

## Clinician Adherence to Evidence Based Use of Anti-platelet Therapy at the Time of Thrombolysis for ST-elevation Myocardial Infarction

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### ABSTRACT

**AIM:** The use of dual anti-platelet therapy prior to, or at the time of thrombolysis for ST-elevation myocardial infarction (STEMI) has been shown to reduce patient mortality. This is a class IA recommendation of international guidelines. In routine real-world clinical practice, it is unclear how well this evidence base is applied. The primary objective of this study was to assess the patterns of pharmacotherapy use, especially anti-platelet therapy, at the time of thrombolysis, and on discharge from hospital admission, and assess whether real-world clinical practice conforms to current guideline recommendations.

**METHODS:** This was a retrospective study carried out in a large regional centre in Victoria, Australia.

**RESULTS:** 58 STEMI patients were treated by thrombolytic therapy in a pharmaco-invasive model over a 12-month period. 28 of these patients belonged to the locally managed pharmaco-invasive subgroup, and 30 patients belonged to pharmaco-invasive transfer subgroup. At the time of thrombolysis, dual anti-platelet therapy was provided for only 44% of patients in the local subgroup and 50% of patients in the transfer subgroup. Various patterns of

dual anti-platelet use were observed, which were not supported by evidence. On discharge from hospital admission, the prescription of dual anti-platelet therapy significantly increased to 88% of patients in the local subgroup ( $P = 0.02$ ), and 90% of patients in the transfer subgroup ( $P = 0.002$ ).

**CONCLUSION:** Clinician adherence to evidence based use of anti-platelet therapy was poor at the time of thrombolysis in a contemporary cohort of Australian STEMI patients. This could represent opportunities to improve care for STEMI patients presenting to regional and rural centres.

**Key words:** Pharmaco-invasive management; Thrombolysis; Rural and remote care; Anti-platelet therapy; Evidence-based practice, Medication adherence, ST-elevation myocardial infarction

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### INTRODUCTION

ST-elevation myocardial infarction (STEMI) is associated with a high rate of morbidity and mortality<sup>[1]</sup>. Primary percutaneous coronary intervention (PCI) is the standard of care for patients with timely access, usually within 90 minutes of first medical contact, to the cardiac catheter laboratory<sup>[2-4]</sup>. In regional and rural centres, or smaller metropolitan centres without on-site cardiac catheter laboratory, primary thrombolytic treatment for STEMI continues to play an important role<sup>[5]</sup>. In the pharmaco-invasive model, STEMI patients receive primary thrombolytic treatment if there are no contraindications to thrombolysis, and get transferred to another centre for early invasive coronary angiography<sup>[6,7]</sup>. Large bodies of evidence and literature exist on the optimal pharmacotherapy

treatment strategies to improve patient outcomes at the time of thrombolysis<sup>[2-4,8]</sup>. The use of dual anti-platelet therapy prior to, or at the time of thrombolysis for STEMI has been shown to reduce patient mortality<sup>[9,10]</sup>. This is a class IA recommendation of international guidelines<sup>[2,3]</sup>. It is unclear whether in real-world clinical practice, where primary thrombolytic treatment is often provided by smaller centres without tertiary cardiology services in the emergency care setting, whether these evidence-based treatment recommendations are adhered to. There is much literature devoted to the importance of medication adherence by patients following myocardial infarction<sup>[11-14]</sup>. Clinician adherence to prescription of optimal evidence based pharmacotherapy, especially at the time of providing thrombolytic treatment, has not been studied previously. This study aimed to study the patterns of pharmacotherapy use for STEMI patients at the time of thrombolysis, and on discharge, with a particular focus on anti-platelet therapy. We studied whether clinicians' practice conformed to established management guidelines and evidence base.

## METHODS

A retrospective analysis of consecutive patients presenting with STEMI to Bendigo Health between February 2013 to January 2014 was performed. This project was approved as a quality assurance project within the Department of Cardiology, Bendigo Health. Bendigo Health is a major regional hospital in Victoria, Australia. It services a large catchment area in country Victoria that includes more than 300,000 patients. Currently, there is one cardiac catheter laboratory that is funded on a part-time basis. STEMI patients were divided into two subgroups: (1) Pharmaco-invasive Local: patients who received primary thrombolytic treatment, followed by coronary angiography at Bendigo Health; (2) Pharmaco-invasive Transfer: patients who received primary thrombolytic treatment, followed by transfer for coronary angiography at another centre. Patients were identified based on admission diagnosis to the emergency department. Demographic data and risk factor profiles were collected. Information regarding pharmacotherapy use was collected by analysing patients' drug charts on presentation to the emergency department, and pharmacy scripts on hospital discharge.

### Statistical analysis

Data were analysed using SPSS 16.0 (SPSS Inc., Chicago). Differences between pharmaco-invasive local and transfer subgroups were analysed using the Chi-Square test for categorical data, and independent samples T test for numerical data.  $P < 0.05$  was considered statistically significant. Results for average/mean were expressed in terms of percentage  $\pm$  standard deviation.

## RESULTS

There were 28 patients in the Pharmaco-invasive Local subgroup: 25 patients received primary thrombolytic treatment; 3 patients were not thrombolysed (2 patients presented late; 1 patient was elderly and had a threatened anterior STEMI). There were 30 patients in the Pharmaco-invasive Transfer subgroup (Transfer): 28 patients received primary thrombolytic treatment; 2 patients were not thrombolysed (1 patient suffered from a recent stroke; 1 patient presented late) (Figure 1).

25 patients in the local subgroup proceeded to coronary angiography after thrombolysis. 3 patients did not receive angiography: 2 patients died in the emergency department

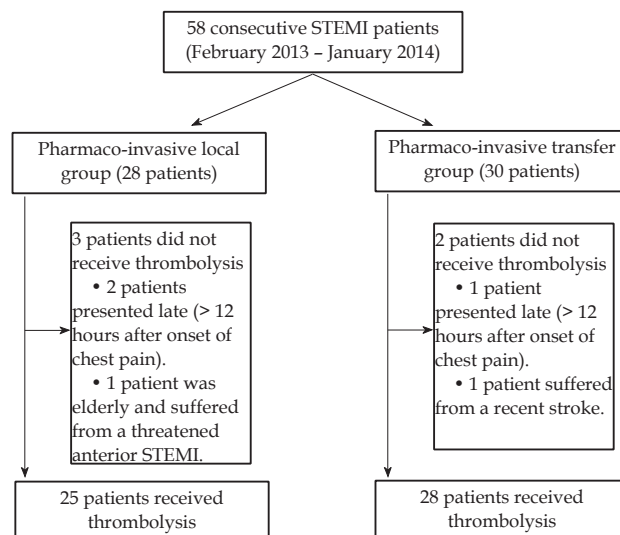


Figure 1 Study design: Pharmacotherapy prescribed and used at the time of thrombolysis was analysed and compared against pharmacotherapy prescription after coronary angiography on hospital discharge.

Table 1 Demographic profiles of the study patients.

	Pharmaco-invasive Local (n=28)	Pharmaco-invasive Transfer (n=30)	P
Age (years; mean $\pm$ standard deviation)	66 $\pm$ 13	65 $\pm$ 11	0.77
Sex (Number of patients, %)			0.27
Male	21 (75)	26 (87)	
Female	7 (25)	4 (13)	
Cardiac risk factors (Number of patients, %)			>0.05
Smoking	18 (64)	12 (40)	0.79
Diabetes mellitus	5 (18)	7 (23)	0.79
Hypertension	21 (75)	21 (70)	0.79
Dyslipidaemia	15 (54)	13 (43)	0.79
Family history of IHD	11 (39)	3 (10)	0.79
Type of STEMI (Number of patients, %)			>0.05
Anterior/Anterolateral	10 (36)	13 (43)	0.79
Inferior/Inferolateral/Inferoposterior	17 (61)	17 (57)	0.12
Right ventricular	1 (4)		N/A
Killip Class (Number of patients, %)			>0.05
Class I	21 (75)	20 (67)	0.79
Class II	4 (14)	6 (20)	0.79
Class III	0 (0)	0 (0)	N/A
Class IV	3 (11)	4 (13)	0.79
Thrombolysis complications (Number of patients, %)	0	3 (11)	0.79

(ventricular fibrillation; cardiogenic shock), 1 patient had multiple co-morbidities and severe aortic stenosis. 29 patients in the transfer subgroup proceeded to coronary angiography. 1 patient died in the cardiac catheter laboratory from electro-mechanical dissociation cardiac arrest prior to angiography.

### Demographics and clinical profiles

The baseline demographic profiles of patients in both subgroups were similar, without any statistically significant differences between the subgroups (Table 1). There were more male than female patients. Many patients possessed one or more risk factors for coronary artery disease. The three commonest risk factors were: hypertension, smoking and dyslipidaemia. Inferior/Inferolateral/Inferoposterior STEMI presentations made up the highest proportion of STEMI presentation in both subgroups (61% in the local subgroup; 57% in the transfer subgroup), followed by anterior STEMI presentations (36% in the local subgroup;

43% in the transfer subgroup). On presentation, the majority of patients belonged to Killip class I (75% in the local subgroup; 67% in the transfer subgroup). A smaller, but clinically significant number of patients presented with STEMI in Killip class IV (11% in the local subgroup; 13% in transfer subgroup).

**Pharmacotherapy use at the time of thrombolysis**

Tenecteplase was the universal thrombolytic agent used for all patients in the study. All patients received aspirin therapy either prior to, or at the time of thrombolysis. Anticoagulation treatment was provided by intravenous heparin administered following thrombolysis. One patient in the local subgroup received subcutaneous enoxaparin as anticoagulation. At the time of thrombolysis, dual anti-platelet therapy was prescribed and used for 47% of patients in the study (44% of patients in the local subgroup; 50% of patients in the transfer subgroup). Of the patients receiving dual anti-platelet therapy, various patterns of anti-platelet therapy prescription were observed. These included prescribing: (1) clopidogrel 75 mg orally; (2) clopidogrel 300mg orally; (3) clopidogrel 600 mg orally; (4) ticagrelor 180 mg orally; (5) clopidogrel 300 mg orally and ticagrelor 180 mg orally. Clopidogrel was prescribed and used for 43% of patients in the study, at the time of thrombolysis (40% of patients in the local subgroup, and 46% of patients in the transfer subgroup). There were no statistically significant differences in pharmacotherapy use at the time of thrombolysis between the subgroups (Table 2).

**Thrombolysis complications**

There were no documented complications from thrombolysis in the local subgroup. Three patients (11%) in the transfer subgroup developed complications from thrombolysis: 2 patients developed haematemesis requiring endoscopy and invasive treatment; 1 patient developed dental bleeding that was managed conservatively.

**Pharmacotherapy prescription on discharge**

All appropriate patients were prescribed aspirin therapy on discharge (96% of patients in the local subgroup; 97% of patients in the transfer subgroup). There was one patient in the local subgroup with an anaphylactic reaction to aspirin. This patient presented with an inferior STEMI, and was diagnosed with triple vessel coronary artery disease on a locally performed coronary angiogram. He received revascularisation treatment with coronary artery bypass graft surgery (CABG). Three patients in the local subgroup died during the index admission: one patient died on post-operative day 6 after CABG from suspected pulmonary embolus; the second patient presented with infero-lateral STEMI, and died on presentation from incessant ventricular arrhythmias despite primary thrombolysis; the third patient presented with inferior and right ventricular STEMI, and died from cardiogenic shock on day 2 of admission. Two patients in the transfer subgroup died during the index admission: one patient died from electromechanical dissociation cardiac arrest in the cardiac catheter laboratory prior to coronary angiography; another patient with anterior STEMI died on day two after ventricular septal defect repair.

The majority of patients were prescribed dual anti-platelet therapy on discharge (88% in the local subgroup; 90% in the transfer subgroup). Patients who were revascularised by CABG were not prescribed dual anti-platelet therapy on discharge (3 patients in the local subgroup; 2 patients in the transfer subgroup). On hospital discharge, the prescription of dual anti-platelet therapy was significantly higher, compared to the time of thrombolysis ( $P = 0.02$  for the local subgroup;  $P = 0.002$  for the transfer subgroup). The

**Table 2** Pharmacotherapy at the time of thrombolysis ( $n$ =number of patients; % = percentage of thrombolysed patients treated with the particular type of pharmacotherapy).

Pharmacotherapy	Pharmaco-invasive	Pharmaco-invasive	P
	Local (n, %)	Transfer (n, %)	
Aspirin	25 (100)	28 (100)	0.68
Tenecteplase	25 (100)	28 (100)	0.68
Heparin	24 (96)	28 (100)	0.68
Enoxaparin	1 (4)	0 (0)	N/A
Dual anti-platelet therapy	11 (44)	14 (50)	0.68
Clopidogrel 75 mg	1 (4)	8 (29)	
Clopidogrel 300 mg	9 (36)	3 (11)	
Clopidogrel 600 mg	0 (0)	2 (7)	
Ticagrelor 180 mg	0 (0)	1 (4)	
Clopidogrel 300 mg + Ticagrelor 180 mg	1 (4)	0 (0)	

**Table 3** Pharmacotherapy on discharge following coronary angiography. In the local subgroup, 25 patients proceeded to coronary angiography. Three patients did not have dual anti-platelet therapy on discharge (2 patients were treated by CABG; one patient was elderly with severe aortic stenosis and multiple co-morbidities). In the transfer subgroup, 29 patients proceeded to coronary angiography. One patient died on day 2 post-operatively ( $n$ =number of patients; % = percentage of patients treated with the particular type of pharmacotherapy on hospital discharge).

Pharmacotherapy	Pharmaco-invasive	Pharmaco-invasive	P
	Local (n, %)	Transfer (n, %)	
Aspirin	24 (96)	28 (97)	0.59
Dual anti-platelet therapy	22 (88)	26 (90)	0.59
Clopidogrel	22 (88)	26 (90)	
Ticagrelor	15 (60)	19 (66)	
Prasugrel	6 (24)	6 (21)	
Statin	1 (4)	1 (3)	
Angiotensin converting enzyme inhibitor (ACEi)	25 (100)	28 (97)	0.59
Beta-blocker	18 (72)	20 (67)	0.59
Anti-coagulant	18 (72)	23 (79)	0.59
Anti-coagulant	1 (4)	5 (17)	0.59

prescription pattern of dual anti-platelet therapy was varied, including clopidogrel, ticagrelor and prasugrel. Clopidogrel was the most commonly prescribed second anti-platelet agent on discharge (60% in the local subgroup; 66% in the transfer subgroup). Statin therapy was prescribed for all appropriate patients on discharge. Rates of prescription of angiotensin converting enzyme inhibitor and beta-blocker therapy were high on discharge in both treatment subgroups. There were no statistically significant differences in pharmacotherapy prescription on hospital discharge between the subgroups (Table 3).

**DISCUSSION**

This study was the first to report on the patterns of prescription and use of optimal pharmacotherapy by clinicians, especially anti-platelet therapy, at the time of thrombolysis for STEMI. It demonstrated that clinician adherence to evidence based use of dual anti-platelet therapy as adjunct treatment at the time of thrombolysis for STEMI was poor. At the time of thrombolysis, dual anti-platelet therapy was prescribed and used for 47% of patients in the study (44% of patients in the local subgroup; 50% of patients in the transfer subgroup). This was in stark contrast to the pharmacotherapy prescribed for STEMI patients after assessment by coronary angiography on hospital discharge. This study demonstrated that clinicians were good at providing optimal pharmacotherapy for STEMI patients after appropriate revascularisation. Pharmacotherapy on discharge was well prescribed and followed evidence based practice. The majority of patients were

prescribed dual anti-platelet therapy on discharge (88% in the local subgroup; 90% in the transfer subgroup). Some therapeutic agents were much more frequently prescribed by clinicians than others. Reassuringly, aspirin was prescribed and used for all appropriate patients either before, or at the time of thrombolysis, and again on hospital discharge. In addition, statin therapy was prescribed for all appropriate patients on hospital discharge.

The exact factors leading to poor clinician adherence to evidence-based pharmacotherapy for STEMI patients at the time of thrombolysis were unclear. We hypothesize that several factors could have contributed. Firstly, STEMI is a time critical medical emergency. Much of the initial emergency medical care for thrombolysed patients is usually provided in the emergency care setting. Primary thrombolysis for STEMI is often provided in the emergency department<sup>[15-17]</sup>. There is a large amount of published literature focusing on the importance of timely provision of thrombolytic therapy for STEMI, with a target door-to-needle time of less than 30 minutes<sup>[15-17]</sup>. Similarly, a large amount of education and training for medical and nursing staff dealing with STEMI patients focuses on the provision of the thrombolytic agent for those patients without contraindications, as quickly as possible. This focus on the provision of thrombolytic therapy may therefore have resulted in non-intentional neglect of the need to provide evidence-based anti-platelet therapy as adjunct STEMI treatment by clinicians. Secondly, the second anti-platelet agent may not be as readily available as aspirin. With the increasing availability of PCI, and the use of other anti-platelet agents peri-procedurally, such as ticagrelor and prasugrel<sup>[18]</sup>, there may be confusion with regard to which anti-platelet agent could be used in the primary thrombolysis setting. Comparatively, most appropriate patients were prescribed optimal pharmacotherapy including dual anti-platelet therapy on hospital discharge. This may reflect the fact that following STEMI, after appropriate revascularisation, all patients would have received specialist management by dedicated cardiology services. During an inpatient cardiology admission, generally, more time and resources would be available compared to the initial emergency care setting, to provide optimal evidence-based secondary prevention pharmacotherapy prior to discharge.

Amongst patients who were prescribed dual anti-platelet therapy, a range of dual anti-platelet prescription patterns was observed, including various doses of clopidogrel (75 mg, 300 mg, 600 mg), ticagrelor, and double-loading with clopidogrel and ticagrelor. The current evidence base and published guidelines support the use of clopidogrel only at the time of thrombolysis, with a recommended loading dose of 300 mg for patients  $\leq 75$  years; or 75 mg for patients  $> 75$  years of age<sup>[2-4]</sup>. The use of other P2Y<sub>12</sub> antagonists at the time of thrombolytic therapy has not been studied by large prospective studies. The heterogeneity in the prescription of dual anti-platelet therapy may result from a lack of clear understanding of the evidence base for anti-platelet therapy in the thrombolysis setting. The TREAT trial (Ticagrelor in patients with ST elevation myocardial infarction treated with pharmacological thrombolysis) will address the efficacy of a loading dose of 180 mg oral ticagrelor versus a loading dose of 300 mg oral clopidogrel, post thrombolysis for ST elevation myocardial infarction<sup>[19]</sup>.

Our study demonstrated that clinician prescription of optimal dual anti-platelet therapy was poor at the time of thrombolysis. This could represent opportunities to improve patient care in pharmaco-invasive STEMI management, particularly in regional and rural centres. This gap could potentially be readily addressed by providing education on evidence-based pharmacotherapy for medical and nursing staff

involved in providing thrombolytic treatment for STEMI patients in the emergency care setting. Further studies are needed to examine if these gaps in evidence based care identified by our study exist in other centres practising pharmaco-invasive STEMI management. By identifying and addressing these gaps, clinical outcomes could be improved for many STEMI patients presenting to non-primary PCI centres.

### Limitations

This study was a single-centre retrospective study over a 12-month period. Further prospective studies in regional Australian centres practising pharmaco-invasive STEMI management are warranted to examine the clinical outcomes, and gaps in evidence-based care for patients managed in regional and remote centres.

## CONCLUSION

Clinician adherence to evidence based use of dual anti-platelet therapy at the time of thrombolysis for STEMI was poor in a contemporary Australian regional cohort of patients. Comparatively, pharmacotherapy on hospital discharge was generally well prescribed and evidence based. This could represent opportunities to improve care for STEMI patients by improving the appropriate use of optimal dual anti-platelet therapy at the time of thrombolysis.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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