacy in AMI. Two thrombolytic agents were used as SK and rt-PA; the former was preferred. SK is still the agent of choice primarily because it has been extensively studied and its acquisition cost is lower than that of rt-PA[3][27-28]. A survey found that 82% of hospitals in England used SK for eligible patients experiencing their first AMI. Other data suggested that SK may represent 53-65% of thrombolytic agent use[3]. The same result was shown in the developing country that among all thrombolytic agents, SK is widely used in the treatment of AMI, reported by Ghosh et al.[29]. In spite of some evidence supporting the superiority of rt-PA over SK, this remains questionable. In GUSTO trials, rt-PA accelerated regimen had been found to be more effective than SK in terms of early coronary patency and of mortality reduction[30].

Our findings did not resonate with those of GUSTO trials. We found that SK and rt-PA did not differ significantly with respect to CK reduction, lengths of hospitalisation, and ejection fraction. Overall both drugs showed similar efficacy in AMI. Although rt-PA seems to be a more attractive choice as it induced greater CK reductions than SK, the clinical significance of this observation is doubtful. This is especially true when these greater reductions did not translate into better-preserved heart function (as measured by post-infarct ejection fraction in our study). Two large trials had reported similar results, where no significant difference between SK and rt-PA was noted[16-17]. Hence, we recommend that other factors such as

adverse effects profile and contraindications should be considered instead when selecting a thrombolytic agent.

Significant higher levels of aPTT, INR, and PT were reported in patients treated with rt-PA, probably owing to the concurrent administration of heparin. This shows that the rt-PA regimen posed a significantly higher risk of bleeding, which is the most important complication of thrombolytic therapy. Minor bleeding can occur in up to 20% of patients receiving thrombolytic therapy for MI; major but non-life-threatening bleeding in 5% to 7%; and fatal bleeding, usually in the form of intracranial haemorrhage (ICH), in 0.5% to 1.5%[11]. GISSI-2 and ISIS-3 trials reported that bleeding risk was higher with rt-PA than with SK. The use of heparin further increased the risk[16-17]. Indeed, in our study rt-PA was predominantly associated with minor bleeding such as gum bleed and haematuria.

Though SK has a lower bleeding risk, one of its major drawbacks is that it can induce a fall in systemic blood pressure during infusion. This adverse event had been recorded in as much as 87% of patients treated with a systemic infusion of SK, and it had seemed to be greater in haemodynamically compromised patients[31-33]. One patient in our study developed bradycardia in response to SK infusion. The mechanism by which SK induces hypotension is not fully understood. Several theories have been proposed, including a direct vasodilator effect of SK, reduction of blood viscosity, allergic reaction, activation of kallikrein, and production of bradykinin, or prostacyclin release as a consequence of triggering of the arachidonic acid cascade by fibrinogen degradation products[33-36].

Besides cardiovascular adverse effects, SK was also commonly associated with allergic reactions. We reported a case of maculopapular rash following administration of SK, which was subsequently withdrawn. SK is a foreign protein derived from streptococci and is antigenic in nature[37]. Possible allergy to SK, such as previous SK use or streptococcal infections, should always be assessed prior to its administration.

It is important to take note that three patients in our study suffered major complications, namely reinfarction and cardiogenic shock; this could indicate primary failure of thrombolytic therapy. Reocclusion can occur after thrombolytic therapy for several reasons. First, when the nidus of coronary thrombus is not removed, rethrombosis can easily occur. Thrombosis and thrombolysis probably represent a subtle balance; reestablishment of the thrombotic state may lead to coronary rethrombosis. Remarkably, plasminogen activation with exogenous compounds has the paradoxical effect of activating both platelets and thrombin in the acute phase. The other reason is incomplete lysis of the thrombus and plaque swelling after thrombolysis which can become the stimulus for rethrombosis[38].

## CONCLUSION

The majority of AMI patients had abnormal lipids, this calling for optimisation of lipid management. Thrombolytic therapy was commonly given within four to six hours of symptom onset. Prompt initiation of thrombolytic therapy improved treatment outcome. Two types of thrombolytic agents were used as SK and rt-PA, with SK being the preferred agent. The two drugs exhibited similar efficacy with respect to CK reduction, ejection fraction, and duration of hospitalisation. Thus, other factors such as adverse effects should be considered when selecting a thrombolytic agent. The rt-PA regimen posed a significantly higher risk of bleeding; whereas SK was associated with cardiovascular adverse effects and allergic reactions.

## REFERENCES

1. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur. Heart J* 2007; 28:1598-1660.
2. Thygesen K, Alpert JS, White HD Universal definition of myocardial infarction. *Eur. Heart J* 2007; 28:2525-2538.
3. National Institute of Clinical Excellence (NICE): Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. Technology Appraisal Guidance No.52. London: NICE; 2002. p.1-25
4. Yang EH, Brilakis ES, Reeder GS, Gersh BJ Modern management of acute myocardial infarction. *Curr Probl Cardiol* 2006; 31:769-817.
5. White HD, Chew DP Acute myocardial infarction. *Lancet* 2008; 372:570-584.
6. Department of Statistics Malaysia Statistics on cause of death Malaysia 2008. 2010. p.1-2
7. Ross AM New plasminogen activators: a clinical review. *Clinical Cardiology* 1999; 22: 165-171.
8. Verstraete M Third- generation thrombolytic drugs. *Am. J. Med* 2000; 109:52-58.
9. Gulba DC, Bode C, Runge MS, Huber K Thrombolytic agents – an updated overview. *Fibrinolysis and Proteolysis* 1998; 12(2):39-58.
10. Guidry UA, Paul SD, Vega J, Harris C, Chaturvedi R, O'Gara PT et al. Impact of a simple inexpensive quality assurance effort on physician's choice of thrombolytic agents and door-to-needle time: implication for costs of management. *J Thromb Thrombolys* 1998; 5:151-157.
11. De Bono DP Thrombolytic therapy of acute myocardial infarction. *Baillieres Clin Haematol* 1995; 8(2):403-412.
12. Leizorovicz A, Boissel JP, Robert F Coronary reperfusion rates in acute myocardial infarction patients after thrombolytic treatment with anistreplase: correlation with the delay from onset of symptoms to treatment: a review of 424 case records of patients admitted to coronary reperfusion studies with anistreplase. *J Cardiovasc Pharm* 1992; 19:34-39.
13. Steg PG, Laperche T, Golmard JL, Juliard JM, Benamer H, Himbert D et al. Efficacy of streptokinase, but not tissue-type plasminogen activator in achieving 90-minute patency after thrombolysis for acute myocardial infarction decreases with time to treatment. *J. Am. Coll. Cardiol.*1998; 31:776-779.
14. Ministry of Health Malaysia, National Heart Association Malaysia & Academy of Medicine Malaysia. Clinical Practice Guidelines. Management of Acute ST Segment Elevation Myocardial Infarction 2007, 2<sup>nd</sup> ed. 2007.p. 1-52.
15. Tisdale JE, Colucci RD, Ujhelyi MR, Kluger J, Fieldman A & Chow MS Evaluation and comparison of the adverse effects of streptokinase and alteplase. *Pharmacotherapy* 1992; 12(6):440-444.
16. GISSI-2, Gruppo Italiano Per lo Studio Della Sopravvivenza Nell' Infarto Miocardico. A factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. *Lancet* 1990; 336:65-71.
17. ISIS-3 (Third International Study Infarct Survival) Collaborative Group ISIS-3: a randomized comparison of streptokinase versus tissue plasminogen activator versus anistreplase and of aspirin plus heparin versus aspirin alone among 41 299 cases of suspected acute myocardial infarction. *Lancet* 1992; 339:753-770.
18. Marrugat J, Sala J & Aboal J Epidemiology of cardiovascular disease in women. *Rev. Esp. Cardiol.* 2006; 59(3):264-274.
19. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH et al. Risk factors for myocardial infarction in women and men: insight from the INTERHEART study. *Eur. Heart J* 2008; 29:932-940.
20. Gurwitz JH, Gore JM, Goldberg RJ, Rubison M, Chandra N & Rogers WJ Recent age-related trends in the use of thrombolytic therapy in patients who have had acute myocardial infarction. *Annals of Internal Medicine* 1996; 124:283-291.
21. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ & Powe NR Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation* 2000; 101:2239-2246.
22. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al. On behalf of the INTERHEART study investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries: case-control study. *The Lancet* 2004; 364:937-952.
23. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction, executive summary: a report of the American College of

- Cardiology/American Heart Association Task Force on Practice Guidelines. *Can J Cardiol* 2004; 20(10):977-1025
24. Zijlstra F, Patel A, Jones M, Grines CL, Ellis S, Garcia E et al. Clinical characteristics and outcome of patients with early (<2h), intermediate (2-4h) and late (>4h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. *Eur. Heart J* 2002; 23:550-557.
  25. Boersma E, Maas ACP, Deckers JW & Simoons ML Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348:771-775.
  26. FTT Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *The Lancet* 1994; 343:311-322.
  27. Baruah DB, Dash RN, Chaudhari MR & Kadam SS Plasminogen activators: a comparison. *Vascular Pharmacology* 2006; 44:1-9.
  28. Siebert WJ, Ayres RW, Bulling MT, Thomas CM, Minson RB & Aylward PE Streptokinase morbidity: more common than previously recognised. *Internal Medicine Journal* 2006; 22:129-133.
  29. Ghosh M, Pulicherla KK, Rekha VPB, Venkat Rao G, Sambasiva Rao KRS A review on successive generations of streptokinase based thrombolytic agents. *Int J Pharm Pharm Sci* 2012; 4(3):38-42.
  30. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N. Engl. J. Med* 1993; 329:673-682.
  31. Gemmil JD, Hogg KJ, Douglas JT, Dunn FG, Lowe GDO, Rae AP et al. The incidence and mechanism of hypotension following thrombolytic therapy for acute myocardial infarction with streptokinase-containing agents - lack of relationship to pretreatment streptokinase resistance. *Eur. Heart J* 1993; 14:819-825.
  32. Herlitz J, Hartford M, Aune S & Karlsson T Occurrence of hypotension during streptokinase infusion in suspected acute myocardial infarction, and its relation to prognosis and metoprolol therapy. *Am J Cardiol* 1993;71:1021-1024.
  33. Lew AS, Laramee P, Cercek B, Shah PK & Ganz W The hypotensive effect of intravenous streptokinase in patients with acute myocardial infarction. *Circulation* 1985; 72:1321-1326.
  34. Andersson RGG, Saldeen K & Saldeen T A fibrinogen derived pentapeptide induces vasodilation, prostacyclin release and an increase in cyclic AMP. *Thromb Res* 1983; 30:213-218.
  35. Green J, Dupe RJ, Smith RAG, Harris GS & English PD Comparison of the hypotensive effects of streptokinase-(human) plasmin activator complex and BRL 26921 (p-anisoylated streptokinase-plasminogen activator complex) in the dog after high dose, bolus administration. *Thromb Res* 1984; 36:29-36.
  36. McGrath K & Patterson R Anaphylactic reactivity to streptokinase. *JAMA* 1984; 252: 1314-1317.
  37. Lynch M, Littler WA, Pentecost BL & Stockley RA Are streptokinase antibodies clinically important? *Brit Heart J* 1994; 71:303-304.
  38. Verheugt FWA, Meijer A, Lagrand WK & Van Eenige MJ Reocclusion: the flip side of coronary thrombolysis. *J. Am. Coll. Cardiol* 1996; 27:766-773.