Pharmacokinetics and pharmacodynamics of oral P2Y12 inhibitors during the acute phase of a myocardial infarction: A systematic review

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Pharmacokinetics and Pharmacodynamics of Oral P2Y12 Inhibitors During the Acute Phase of a Myocardial Infarction: A Systematic Review.

Abstract

Background: The immediate administration of oral antiplatelet therapy in the form of aspirin plus a P2Y12 inhibitor is the universally recognised standard of care for patients who present with acute myocardial infarction. Despite strong recommendations for their use, there are a paucity of data describing their onset of action and clinical efficacy during the short time frames from confirmation of diagnosis to reperfusion with primary percutaneous coronary intervention.

Objectives: To complete a systematic review evaluating the currently available evidence regarding the pharmacokinetic and pharmacodynamic activity of orally administered clopidogrel, prasugrel and ticagrelor during the acute phase of a myocardial infarction in relation to mechanical reperfusion with primary percutaneous coronary angioplasty.

Methods: We searched Pubmed and EMBASE databases up to January 2016 using the terms outlined in our search strategy.

Results: Twelve papers were included in our final analysis; seven relating to pharmacodynamic studies, one to a pharmacokinetic study and four to a pharmacokinetic/pharmacodynamic study.

Conclusion: Our results indicate that despite the administration of oral P2Y12 inhibitors including newer more potent agents that should allow for greater and more consistent levels of platelet inhibition, the physiological state of ST

segment elevation MI (STEMI) and the co-administration of opioid based analgesia are associated with a reduction in the degree of platelet inhibition achieved following their administration.

Keywords

P2Y12 inhibitors, primary percutaneous coronary intervention, ST elevation myocardial infarction, inhibition of platelet activity (IPA), platelet function assays**,** STEMI, aspirin, clopidogrel, ticagrelor, prasugrel

Introduction

Despite significant advances in both the interventional and pharmacological management of patients who present with STEMI, there remains significant morbidity, mortality and a sizable pharmacoeconomic burden associated with the condition (1). 2014 British Heart Foundation statistics data indicate that in the United Kingdom alone, 2.3 million people have a current diagnosis of coronary heart disease, with approximately 11% of men and 15% of women admitted to hospital following a myocardial infarction dying within 30 days of presentation (2).

Of all the acute coronary syndromes, STEMI patients suffer the highest early mortality and therefore urgent reperfusion and early pharmacological intervention are advised and mandated (3).

The principal aim of treatment, following diagnosis of STEMI is to ensure timely, rapid and complete restoration of blood flow to the affected part of the

myocardium to minimise myocardial cell death and preserve myocardial function (4). Whilst thrombolysis can be considered an option to allow for early reperfusion, the likelihood of achieving vessel patency is as low as 50% even with the most efficacious agents. Also the increased risk of early reinfarction following its administration is associated with adverse outcomes and increased mortality (5). PPCI achieves infarct vessel patency in over 90% cases and unequivocally improves outcomes in the majority of patients when compared to thrombolysis. (6).

Pathophysiology of Myocardial Infarction

The pathophysiology of STEMI in the vast majority of cases relates to the rupture of a vulnerable atherothrombotic plaque, with subsequent platelet activation and adhesion leading to complex thrombus formation with activation of the clotting cascade and abrupt vessel occlusion (7-9). Although mechanical reperfusion via PCI is a highly effective procedure allowing for rapid restoration of coronary blood flow to the affected section of the myocardium, the administration of adjunctive antithrombotic drug therapies is necessary to mitigate against both peri-procedural and post-procedural ischaemic and thrombotic complications.

Current Antiplatelet Treatment Options

Since platelets play such a critical role in the underlying disease process and associated complications of a myocardial infarction, the recommended standard of care following a diagnosis of STEMI is for the immediate administration of dual antiplatelet therapy with aspirin plus a second antiplatelet agent belonging to the P2Y12 inhibitor class, to prevent further

adverse cardiovascular and cerebrovascular events (MACCE) and stent thrombosis (10, 11).

Aspirin, the most commonly prescribed antiplatelet agent in clinical practice, leads to a 23% reduction in mortality in the context of an acute myocardial infarction and a 25% reduction in MACCE (12, 13). However, despite these proven benefits, aspirin monotherapy in the context of STEMI and subsequent coronary artery stent implantation is insufficient to protect against complications such as stent thrombosis, a potentially fatal complication, occurring in up to 3% of PPCI cases that is associated with a mortality of 40% (14-16).

The armamentarium of antiplatelet therapies and in particular the oral P2Y12 inhibitors have evolved considerably over the last decade. Clopidogrel, a second generation thienopyridine, is an effective orally administered P2Y12 inhibitor that is supported by an evidence base that spans not only decades but also the entire spectrum of acute coronary syndromes, from medically managed patients to those who undergo PPCI. It is, however, subject to a number of limitations, which hamper its use in clinical practice. Firstly, it is a pro-drug that requires metabolic conversion to its active form; which occurs following a two-step biotransformation process dependent on the cytochrome P450 3A4 and 2C19 enzymes (17, 18). There is significant heterogeneity within the general population with regards to the activity of the C19 allele, which in turn can lead to impaired conversion of clopidogrel to its active form

(18). These genetic polymorphisms lead to significant inter-individual variability in response to its administration; those patients in whom effective conversion of clopidogrel to its active form does not take place are at increased risk of further thrombotic events (14, 18). In addition, clopidogrel is relatively slow in terms of its onset of action and ability to effectively inhibit platelet activity (19, 20). This is a potential major disadvantage in the context of PPCI, where effective and optimal levels of platelet inhibition are required almost immediately.

In comparison to clopidogrel, both prasugrel and ticagrelor have demonstrated less inter-individual variability in response and are more rapid in onset of action providing greater and more consistent levels of platelet inhibition (21, 22). The enhanced pharmacodynamic profile of prasugrel and ticagrelor translates into improved clinical efficacy and outcomes with a reduction in MACCE and stent thrombosis when compared to clopidogrel as demonstrated by the findings of the pivotal TRITON-TIMI 38 (for prasugrel in ACS patients undergoing PCI) and PLATO trial (for ticagrelor in patients with ACS undergoing both medical and interventional treatment) (23, 24).

Rapid, and effective inhibition of platelet activity is highly desirable and of paramount clinical importance in the context of STEMI managed with PPCI since the time scales involved from symptom onset to the restoration of blood flow are very short; with UK recommendations stipulating a time frame of 120 minutes from call to balloon time and 90 minutes from arrival to a PPCI capable centre to myocardial reperfusion/angioplasty (door to balloon time) to

ensure maximal myocardial salvage, preservation of left ventricular function, improved outcomes and survival (4) (25, 26).

Following the administration of an oral loading dose, the pharmacodynamic data supporting the speed of onset of prasugrel and ticagrelor indicates that optimal levels of platelet inhibition are achieved within 30 and 60 minutes respectively, however, these data are derived from healthy volunteers or patients with stable coronary artery disease and as such is not reflective of the physiological state of STEMI in which drug handling is invariably altered (21, 22, 27).

Although dual antiplatelet therapy with aspirin and either clopidogrel, prasugrel or ticagrelor in the management of acute coronary syndromes is supported by an evolving evidence base, there is a lack of pharmacodynamic and pharmacokinetic data regarding the efficacy of orally administered P2Y12 inhibitors during the acute phase of a myocardial infarction. In view of the short times scales involved in PPCI and the physiological changes that manifest during a STEMI, ideally antiplatelet agents should be administered that are rapid onset of action and exhibit a uniform powerful antiplatelet effect.

Study Objective

To undertake a systematic review of the available evidence regarding the pharmacokinetic and pharmacodynamic properties of orally administered P2Y12 inhibitors (clopidogrel, prasugrel and ticagrelor) during the acute phase of a STEMI.

Methods

Our systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on June 19th 2015 in accordance with the recommendations stipulated within the PRISMA-P guidelines and was last updated on September 6th 2015 (CRD 42015023393) (28, 29)

Search Strategy

An initial literature search was undertaken to determine whether this research question has already been addressed. At the time there were no indications that a review of this nature had already been completed. The main reviewer (NK) and secondary reviewer (AC) agreed the systematic review question, search terms, search strategy and inclusion/exclusion criteria for the final studies to be included. A structured and comprehensive literature search was performed in January 2015 using Pubmed (from inception to January 2016) and EMBASE (Ovid) (from 1974 to December week 3 2015). In addition, a search of the Cochrane database of systematic reviews was also undertaken, however, this did not reveal any relevant or related review topics. Secondary references found during the initial literature search were deemed to fall under the category of “grey” data/literature.

Study Selection

The key medical subheading search terms used during the literature search included, clopidogrel, prasugrel, ticagrelor, P2Y12 inhibitors, myocardial infarction, STEMI, gastrointestinal absorption, cardiogenic shock, pharmacokinetics and pharmacodynamics.

As shown in figure 1, a total of 5,760 papers were retrieved following the initial literature search using PubMed and a further 4,065 from EMBASE. The search results were exported to a reference manager programme (EndNote) where duplicate searches were excluded. Of those searches that remained (n = 6,374), a title and abstract review was undertaken to determine whether the contents of the selection were in line with the inclusion and exclusion criteria stipulated at the outset (Appendix 1). For the final title/abstracts selected, full papers were retrieved and the contents scrutinised in more detail to determine their relevance in relation to the research question and inclusion criteria. Any discrepancies in the search results identified were discussed by NK and AC, compared against the inclusion/exclusion criteria and screening questions and a decision made as to whether the paper should be included in the final review. Where a decision regarding inclusion could not be made, the opinion of a third reviewer JC was sought. In order to ensure the appropriateness of the final selections, a number of screening questions, based on the CASP and SURE toolkits were devised and utilised (Appendix 2).

Results

Study Selection and Data Extraction

The screening and selection criteria for the final included citations are outlined in figure 1. We reviewed the full text of 117 of the 6,474 records identified through the initial database search. Of these, a final twelve papers fulfilled our criteria for inclusion in the analysis; seven relate to pharmacodynamic studies and four to both pharmacodynamic and pharmacokinetic studies and

the remainder is a pharmacokinetic study only. Table 1 provides a summary of the final articles selected for inclusion in the systematic review along with their main findings.

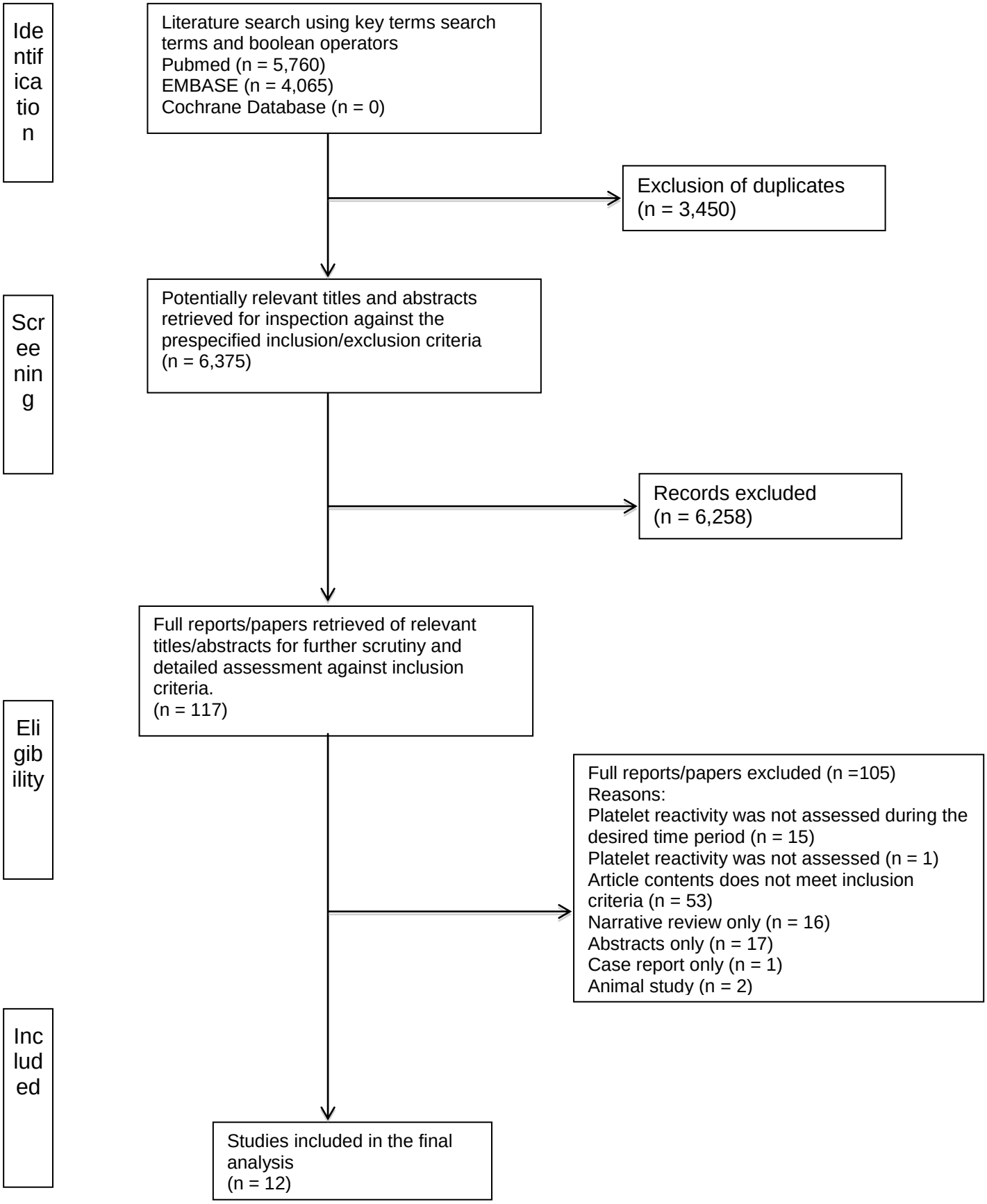
Table 1: Study, patient characteristics and findings

Reference	Study type	Population/ Intervention	Comparators	Main findings
Alexopoulos (30)	PD	STEMI (n = 55) PPCI	Prasugrel 60mg (PO) (n = 28) Ticagrelor 180mg (PO) (n = 27)	VerifyNow PRU at 1hr for prasugrel PRU 257 and ticagrelor PRU 231. (PRU ≥ 230 indicates HTPR). There is an initial delay in antiplatelet effect; taking approx. 2hrs to see sufficient levels of IPA (PRU <208)
Alexopoulos (31)	PK & PD	STEMI (N = 20) PPCI	Ticagrelor 180mg crushed tablets (PO) compared with Ticagrelor 180mg integral tablets (PO)	PD: PRU at 0.5 and 1h, lower platelet reactivity and higher % platelet inhibition observed following administration of crushed compared with integral ticagrelor. PK: Plasma exposure of both ticagrelor and its active metabolite are greater following administration of crushed vs integral tablets.
Beigel (32)	PD	STEMI (n = 79) PPCI	Clopidogrel 600mg (PO) (n = 49) Prasugrel 60mg (PO) (n = 30)	At baseline, ADP induced aggregation – comparable between prasugrel and clopidogrel. At PPCI - ADP induced platelet aggregation significantly less in the prasugrel group compared with clopidogrel group; but less than 50% of prasugrel treated patients achieve IPA < 70%.
Heestermans (33)	PK	STEMI vs healthy controls (n = 21) PPCI vs no intervention	STEMI - clopidogrel 600mg (PO) (n = 11) Healthy controls - clopidogrel 600mg (PO) (n = 10)	Plasma concentration of the active thiol metabolite of clopidogrel is significantly lower in STEMI patients compared to the healthy controls. Impaired bioavailability of clopidogrel in STEMI patients leads to suboptimal levels of IPA.
Hobl (34)	PK & PD	Healthy subjects (n = 24) No intervention	Clopidogrel 600mg (PO) + morphine 5mg (IV) Compared with clopidogrel 600mg (PO) + placebo (IV)	PD: morphine administration is associated with a 2hr delay in achieving maximal IPA PK: morphine administration significantly reduces the maximal concentration on the active thiol metabolite (Cmax) and prolongs the time taken to reach maximal concentration (Tmax) A clinically significant drug/drug interaction is apparent following the co-administration of morphine and clopidogrel.
Hobl (35)	PK & PD	Healthy (n = 12) No intervention	Prasugrel 60mg (PO) + morphine 5mg (IV) compared with prasugrel 60mg (PO) + Placebo (IV)	PD: In healthy volunteers, the administration of morphine does not affect levels of IPA PK: although morphine administration reduces the maximal plasma concentration of prasugrel AM (Cmax), it does not have any effect on total exposure (AUC) or the time taken to achieve maximum concentrations (Tmax).
Kubica (36)	PK & PD	STEMI (n = 45) NSTEMI (n = 15) PCI	Ticagrelor 180mg (PO) + morphine 5mg (IV) compared with Ticagrelor 180mg (PO) + placebo (IV)	PD: co-administration of morphine leads to an impaired antiplatelet effect as demonstrated by an increase in platelet reactivity compared to those patients administered placebo. PK: co-administration of morphine leads to a reduction in total exposure to ticagrelor and its active metabolite (reduced AUC and Tmax) and a reduced Cmax (maximal plasma concentration)

Orban (37)	PD	STEMI, complicated by cardiogenic shock (n = 145) PPCI	Clopidogrel 600mg (PO) (n = 95) Prasugrel 60mg (PO) (n = 50)	42% of patients showed HTPR following loading doses of either clopidogrel or prasugrel. All-cause mortality lower at 30 days in patients treated with prasugrel without any increase in bleeding risk.
Osmancik (38)	PD	Critically ill STEMI (n = 40) PPCI	Clopidogrel 600mg (PO) unstable STEMI (n=20) Clopidogrel 600mg (PO) stable STEMI (n=20)	PRI >53% is indicative of clopidogrel unresponsiveness. A greater reduction in %PRI was observed in stable compared to unstable STEMI patients.
Parodi (39)	PD	STEMI (n = 50) PPCI	Prasugrel 60mg (PO) (n = 25) Ticagrelor 180mg (PO) (n = 25)	Only 50% of patients demonstrate effective levels of IPA at 2hrs and at least 4 hrs is required to see sufficient IPA in the majority of patients. The administration of morphine is an independent predictor of HRPR at 2 hrs
Parodi (40)	PD	STEMI (n = 300) PPCI	Prasugrel 60mg (PO) +/- morphine (n = 95) Ticagrelor 180mg (PO) +/- morphine (n = 205)	The administration of morphine is associated with delayed onset of action and HRPR for both prasugrel and ticagrelor.
Parodi (41)	PD	STEMI (N = 82) PPCI	Ticagrelor 180mg crushed (PO) compared with Ticagrelor 180mg integral (PO)	At 1h, PRU 162 for crushed ticagrelor compared with PRU 252 for integral ticagrelor with no difference at 2h.

AMI – acute myocardial infarction, DTB –door to balloon time, PPCI - primary percutaneous coronary intervention, PD – pharmacodynamics PK – pharmacokinetic UFH – unfractionated heparin GPI – Glycoprotein IIb/IIIa inhibitor PRU – P2Y12 reactivity units PRI – platelet reactivity index IPA – inhibition of platelet activity HTPR – high on treatment platelet reactivity LTA – light transmission aggregometry LCMS – liquid chromatography tandem mass spectrometry

Figure 1: PRISMA-P Flowchart/Study Selection



Discussion

Although the place in therapy and longer-term benefits of DAPT are well established, there are very little data regarding the clinical utility oral P2Y12 inhibitors during the acute phase of a STEMI. Our systematic review highlights that the evidence base regarding the use of oral antiplatelet agents in this context is evolving as demonstrated by a number of trials that have been designed to assess the speed of onset, degree of platelet inhibition and clinical efficacy of the currently available oral $P2Y_{12}$ inhibitors during the narrow door to balloon times that are necessary for PPCI.

The pharmacodynamic and pharmacokinetic data collated and scrunitised during this review demonstrates inadequate levels of platelet inhibition in the first few hours after presentation in STEMI patients.

Phamacodynamic Studies

The pharmacodynamic studies included compare the administration of clopidogrel, prasugrel or ticagrelor in various patient populations; healthy volunteers, STEMI patients who were haemodynamically stable and unstable, or STEMI complicated by cardiogenic shock. A number of platelet function assays were utilised and the time points at which samples were collected in relation to the administration of the loading doses were variable. Irrespective of the differences in study designs, drugs administered and platelet function assays used, a number of key themes are apparent.

Firstly, despite the administration of prasugrel or ticagrelor loading doses, there is an initial delay in their onset of action, with an increase intrinsic

platelet reactivity present at 2 hours as demonstrated by PRU ≥ 230, indicating that neither agent has a particularly potent antiplatelet effect at the time of PPCI (30, 39)

STEMI is a highly pro-thrombotic state, in which vulnerable plaque rupture and the subsequent endovascular injury that ensues stimulates an increase in platelet reactivity even prior to antiplatelet therapy. Once treated with an antiplatelet agent, a poor response is referred to as high residual platelet reactivity (HRPR) and has been shown in a number of studies to be associated with poor outcomes following percutaneous intervention (9, 42).

Secondly, STEMI is a clinical state, which is often accompanied by haemodynamic instability and complications such as cardiogenic shock, the administration of catecholamines, systemic vasoconstriction, adrenergic activation and shunting of blood flow away from non-essential organs. This leads to reduced perfusion of the gut and liver with subsequent impairment of gastrointestinal absorption and metabolic biotransformation of orally administered drugs into their pharmacologically active forms. The impact of such physiological changes on the pharmacological effect of the oral P2Y12 inhibitors has been investigated and quantified for clopidogrel and prasugrel, with both agents being subject to HRPR (37-39, 43).

In the context of STEMI, all three agents (clopidogrel, prasugrel and ticagrelor) demonstrate significant variability in their onset of action and

degree to which they exert their therapeutic effect as demonstrated by the variable IPA results reported.

Our review highlights that the concept of interindividual variability to response is not a limitation that is unique to clopidogrel only, but is also manifest with prasugrel and ticagrelor, albeit to a lesser extent. With the platelet response to both prasugrel and ticagrelor being highly variable at the time of PPCI, suggesting that this interindividual variability is affected by impaired gastrointestinal absorption and additionally for prasugrel a subsequent reduction in metabolic conversion (via the liver) to its active metabolite (44).

Thirdly, the co-administration of morphine introduces a clinically significant drug-drug interaction, which leads to a delay in the onset of action of all three agents, with a consequent reduction in IPA and corresponding HRPR (40).

Lastly, recent trial data has demonstrated that modifying the formulation of ticagrelor administered to STEMI patients provides earlier and more pronounced levels of platelet inhibition (31, 41). The administration of crushed tablets dispersed in water (unlicensed use) rather than intact film coated tablets allows for faster and enhanced drug absorption, particularly in the first hour following administration and results in higher plasma levels of ticagrelor and its active metabolite and consequently greater reduction in platelet reactivity (31, 41). While modification of the dosage form represents an unlicensed, off-label use of ticagrelor, administration in such a manner often occurs as part of our routine clinical practice, for example in patients who are unconscious and/or intubated. The works of Alexopoulos and Parodi

provide some reassurance and demonstrate that crushing oral antiplatelets does not compromise their efficacy or lead to an increase in adverse effects e.g. stent thrombosis (31, 41).

Pharmacokinetic Studies

Only one study reports on pharmacokinetic data in the form of clopidogrel active metabolite generation in the context of STEMI; there are no data for prasugrel or ticagrelor active metabolite generation in this setting.

The work of Heestermans et al (2008), which focuses on clopidogrel pharmacokinetics, provides some insights into and quantifies the altered drug handling that occurs secondary to a STEMI. Generation of the clopidogrel active metabolite was shown to be significantly reduced in STEMI patients when compared to healthy controls. The consequent reduction in bioavailability and platelet inhibition is thought to be secondary to impaired GI absorption (33).

Although not undertaken in STEMI patients, the work of Hobl et al (34, 35) has been included in this systematic review, since both studies investigate the extent of the morphine-antiplatelet drug interaction in healthy patients. Hobl's work demonstrates that the co-administration of morphine leads to a reduction in clopidogrel active metabolite generation, demonstrated by a delay in the time take to achieve maximum concentration (Tmax), decrease in maximum concentration (Cmax) and a 34% reduction in area under the curve (AUC). Consequently, a decrease in antiplatelet effect is seen as demonstrated by a PRI >50% (34). In contrast, although the co-administration of morphine and

prasugrel in healthy volunteers resulted in a 31% reduction in prasugrel active metaboltite generation, there was no overall observed reduction in the degree of platelet inhibition achieved (35). It should be noted, however, that these results reflect the co-administration of morphine and prasugrel in healthy subjects; in the context of STEMI a reduction in antiplatelet effect in the first two hours after administration is likely (40, 45).

Opioid based analgesia and antiplatelet drug interaction

A growing body of evidence demonstrates that the administration of morphine inhibits peristalsis of the gut which delays gastric emptying as shown by a reduction in IPA (PRU >230 and %PRI >50%) as demonstrated in the studies included in this systematic review.

The deleterious effects of opioid administration on gastric absorption on the background of the physiological changes that occur during a STEMI have been discussed from as early as the 1980's. Kumana et al, very eloquently summarised that the absorption and subsequent pharmacological handling of orally administered drugs is altered and impaired during an acute MI. Pharmacokinetic and pharmacodynamic profiles are altered secondary gastrointestinal hypoperfusion, the presence of nausea and vomiting and the administration of opioid based analgesia such as morphine that can predispose to gastric stasis (46) This concept is further supported by Heestermans who demonstrated that physiological state of STEMI adversely influences intestinal absorption of orally administered clopidogrel (33). The speed of onset of both prasugrel and ticagrelor in the context of STEMI is also delayed, with recent data demonstrating that effective levels of platelet

inhibition are not seen for at least 2 to 4 hours following the administration oral loading doses (36, 39, 45)

The importance of gastric emptying as a predictor of pharmacological efficacy and subsequent clinical outcomes is demonstrated by the reduction in IPA, presence of HRPR and increased PRU as seen in the pharmacodynamic studies included in this review. Morphine administration is an important contributing factor in the delays seen in achieving maximal levels of IPA. For example, the adverse impact of morphine on ticagrelor pharmacodynamics was also highlighted during the ATLANTIC study. Although a directly acting agent that does not require metabolic activation, the co-administration morphine in the ambulance leads to a delay in the onset of action of ticagrelor (47). Thereby indicating that ticagrelor is still reliant on gastric absorption in order to exert its therapeutic effect.

As such, this review questions the administration of opioid based analgesia in the context of ACS in general, since its use has previously been associated with increased mortality in NSTEMI patients (48) and more recently a delay in the onset of action for clopidogrel, prasugrel and ticagrelor when administered to patients in the setting of STEMI (33, 36, 40, 49).

Alternative Treatment Options – Antiplatelet Therapy

In summary, despite administration of clopidogrel, prasugrel and ticagrelor loading doses, a significant proportion of patients undergoing PPCI do not achieve optimal levels of platelet inhibition. Gastrointestinal and hepatic hypoperfusion lead to impaired gastrointestinal absorption and subsequent metabolic conversion of clopidogrel and prasugrel. Ticagrelor, a directly acting agent that does not require metabolic conversion to its active form, is dependent on GI absorption and as such will also be subject to a delayed onset of action in STEMI patients. Consequently, all three agents display sup-optimal levels of IPA in the context of STEMI patients who undergo PPCI.

In the highly prothrombotic state encountered in the setting of STEMI, more rapid and profound platelet inhibition, as achieved by intravenous agents such as cangrelor, may be advantageous in patients undergoing PPCI.
Intravenous cangrelor offers the ability to achieve optimal levels of IPA in the narrow door to balloon time window, while the ability to transition to oral prasugrel/ticagrelor will allow for the longer-term benefits that are derived from DAPT (50). Cangrelor also has a rapid offset of action, which may be of value in certain patient subsets, for example those undergoing surgery or with bleeding complications (51).
While there are no head to head trials comparing the effectiveness of intravenous cangrelor with intravenous GPIs (abciximab, eptifibatide, tirofiban), both have proven efficacy in achieving rapid, high levels of platelet inhibition.
Previous guideline recommendations for the use of GPIs are based on data derived from clinical trials that precede recent pharmacological advances in

oral antiplatelet therapies. A number of studies have questioned the co-administration of GPIs in combination with the more potent oral antiplatelet agents, prasugrel and ticagrelor, particularly in view of the additional bleeding complications that can arise following such a combination (52, 53). A number of large-scale clinical trials have failed to demonstrate a significant clinical benefit following the administration to GPI +/- UFH in STEMI patients, such that even international guideline recommendations are unable to provide definitive endorsements regarding the utility of GPI in the era of potent oral P2Y12 inhibitors (11, 52, 54).

Alternative Treatment Options – Analgesia

While there is little evidence base to support the use of intravenous paracetamol in ACS patients, it does have a place in other cardiac settings e.g. post cardiac surgery, post-transcatheter aortic valve implantation and during renal denervation procedures and has been shown to have comparable efficacy to intravenous morphine in some settings (55-57). Further research is required to evaluate other analgesic agents, such as IV/PR paracetamol or parenteral non-steroidal anti-inflammatory drugs (NSAIDs) in the setting of STEMI.

Limitations

In common with all systematic reviews, this analysis is limited by the amount of currently available clinical data. We have included studies of heterogeneous endpoints and subject characteristics, in order to find a meaningful sample.

In addition, the timing of maximal IPA in relation to administration of the loading dose is not always clear and the use of background antithrombotic therapy between the different studies was markedly different. The reporting of clinical outcomes, pharmacodynamic and pharmacokinetic data is variable and the impact this may have on patient outcomes is not clear. Lastly, the studies included are not adequately powered to make inferences with regards to clinical outcomes, but they do provide further insights into, and support emerging evidence, indicating that even the newer generation oral P2Y12 inhibitors are not effective in the setting of STEMI when compared to normal controls.

Conclusion

The narrow time frames from symptom onset and subsequent mechanical reperfusion coupled with the pathophysiological changes that occur during a STEMI impose immediate barriers that significantly limit the clinical utility of orally administered $P2Y_{12}$ inhibitors in patients who present following a STEMI.

The outcomes of this systematic review highlight that even though newer agents such as prasugrel and ticagrelor allow for greater and more consistent levels of inhibition of platelet activity, in the setting of STEMI, they still do not achieve adequate or effective levels of platelet inhibition at the time of mechanical reperfusion (angioplasty). An alternative treatment option such as intravenous cangrelor provides an important step forward in the attempt to overcome the variability in response seen with all three currently available orally administered P2Y12 inhibitors. In addition, the possible administration

of intravenous paracetamol as an alternative form of analgesia may well prove to be an avenue of investigation in future studies.

Key messages

- Despite providing faster, greater and more consistent inhibition of platelet activity (IPA), prasugrel and ticagrelor in the setting of STEMI are still subject to HRPR and take at least 2 to 4 hours to achieve effective levels of platelet inhibition.
- The administration of morphine impairs gastrointestinal absorption of all three orally administered P2Y12 inhibitors with a consequent delay in their activity as demonstrated by a reduction in active metabolite generation and increased PRU and %PRI values following their co-administration.
- It is possible that modifying the formulation of currently available P2Y12 agents will lead to earlier onset and higher levels of platelet inhibition in the context of STEMI. However, it should be noted that a change in formulation is considered to be off-label use.

Addendum

All authors have actively contributed to the manuscript as follows:

N. Khan, A. Cox and J Cotton were responsible for the conception, design, data abstraction and the analysis and interpretation of data. N. Khan and J Cotton were responsible for the critical appraisal and review of data collated and manuscript writing. J Cotton gave final approval.

Appendix 1 Systematic Review - Inclusion and Exclusion Criteria

	Inclusion Criteria		Exclusion Criteria	
Populations	PD/PK human studies (Phase II, Phase III or dose finding studies)		PD/PK animal studies	
	Adults > 18 years		Children < 18 years	
	Adults < 70 years		Adults > 70 years (co-morbidities make DAPT difficult)	
	Patients diagnosed with/recruited following an MI - STEMI - NSTEMI		Primary prevention or other non-cardiac disease states	
	Patients with unstable angina		Patients with chronic stable angina (stable coronary artery disease)	
			Those who undergo elective PCI	
			Those who are medically managed	
			Doesn't relate to inclusion criteria	
Interventions	Primary PCI		Thrombolysis	
	Antiplatelets - Oral P2Y12 inhibitors: Clopidogrel, Prasugrel, Ticagrelor Plavix, Efient, Brilique Pre-procedural loading Intravenous antiplatelet agents: Cangrelor, eptifibatide, abciximab, tirofiban		Oral antiplatelets: Cilostazol, dipyridamole, ticlodipine Oral P2Y12 inhibitor (clopidogrel/prasugrel/ticagrelor) loading post-PCI	
	Other medications administered at the time of PCI – morphine/diamorphine			
Comparators	STEMI vs NSTEMI		Doesn't relate to inclusion criteria Papers on HTPR with clopidogrel and clopidogrel pharmacogenomics.	
	Drug handling - ADME			
	Degree of IPA STEMI vs NSTEMI vs healthy volunteer			
	Clopidogrel, prasugrel, ticagrelor, cangrelor			
	In extremis vs healthy			
Outcomes	%IPA			
	PRI			
	PRU			
	Adverse events (relate back to question)			
	Mortality (relate back to question)			
	Bleeding complications (relate back to question)			
Study Design	RCTs		Abstracts	
	Comparative studies		Case reports	
	Placebo controlled studies			
	English only papers			

Appendix 2 - Screening questions to assess the quality and appropriateness of the final articles selected for scrutiny prior to inclusion in the systematic review.

	Yes	Unclear	No
1. Does the study/paper relate back to the research question? (Is there a clear statement of the aims of the research/paper?)			
Population/problem?			
Intervention?			
Comparator/control?			
Outcomes? (is primary outcome identified?)			
RCT			
2. Was the population randomised? If yes, were the methods appropriate?			
Was allocation to a comparator/group concealed?			
Were the participants/investigators blinded to group allocation?			
Were interventions/comparators well described and appropriate?			
Were the groups similar at the start of the trial?			
Was the sample size sufficient?			
Were participants appropriately accounted for?			
Data analysis – appropriate?			
Results – were outcomes measures reliable and complete?			
Qualitative			
3. Was the qualitative methodology appropriate?			
4. Was the research strategy appropriate to the aims of the research?			
5. Was the recruitment strategy appropriate to the aims of the research?			
6. Was the data collected in a way that addressed the research issue?			
7. Have ethical issues been taken into consideration?			
8. Was the data analysis sufficiently rigorous?			
9. Is there a clear statement of findings?			
10. Are there any major limitations?			
11. How well does the paper/research relate back to your research question?			

	Yes/No	Explanation
Include		
Exclude		

Appendix 3 – Supplementary data – Comprehensive overview of the final studies selected for inclusion in the systematic review detailing study design, patient populations, interventions and drug therapies administered in addition to main trial outcomes.

Reference	Alexopoulos (30)
Study type	Pharmacodynamic
Population	STEMI (n = 55)
Intervention	PPCI
Comparators	Prasugrel 60mg (PO) (n = 28) Ticagrelor 180mg (PO) (n = 27)
Background antithrombotic therapy	Unspecified
Platelet function tests/Analysis undertaken	VerifyNow and Multiplate Analyser samples taken at baseline, 1,2,6, 24 hours and 5 days post loading
Findings	VerifyNow results demonstrate that PRU at 1hr prasugrel 257 and ticagrelor 231. (PRU ≥ 230 indicates HTPR). There is an initial delay in antiplatelet effect; taking approx. 2hrs to see sufficient levels of IPA (PRU <208)

Reference	Alexopoulos (31)
Study type	Pharmacokinetic and pharmacodynamic
Population	STEMI (n = 20)
Intervention	PPCI
Comparators	Ticagrelor 180mg crushed tablets (PO) compared with Ticagrelor 180mg integral tablets (PO)
Background antithrombotic therapy	Aspirin 325mg (PO) UFH 70U/kg +/- bivalirudin
Platelet function tests/Analysis undertaken	PD assessment: VerifyNow PK assessment: LC/MS Samples collected for analysis at baseline, 0.5h, 1h, 2h and 4h
Findings	PD: PRU at 0.5 and 1h, lower platelet reactivity and higher % platelet inhibition observed following administration of crushed compared with integral ticagrelor. PK: Plasma exposure of both ticagrelor and its active metabolite are greater following administration of crushed vs integral tablets.

Reference	Beigel (32)
Study type	Pharmacodynamic
Population	STEMI (n = 79)
Intervention	PPCI
Comparators	Clopidogrel 600mg (PO) (n = 49) Prasugrel 60mg (PO) (n = 30)
Background antithrombotic therapy	Aspirin 100mg (PO) +/- GPI (tirofiban)

Platelet function tests/Analysis undertaken	LTA at baseline, at PPCI and after 72hrs
Findings	Mean DTB – 48 +/-20 mins At baseline, ADP induced aggregation – comparable between prasugrel and clopidogrel. At PPCI - ADP induced platelet aggregation significantly less in the prasugrel group compared with clopidogrel group; but less than 50% of prasugrel treated patients achieve IPA <70%.

Reference	Heestermans (33)
Study type	Pharmacokinetic
Population	STEMI vs healthy controls (n = 21)
Intervention	PPCI
Comparators	STEMI - clopidogrel 600mg (PO) (n = 11) Healthy controls - clopidogrel 600mg (PO) (n = 10)
Background antithrombotic therapy	Aspirin 900mg (IV) + UFH 70IU/kg
Platelet function tests/Analysis undertaken	LCMS pre-dose, 0.5hrs, 1hrs, 1.5hrs, 2hrs, 3hrs, 4hrs, 6hrs and 24 hrs post-loading
Findings	Plasma concentration of the active thiol metabolite of clopidogrel is significantly lower in STEMI patients compared to the healthy controls. Impaired bioavailabilty of clopidogrel in STEMI patients leads to suboptimal levels of IPA.

Reference	Hobl (34)
Study type	Pharmacokinetic and Pharmacodynamic
Population	Healthy subjects (n = 24)
Intervention	None
Comparators	Clopidogrel 600mg (PO) + morphine 5mg (IV) compared with Clopidogrel 600mg (PO) + placebo (IV)
Background antithrombotic therapy	None administered
Platelet function tests/Analysis undertaken	PD assessment: VASP phosphorylation assay PK assessment: LC/MS
Findings	PD: morphine administration is associated with a 2hr delay in achieving maximal IPA PK: morphine administration significantly reduces the maximal concentration on the active thiol metabolite (Cmax) and prolongs the time taken to reach maximal concentration (Tmax) A clinically significant drug/drug interaction is apparent following the co-administration of morphine and clopidogrel.

Reference	Hobl (35)
Study type	Pharmacokinetic and Pharmacodynamic
Population	Healthy (n = 12)
Intervention	None

Comparators	Prasugrel 60mg (PO) + morphine 5mg (IV) compared with Prasugrel 60mg (PO) + Placebo (IV)
Background antithrombotic therapy	None administered
Platelet function tests/Analysis undertaken	PD assessment: VASP phosphorylation assay and Multiplate Analyser PK assessment: LC/MS
Findings	PD: In healthy volunteers, the administration of morphine does not affect levels of IPA PK: although morphine administration reduces the maximal plasma concentration of prasugrel AM (Cmax), it does not have any effect on total exposure (AUC) or the time taken to achieve maximum concentrations (Tmax).

Reference	Kubica (35)
Study type	Pharmacokinetic and Pharmacodynamic
Population	ACS (STEMI = 45 and NSTEMI = 15)
Intervention	Ticagrelor 180mg (PO) + morphine 5mg (IV) compared with ticagrelor 180mg (PO) + placebo (IV)
Comparators	
Background antithrombotic therapy	Aspirin 300mg (PO) +/- GPI
Platelet function tests/Analysis undertaken	PD: VASP phosphorylation assay, Multiplate Analyser, VerifyNow PK: LC-MS/MS Samples taken at baseline, 0.5h, 1h, 2h, 3h, 4h, 6h and 12h
Findings	PD: co-administration of morphine leads to an impaired antiplatelet effect as demonstrated by an increase in platelet reactivity compared to those patients administered placebo. PK: co-administration of morphine leads to a reduction in total exposure to ticagrelor and its active metabolite (reduced AUC and Tmax) and a reduced Cmax (maximal plasma concentration)

Reference	Orban (37
Study type	Pharmacodynamic
Population	STEMI (complicated by cardiogenic shock) (n = 145)
Intervention	PPCI
Comparators	Clopidogrel 600mg (PO) (n = 95) Prasugrel 60mg (PO) (n = 50)
Background antithrombotic therapy	Aspirin 500mg (IV) + UFH 5,000IU
Platelet function tests/Analysis undertaken	Multiplate Analyser
Findings	42% of patients showed HTPR following loading doses of either clopidogrel or prasugrel. All-cause mortality lower at 30 days in patients treated with prasugrel without any increase in bleeding risk.

Reference	Osmancik (38)
Study type	Pharmacodynamic
Population	Critically ill STEMI (n = 40)
Intervention	PPCI
Comparators	Clopidogrel 600mg (PO) unstable STEMI (n=20) Clopidogrel 600mg (PO) stable STEMI (n=20)
Background antithrombotic therapy	Aspirin 500mg (IV) + UFH 150IU/kg +/- GPI
Platelet function tests/Analysis undertaken	VASP phosphorylation assay at baseline, 4, 24 and 48 hrs post clopidogrel loading
Findings	PRI >53% is indicative of clopidogrel unresponsiveness. A greater reduction in %PRI was observed in stable compared to unstable STEMI patients.

Reference	Parodi (35)
Study type	Pharmacodynamic
Population	STEMI (n = 50)
Intervention	PPCI
Comparators	Prasugrel 60mg (PO) (n = 25) Ticagrelor 180mg (PO) (n = 25)
Background antithrombotic therapy	Aspirin 500mg (IV) + bivalirudin only
Platelet function tests/Analysis undertaken	VerifyNow at baseline, 2,4,8 and 12hrs post loading
Findings	Only 50% of patients demonstrate effective levels of IPA at 2hrs and at least 4 hrs is required to see sufficient IPA in the majority of patients. The administration of morphine is an independent predictor of HRPR at 2 hrs

Reference	Parodi (40)
Study type	Pharmacodynamic
Population	STEMI (n = 300)
Intervention	PPCI
Comparators	Prasugrel 60mg (PO) +/- morphine (n = 95) Ticagrelor 180mg (PO) +/- morphine (n = 205)
Background antithrombotic therapy	Aspirin 300-500mg + bivalirudin only
Platelet function tests/Analysis undertaken	VerifyNow 1,2,and 4hrs post loading
Findings	The administration of morphine is associated with delayed onset of action and HRPR for both prasugrel and ticagrelor.

Reference	Parodi (41)
Study type	Pharmacodynamic
Population	STEMI (n = 82)

Intervention	PPCI
Comparators	Ticagrelor 180mg (PO) crushed compared with Ticagrelor 180mg (PO) integral
Background antithrombotic therapy	Not specified in trial protocol.
Platelet function tests/Analysis undertaken	VerifyNow at 0h, 1h, 2h, 4h and 8h
Findings	At 1 h, PRU 162 for crushed ticagrelor compared with PRU 252 for integral ticagrelor with no difference at 2h.

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