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A Review of the Short-term Outcomes of Thrombolytics and Percutaneous Coronary Intervention in the Treatment of ST-segment Elevation Myocardial Infarction

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Abstract

Coronary heart disease is the single largest cause of mortality in the UK with acute myocardial infarction (AMI) being responsible for the greatest amount of deaths. Improving perfusion to the myocardium to prevent further damage or death of the cardiac tissue is the aim of treating AMI. In the UK reperfusion is achieved either through the use of an thrombolytic agent (streptokinase, alteplase, reteplase or tenecteplase) or by percutaneous coronary intervention (PCI). Reteplase and tenecteplase are newer agents, to the author's knowledge; no review has been conducted that has included these agents. This review will compare all licensed reperfusion strategies in the UK to determine the optimum reperfusion strategy. The databases PubMed, Medline, Science Direct and EBSCO were searched to identify randomised control trials (RCT's) comparing streptokinase, alteplase, reteplase, tenecteplase and PCI in the prevention of 30-day mortality, stroke and re-infarction. 99 articles were identified but after application of the inclusion and exclusion criteria a total of 12 trials (n=36,161) remained. Data analysis was performed using IBM SPSS Statistics 20.

PCI is the most effective intervention for the reduction of mortality, stroke and re-infarction in the short term (incidences of 5.1% (ϕ=0.8), 0.6% (ϕ=0.78) and 2.2% (ϕ=0.6) respectively) despite being associated with the greatest time delay between symptom onset and treatment receipt. Tenecteplase is the most effective thrombolytic agent at reducing 30-day mortality (incidence of 6.2% (ϕ=0.8)) and has a comparable re-infarction risk to alteplase and reteplase but does have a greater stroke risk. Tenecteplase has the shortest time-to-treatment however time-to-treatment had no significant impact on 30-day mortality within, and across treatment groups (OR=1.0, P<0.05). PCI is the most effective method of reperfusion and should be first choice. Tenecteplase is showing great promise in efficacy and ease of use and should be the thrombolytic agent of choice if PCI is unavailable and the patient's stroke risk is low.

Keywords: Thrombolytics, PCI, STEMI, Outcomes.

Introduction

Coronary heart disease (CHD) is the single largest cause of mortality in the UK with acute myocardial infarction (AMI) being responsible for the greatest proportion of these deaths. It is well understood that thrombus formation is the aetiology behind an acute myocardial infarction, leading to ischaemia[1]. Improving perfusion to the myocardium to prevent further damage and tissue necrosis is the aim of treating AMI. In the UK reperfusion is achieved either through the use of a licensed thrombolytic agent (streptokinase, alteplase, reteplase and tenecteplase) or by percutaneous coronary intervention (PCI). Streptokinase and alteplase have been compared to PCI in a systematic review previously [2], however the newer thrombolytics; reteplase and tenecteplase, have not been included in such a review, to the authors knowledge, and hence the need for this mini review. The newer agents can be administered via IV bolus injection, meaning a shorter time-to-treatment from symptom onset, providing a potential reduction in myocardial necrosis and potential improvement in prognosis [3]. Furthermore, when reteplase and tenecteplase have been compared to PCI in separate randomised control trials (RCTs) no significant difference could be found between reteplase and PCI nor tenecteplase and PCI in the incidence of short-term mortality[4,5].

As such, an updated review of the reperfusion interventions in ST elevated myocardial infarction (STEMI) treatment with regards to the optimal reperfusion strategy is required to establish the appropriate place in the treatment hierarchy for reteplase and tenecteplase.

The primary aim is to determine the most effective reperfusion strategy in the treatment of STEMI; through investigation of the primary outcome of efficacy; incidence of 30-day mortality, and the secondary outcomes of 30-day stroke and 30-day re-infarction.

Method

A literature search identified all RCTs published up until 30th

September 2014 comparing streptokinase, alteplase, reteplase and tenecteplase to one another or to PCI in the treatment of STEMI. The reference lists of identified papers were screened for further relevant RCTs. The databases PubMed, Medline, Science Direct and EBSCO were used and were searched using the key terms: acute myocardial infarction, myocardial infarction, ST-segment elevation myocardial infarction, mortality, time-to-treatment, and the nomenclature of the treatment options e.g. alteplase/t-PA. Only RCTs, meta-analyses and systematic reviews were requested. No time or language restrictions were placed. 99 articles were retrieved. The search strategy is outlined in Figure 1.

The defined inclusion criteria were: patients with confirmed AMI with ST-elevation above 1mm, presented within 12 hours of symptom onset or up to 24hours after symptom onset with evidence of continuing ischaemia. However, the trials had varying limits on maximum symptom onset time at presentation below

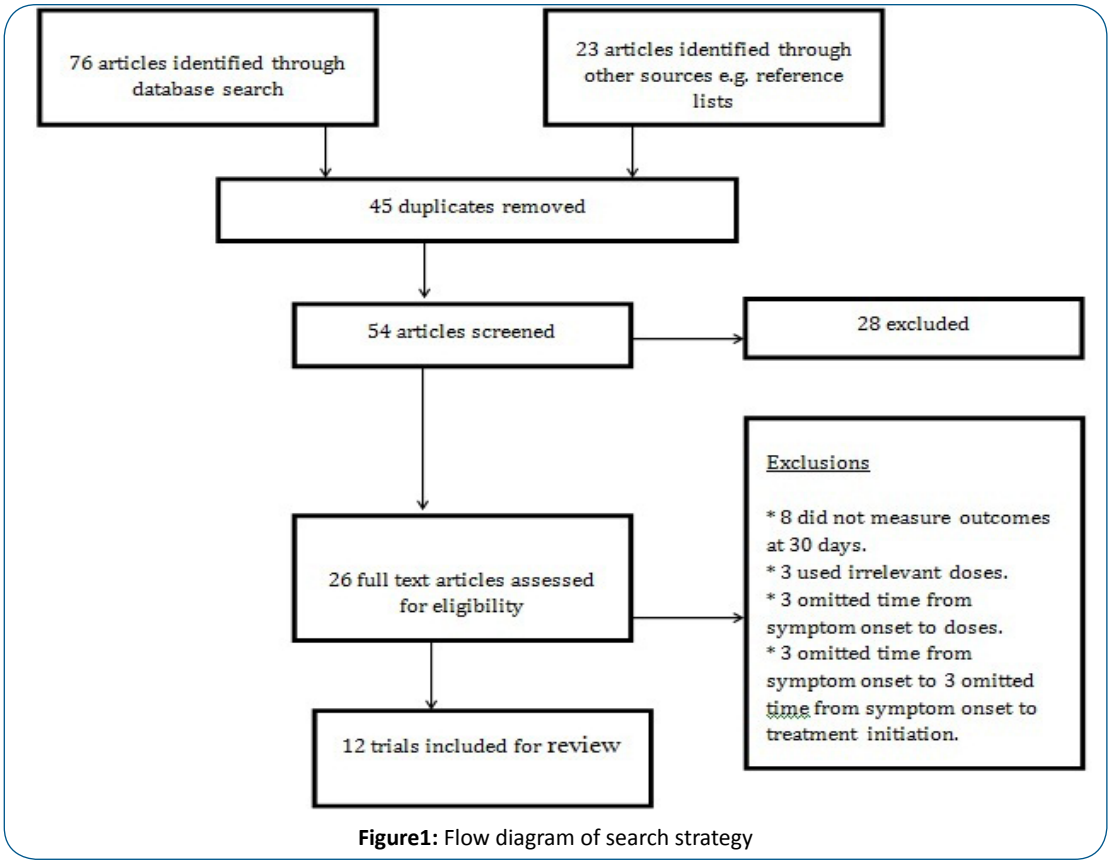

Figure1: Flow diagram of search strategy

this point. Patients must be over 18 years of age with no upper age limit was imposed. Articles were included that compared two of the target interventions, reported one of the outcomes and reported average time-to-treatment values for the interventions. The defined exclusion criteria set were: trial duplicates, omission of the primary and/or secondary outcomes, omission of time-to-treatment from symptom onset, investigation of doses outside of the licensed doses for treating AMI in the UK and unavailability of full text. After application of the inclusion and exclusion criteria; 12 papers were included in the review, which can be seen in Table 1.

The data for each intervention were extracted from the included articles and pooled. The statistics package IBM SPSS Statistics 20 was used to calculate all the results reported. Heterogeneity tests were performed using the Levene's test of homogeneity with a P value ≤ 0.05 displaying significance. All outcomes displayed significant heterogeneity and therefore non-parametric measures were performed. The Kruskal-Wallis test was used to assess variance between groups for 30-day mortality, stroke and re-infarction outcomes and to assess variance in time-to-treatment between interventions. The results of the Kruskal-Wallis tests are presented in medians. Effect size Phi (ϕ) calculations accompanied the results of Kruskal-Wallis tests, where effect sizes 0.3, 0.5 and 0.8 depicted small, moderate and large effect sizes respectively [6]. Binary logistic regression was performed to establish the relationship between time-to-treatment and the incidence of 30-day mortality. Logistic regression results were accompanied by P values where a $P < 0.05$ was considered significant [7].

Results

30-day Mortality

The results for 30-day mortality can be seen in Figure 2 below, where the Kruskal-Wallis null hypotheses of equal distribution and equal medians for 30-day mortality across treatment groups were rejected as there was significant variation between interventions ($P<0.05$). The effect size; $\phi=0.8$ demonstrated that mortality was largely dependent on intervention. The median of 30-day mortality across all groups was reported as 6.17% ($P < 0.05$).

10.8% of participants receiving streptokinase died within 30 days of treatment, showing a greater incidence of mortality than alteplase, reteplase, tenecteplase and PCI with 30-day mortalities of 6.5%, 7.4%, 6.2% and 5.1% respectively. Patients receiving PCI are the least likely to suffer short-term mortality. Of those patients receiving thrombolytic therapy, those administered with

Table 1: Characteristics of Included Trials

Trials	Trial Population	Intervention				
		Streptokinase	Alteplase	Reteplase	Tenecteplase	PCI
Widmiský *et al,* 2000[11]	200	✓	X	X	X	✓
Widimský *et al,* 2003[12]	850	✓	X	X	X	✓
Ribichini *et al,* 1998[13]	110	X	✓	X	X	✓
GUSTO IIb investigators, 1997[14]	1,138	X	✓	X	X	✓
Bonnefoy *et al*, 2002[15]	840	X	✓	X	X	✓
SchÖmig *et al*, 2000[16]	140	X	✓	X	X	✓
Kastrati *et al*, 2002[17]	162	X	✓	X	X	✓
Svensson *et al*, 2006[5]	205	X	X	✓	X	✓
GUSTO III investigators, 1997[18]	15,059	X	✓	✓	X	X
Smalling *et al*, 1995[19]	308	X	✓	✓	X	X
ASSENT-2 investigators, 1999[20]	16,949	X	✓	X	✓	X
Armstrong, 2007[4]	200	X	X	X	✓	✓

Notes: Total review population 36,161 (520 were assigned to streptokinase, 14,760 to alteplase, 10,396 to reteplase, 8,561 to tenecteplase and 1,924 to PCI. ✓ = intervention included. X = intervention not included

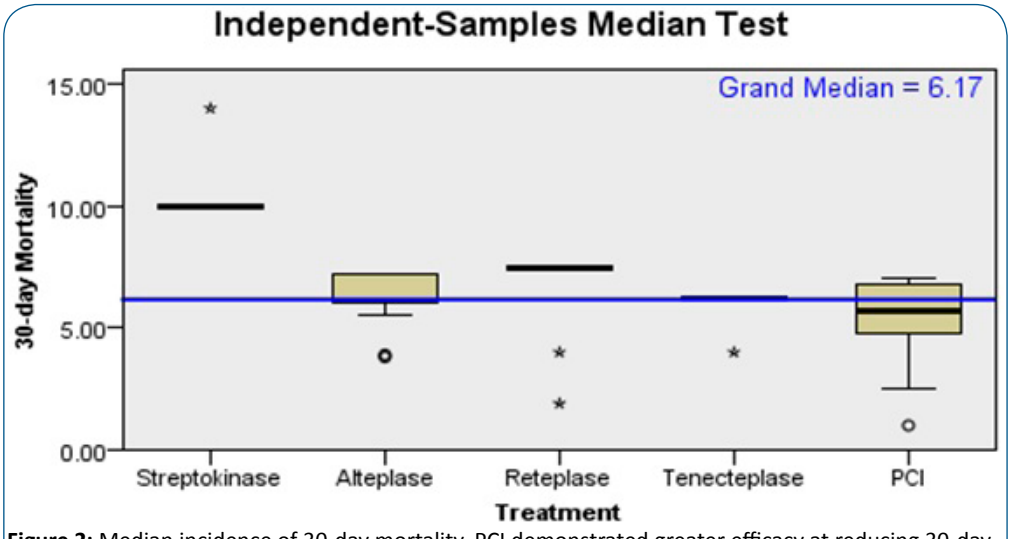

Figure 2: Median incidence of 30-day mortality. PCI demonstrated greater efficacy at reducing 30-day mortality and was the only intervention to have an incidence less than the grand median

tenecteplase are least likely to die within 30 days.

30-day stroke

The results for 30-day stroke can be seen in Figure 3 below, where the Kruskal-Wallis null hypotheses of equal distribution and equal medians for 30-day stroke across interventions were rejected as distribution and mean variations were significantly different ($p<0.05$). The treatment effect size was approaching large ($\phi=0.78$) showing that the intervention choice had a moderate-large effect on the incidence of stroke within 30 days. The grand median stroke incidence after 30-days was 1.6% ($p<0.05$).

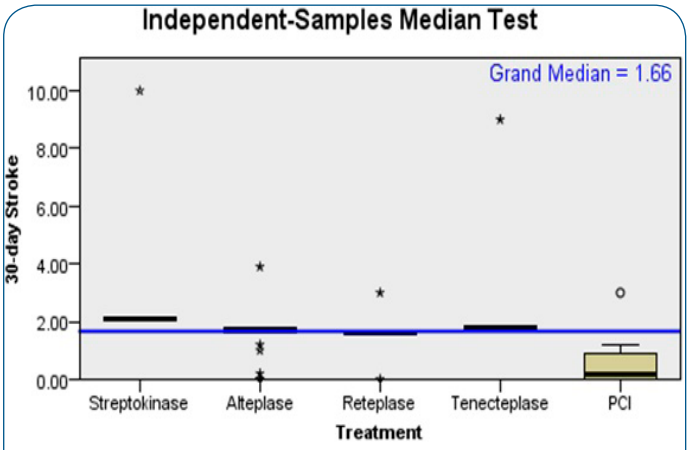

Figure 3: Incidence of 30-day Stroke. PCI demonstrated clear superiority in safety as it was responsible for the fewest number of strokes

3.7% of streptokinase recipients had a stroke within 30 days of treatment. Streptokinase therapy had a greater incidence of stroke than alteplase, reteplase, tenecteplase and PCI with 30-day stroke incidences of 1.6%, 1.6%, 1.9% and 0.6% respectively. Patients receiving PCI were least likely to have a stroke within 30 days of treatment. Of the patients receiving thrombolytics, those administered alteplase and reteplase were the least likely (both 1.6%) to have a stroke within 30 days. There was little increase in stroke incidence in patients receiving Tenecteplase (1.9%).

30-day Re-infarction

The results for 30-day re-infarction can be seen below in Figure 4. The null hypotheses that the distribution and median of 30-day re-infarction would be equal across treatment groups were both rejected. It was found that the distribution and medians for re-infarction at 30 days post AMI were significantly different across treatment arms ($p<0.05$). There was a moderate treatment effect size $\phi= 0.6$, meaning the selected intervention had a moderate impact on re-infarction probability. The grand median for 30-day re-infarction across all treatment groups was 4.10% ($p<0.05$).

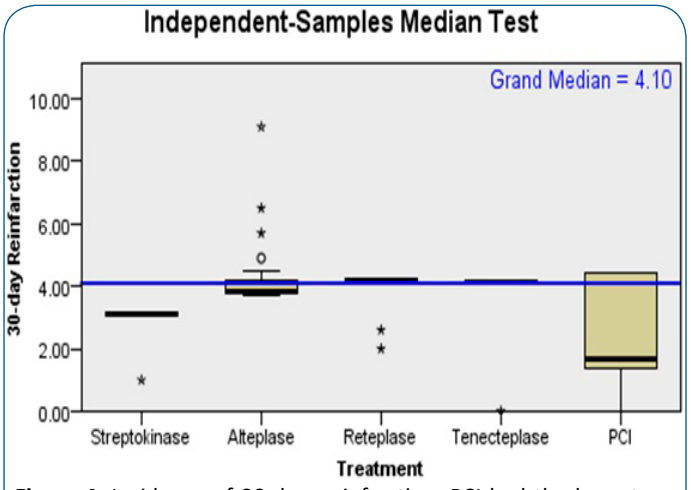

Figure 4: Incidence of 30-day re-infarction. PCI had the lowest re-infarction incidence, suggesting it has superior long-term effects compared to thrombolytic agents

Participants treated with streptokinase had a low 30-day re-infarction incidence (2.7%); lower than alteplase, reteplase and tenecteplase with incidences of 4.1%, 4.2% and 4.1% respectively. Streptokinase was inferior to PCI; 30-day re-infarction incidence of PCI recipients was 2.2%. PCI is the most effective intervention as it carries the lowest risk of short-term re-infarction. Of those patients receiving thrombolytic therapy; streptokinase recipients had the lower risk of re-infarction (2.7%).

Time-to-treatment

Time-to-treatment is shown in Figure 5 below. The null-hypotheses of equal distribution and equal median time-to-treatments between treatment groups were rejected as the distribution and median variation between groups was found to be significant ($p<0.05$). The time between symptom onset and treatment receipt was largely dependent on intervention ($\phi= 0.8$).

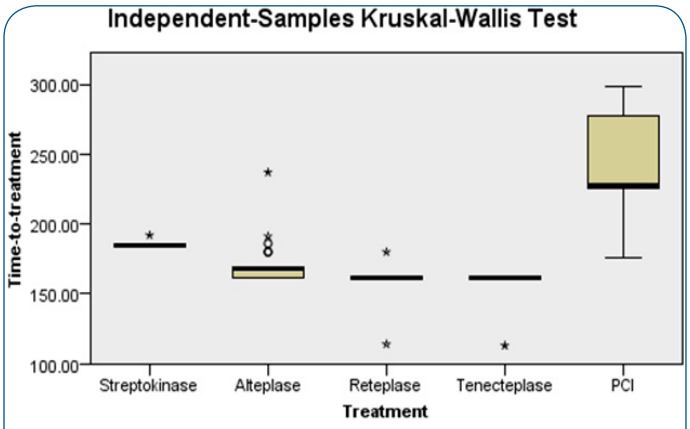

Figure 5: The relationship between time-to-treatment and treatment choice. Tenecteplase and reteplase are associated with a lower time delay between symptom onset and treatment initiation

Logistic regression on the impact of time-to-treatment on the risk of 30-day mortality showed no difference in outcome between the times investigated in this review; streptokinase, alteplase, reteplase, tenecteplase and PCI with OR: 0.95, 1.01, 1.00, 0.99 and 1.00 respectively. The only odds ratio to reach statistical significance was the OR corresponding to alteplase where $p<0.05$.

Discussion

The results from the mini review suggest PCI is responsible for preventing the greatest number of deaths, strokes and re-infarctions in the first 30 days post ST-segment myocardial infarction, and thus demonstrating that PCI is the superior reperfusion intervention in terms of efficacy and safety. Tenecteplase was shown to be the most effective thrombolytic drug in reducing 30-day mortality however had the highest stroke risk out of the thrombolytic agents. Tenecteplase was equivalent to alteplase and reteplase for re-infarction risk. Reteplase failed to show any benefits over alteplase in all three of the clinical

outcomes studied.

Time-to-treatment from symptom onset was much lower in tenecteplase and reteplase recipients. This had no significant impact on 30-day mortality. PCI had the greatest treatment latency yet had the superior outcome measures.

The findings of this review are supported by the results of a previous systematic review by Keeley *et al.* [2]. The author compared streptokinase and alteplase to PCI and reported that PCI was superior to the older thrombolytics; as is suggested in this review.

Dundar *et al.* [8] investigated the efficacy of streptokinase, alteplase, reteplase and tenecteplase in the treatment of STEMI through measurement of 35-day mortality and 35-day stroke occurrence. They found no difference in mortality between the thrombolytic agents and found streptokinase to be superior to the other treatments in stroke prevention. This is in opposition to this review. This review investigated those trials that presented data of clinical outcome occurrence within 30 days and presented with time-to-treatment values, meaning numerous trials included by Dundar *et al.* were excluded. This variation in trial selection may be responsible for the differences. Inclusion and exclusion criteria are lacking from the Dundar *et al* review and therefore make comparison difficult. Dundar's review was performed over a decade ago and since then more studies are available for the newer agents. As such this review contains a more up-to-date review of the current evidence and provides greater power to investigations pertaining to the newer thrombolytics. This power difference is magnified as Dundar excluded all RCTs where thrombolytic agents were compared to PCI, which led to an even smaller reserve of trial availability for the newer agents. Furthermore the trials comparing the newer agents to PCI showed more favourable mortality outcomes for the newer agents compared to trials where they were compared to other thrombolytics. Including the PCI-containing trials may have caused the difference in mortality results between this review and Dundar's.

Unlike Nallamothu *et al.* [9] this review found no significant impact on 30-day mortality when time-to-treatment was varied across interventions. This is particularly important because the greater latency in treatment time in PCI therapy is one of the stronger disadvantages of using it. However, time-to-treatment and its impact on adverse events was an area of interest in this review but not an outcome. Therefore this review may not have the power to identify any significant changes as a broad range of time-to-treatments was not searched specifically.

Applying the results from this review into practice shows a preference for PCI over any UK licensed thrombolytic agent. However, facilities and trained staff required for PCI are not available in all areas and therefore the results would only be applicable in areas with well-established PCI teams [10]. Based on the prevention of death alone tenecteplase would be the thrombolytic agent of choice, however due to tenecteplase having a greater risk of stroke, second only to streptokinase, the patient's risk of stroke must be considered. Alteplase would be the second option in practice due to it having a better mortality profile than reteplase. Drug and administration costs also need to be considered, however this is outside the scope of this review.

Conclusion

This mini review provides an up to date comparison of current reperfusion strategies licensed in the UK and provides a treatment hierarchy not produced elsewhere in literature. This allows for optimum treatment of STEMI in the future.

PCI is the most effective reperfusion strategy currently licensed for STEMI treatment despite the delay in time-to-treatment compared to thrombolytic agents with incidences of 5.1% (ϕ=0.8), 0.6% (ϕ=0.78) and 2.2% (ϕ=0.6) for mortality, stroke and re-infarction respectively. Tenecteplase is the most effective thrombolytic drug (incidence of mortality 6.2%, ϕ=0.8) but stroke risk should be considered prior to use. Alteplase could be a suitable alternative.

Acknowledgment

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