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Use of glycoprotein IIb/IIIa antagonists to prevent stent thrombosis in morphine-treated patients with ST-elevation myocardial infarction

Running head: Glycoprotein IIb/IIIa antagonists to prevent stent thrombosis

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ABSTRACT

Morphine can delay absorption of $P2Y_{12}$-inhibitors in ST-elevation myocardial infarction (STEMI) patients, which has the potential to expose these patients to increased stent thrombosis risk after primary percutaneous coronary intervention (PPCI). Limited evidence exists for pharmacotherapeutic strategies aiming to mitigate this risk. We evaluated the impact of guideline-driven 'routine' glycoprotein IIb/IIIa antagonist (GPI) use in morphine-treated patients undergoing PPCI. 3224 consecutive STEMI patients undergoing PPCI at a large tertiary cardiac centre between 2012 and 2017 were evaluated. GPI use and outcomes before and after introduction of a local guideline were compared, and rates of definite stent thrombosis were identified at 24 hours and 30 days. GPI use increased from 42.4% to 69.9% after the introduction of the new guideline. Stent thrombosis occurred in 1.3% (26/1947) pre-guideline and 0.6% (7/1244) post-guideline (P = 0.037). Of the 33 stent thrombosis cases, 90% (27/30) had received morphine, of whom 85.2% (23/27) had not received adjunctive GPI. Complete records for assessing 30-day bleeding rates were only available in 374 patients and, in this subset, there was no significant difference in rates of GUSTO moderate or severe bleeding before vs. after introduction of the local guideline (1.7% vs 2.8%; P = 0.47) although, in both cohorts combined, any GUSTO bleeding was observed more frequently in GPI-treated patients (21.8%) compared to those not receiving a GPI (10.0%; P = 0.002). In conclusion, routine GPI use in morphine-treated STEMI patients undergoing PPCI appears to protect against stent thrombosis. Large-scale studies are needed to establish the overall risk-benefit of GPI therapy in morphine-treated PPCI patients and to assess alternative strategies for preventing acute stent thrombosis in these patients.

ABBREVIATIONS LIST

ACS	Acute coronary syndrome
DAPT	Dual Antiplatelet Therapy
GPI	Glycoprotein IIb/IIIa antagonist
GUSTO	Global Utilization of Streptokinase and tPA for Occluded arteries
PPCI	Primary Percutaneous Coronary Intervention
STEMI	ST-elevation myocardial infarction

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care for the management of acute coronary syndromes (ACS) and for percutaneous coronary intervention (PCI), being recommended in the current international guidelines.[1,2,3,4] In the setting of ST-elevation myocardial infarction (STEMI) and other ACS manifestations, the $P2Y_{12}$ inhibitors ticagrelor and prasugrel are now preferred to clopidogrel as first-line therapy in those without contraindications, except in those requiring oral anticoagulant therapy.[1,24] Morphine is often used in patients with STEMI for analgesia, sedation, anxiolysis and reduction of adrenergic drive, heart rate and myocardial oxygen consumption.[1,2,5] However, morphine has been shown to delay absorption of $P2Y_{12}$-inhibitors in STEMI patients, which has the potential to expose these patients to increased thrombotic risk.[6,7,8,9] Some evidence of a harmful effect comes from the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study, which showed a significant interaction between morphine use and the effects of pre-hospital administration of ticagrelor; pre-hospital compared to in-hospital ticagrelor administration appeared to improve resolution of ST-elevation in those who did not receive morphine whereas no apparent benefit was seen in morphine-treated patients.[10] Another study found that morphine-treated STEMI patients exhibited larger infarct size and lower myocardial salvage index[11], although a further observational study found no differences in in-hospital complications or 1-year mortality.[12] Evidence for clinical efficacy of GPI use in morphine-treated patients with STEMI is limited. In a small observational study (32 STEMI patients treated with prasugrel), a bridging strategy with abciximab in morphine-treated patients appeared to ensure adequate platelet inhibition as measured with Multiplate electrode aggregometry.[13] However, no evidence is available regarding clinical outcomes with such a strategy and no data exist about the effect in ticagrelor-treated patients in this setting. The

recommendations for GPI use in addition to $P2Y_{12}$ inhibitors in the current guidelines are restricted to specific situations (bail-out strategy, no-reflow or angiographic evidence of a large thrombus).[24] No specific recommendations are given for morphine-treated patients. Although the aforementioned studies suggest that platelet function and clinical outcomes are worse in morphine-treated STEMI patients, no accepted strategies exist to overcome this issue. Therefore, an institutional guideline was introduced in our hospital in 2012 with the purpose of improving the outcomes of morphine-treated STEMI patients.

The aim of the current observational cohort study was to compare the effect of GPI before and after the introduction of this guideline for morphine-treated STEMI patients in terms of stent thrombosis and mortality, as well as to obtain pilot data on bleeding events.

METHODS

Consecutive patients undergoing primary PCI for STEMI at South Yorkshire Cardiothoracic Centre, Sheffield, United Kingdom, between 1 April 2012 and 28 February 2017 were included. This hospital provides a primary PCI service for the surrounding population of approximately 1.8 million people. Standard antithrombotic therapy throughout the observation period consisted of aspirin and ticagrelor (or prasugrel if ticagrelor was not tolerated or cautioned for reasons other than bleeding risk). Heparin was given intravenously or intra-arterially at a dose of approximately 70 units/kilogram. Use of GPI in morphine-treated patients was encouraged after introduction of the local protocol in March 2015, which specifically recommended that "in the absence of contraindication, tirofiban should be considered routinely in patients who have received morphine prior to or shortly after loading dose of $P2Y_{12}$ inhibitor" at an intravenous bolus dose of tirofiban 25 mcg/kg followed by maintenance dose of 0.15 mcg/kg/min for a duration of 6 hours, unless a reduced dose was

indicated for renal failure or longer duration was indicated for management of residual thrombus.

GPI use as documented in the procedure information system was collected and compared between the pre-guideline group (April 2012 to February 2015) and the post-guideline group (from March 2015 to February 2017).

A search was performed for patients undergoing a re-PCI within 30 days and PCI reports were reviewed to identify any possible cases of stent thrombosis. Cases that met the Academic Research Consortium criteria for definite stent thrombosis[14] were recorded and additional details regarding morphine were collected for these patients. 30-day vital status was available for all patients from the national register of deaths.

Bleeding rates in local cohort

Bleeding rates and details of in-ambulance morphine use were not available for many patients, partly due to transfer to local hospitals after 12 hours, meaning that complete hospital records were not available, or due to incomplete records of the in-ambulance treatment. Consequently, a detailed analysis was performed in a sub-cohort of 374 local STEMI patients in order to provide pilot data on bleeding rates, according to Global Utilization of Streptokinase and tPA for Occluded arteries (GUSTO) criteria for mild, moderate and severe bleeding, in the first 30 days. Bleeding rates were compared between the pre-guideline cohort and the post-guideline cohort, between GPI-treated patients and patients not treated with GPI, and, finally, in patients who received the institutional "guideline-based therapy" (i.e. morphine-treated patients who received GPI or patients who did not receive morphine and did not receive GPI) versus patients not receiving the institutional guideline-based therapy. Patients were excluded if they were transferred after PCI to their local district general hospital. For the bleeding outcomes, only procedures performed by operators using predominantly radial access at the beginning of the

census date (1 April 2012) were included in order to reduce bias from increased adoption of, and skill in using, radial artery access during the second period leading to reduced bleeding risk.[1-2, 15]

Statistical analysis

Categorical variables were summarized by frequencies and percentages and Chi-square tests were used in intergroup comparisons of categorical variables. Fisher's Exact Test was used for low frequency events. Continuous variables were summarized as mean and standard deviation, and values were compared using a standard t-test for normally distributed data. Stent thrombosis rates were compared with Kaplan Meier plots using log ranks test. The primary outcome was definite stent thrombosis at 30 days and secondary outcomes were definite stent thrombosis at 24 hours and all-cause mortality at 30 days.

RESULTS

Study population

3224 consecutive STEMI patients undergoing primary PCI were included. Details of repeat PCI procedures and all-cause deaths within 24 hours and at 30 days were available for all these patients. In the post-guideline cohort, radial access was more common, and patients presented more frequently with cardiogenic shock, whereas peripheral arterial disease was less common (Table 1). Details regarding GPI use were available in 2297/3224 (71.2%) of patients. GPI use increased from 42.4% to 69.9% after the introduction of the new guideline (Table 2).

Outcomes

85 of 3224 patients underwent re-PCI within 30 days, in whom 33 cases of definite stent thrombosis were identified (1.0%). 26 stent thrombosis events occurred in the cohort before the

introduction of the guideline (26/1973; 1.3%) compared with 7 stent thrombosis events (7/1251; 0.6%) occurring after the introduction of the new guideline (p=0.037, log-rank test)(Figure 1A). The majority of stent thrombosis events (29/33) were acute (i.e. occurring within 24 hours) with fewer events post-guideline compared with pre-guideline (P = 0.037, log-rank test)(Figure 1B). For 30 out of 33 stent thrombosis patients, details on morphine use were available: 27/30 (90%) patients had received morphine, of whom 23/27 (85.2%) had not received adjunctive GPI. No significant difference in 30-day mortality was observed between the pre- and post-guideline group (5.9% vs. 7.3%, p=0.13).

When stratified for GPI use rather than time period, 5/1217 (0.4%) of patients receiving GPI suffered a stent thrombosis vs. 28/1080 (2.6%, p<0.0001) of patients who did not receive GPI (Table 3).

Bleeding rates in local subgroup

2387 patients were transferred back to their local hospital following their primary PCI procedure. Of the remaining 937 patients, a total of 374 patients were included in the bleeding analysis (Figure 2). Details regarding GPI use were available in all patients and details regarding morphine use were available in 363 of 374 patients (97.1%). Baseline characteristics were similar to the overall cohort (Table 1). Following introduction of the institutional guideline, GPI use increased from 42.9% to 66.4%. Any GUSTO bleeding occurred in 17.6% of patients pre-guideline and 13.5% of patients post-guideline (p=0.29) and GUSTO moderate or severe bleeding occurred in 1.7% and 2.8%, respectively (p=0.47).

In GPI-treated patients during either time period, any GUSTO bleeding was more frequently observed compared with patients not treated with GPI (21.8% vs. 10.0%, respectively; p=0.002) but differences in GUSTO moderate or severe bleeding were numerically but not statistically significant (3.1% vs. 1.1%; p=0.29). Despite the aim of limiting differences in

radial access use between the two time periods, there was an increase in use of radial access in the post-guideline period (Table 1).

DISCUSSION

The introduction of a new guideline in our centre has led to a 65% relative increase of GPI use in patients with STEMI undergoing primary PCI. There was a significant decrease in the number of definite stent thrombosis cases after the introduction of the new guideline. Overall, a significantly lower incidence of stent thrombosis was observed in GPI-treated patients. The majority of patients suffering a stent thrombosis had received morphine but not adjunctive GPI. More bleeding events were observed with GPI use but there was not a statistically significant increase in moderate-to-severe GUSTO bleeding. The increased risk of major bleeding with GPI is well documented and consequently this strategy may not be the optimal means of preventing acute stent thrombosis in morphine-treated primary PCI patients. Indeed, we have recently conducted a pharmacodynamic study to assess the impact of a bolus and 6-hour infusion of enoxaparin in primary PCI patients as an alternative strategy to routine use of GPI in morphine-treated patients and are currently comparing this against a strategy of routine use of tirofiban with unfractionated heparin (NCT03568838)[16]. Cangrelor is a rational option for providing parenteral $P2Y_{12}$ inhibition pending the absorption of an oral $P2Y_{12}$ inhibitor although a standard 2-hour cangrelor infusion may not be sufficient to cover the period of delayed absorption of the oral inhibitor in all patients and care must be taken if clopidogrel or prasugrel is used as the oral inhibitor since cangrelor can block the binding of clopidogrel and prasugrel active metabolites to the $P2Y_{12}$ receptor.[17, 18]

This observational study is the first to describe the feasibility and outcomes of 'routine' GPI use in morphine-treated patients undergoing primary PCI. Overall, the adherence to the

protocol was fair. Whereas the use of GPI has substantially increased after the introduction of the new guideline, still not all morphine-treated patients received adjunctive GPI. This could in part be explained by other factors playing a role in clinical practice, such as patient bleeding risk and possible contra-indications. Equally, other patients received GPI without being treated with morphine, thus a reflection of other perceived indications for GPI use, such as residual thrombus load after PCI.

Limitations

The observational and retrospective nature of this registry, evaluating the effects of the introduction a new local guideline, implies that treatment strategy was not randomised. Patients were not followed up prospectively and so we cannot be certain that events were not missed. However, since our hospital is the only one providing a PCI service to the surrounding population, we considered that re-PCI rates for non-fatal stent thrombosis at our centre are a reasonable reflection of the impact of a change in protocol on event rates.

Details of morphine use were only available in a sub-cohort of patients, which meant that the study was not designed to explore the effect of morphine on stent thrombosis risk. Consequently, the observation of a high rate of morphine use (90%) in the stent thrombosis patients is subject to bias and can only be viewed as hypothesis-generating.

A further limitation is that details on bleeding outcomes were only available in a local sub-cohort that was relatively small since a substantial number of patients had been excluded, mostly due to repatriation within 12-24 hours of patients to district general hospitals following primary PCI, and so our analyses are not sufficient to evaluate the safety of increased use of GPI. Selection on the basis of geography is unlikely to alter the finding of this registry other than to reduce the sample size. However, the unavailability of a large number of complete records may have biased the findings and further prospective studies are required for more

reliable assessment of bleeding rates. The increased use of radial artery access may have attenuated the effect of increased GPI use on bleeding events. As such, the bleeding data are intended only to provide crude pilot data for planning such studies and also do not provide any guide to the safety of increased GPI use when femoral artery access is used.

Finally, over time between the two observation periods, procedural techniques might have changed. Although adjustment for possible confounding variables was not possible, we assume that changes in procedural techniques were limited, as the total time period (<5 years) of this registry was relatively small. Moreover, as illustrated in Table 1, no major differences with regard to baseline clinical and procedural characteristics were observed between the two cohorts other than an increased use of radial artery access.

CONCLUSIONS

This observational study is the first to describe the feasibility and outcomes of 'routine' GPI use in morphine-treated patients undergoing primary PCI. Our results suggest that GPI use is highly protective for the occurrence of acute stent thrombosis. Further large-scale registries and clinical trials are needed to further establish the overall risk-benefit of GPI therapy in morphine-treated STEMI patients and to assess alternative strategies for preventing acute stent thrombosis in morphine-treated patients.

Declaration of Interest

B. Zwart has received speaker fees from Bayer and AstraZeneca. R.F. Storey has received research grants, consultancy fees and honoraria from AstraZeneca; research grants and consultancy from PlaqueTec; consultancy fees and honoraria from Bayer and Bristol-Myers Squibb/Pfizer; and consultancy fees from Haemonetics, Idorsia, Novartis and Thromboserin.

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TABLES

FIGURES

Figure 1 Rates of definite stent thrombosis pre- and post-introduction of local guideline

Figure 2 Flow Chart of Patient Selection

Legend:
PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; STE, ST elevation

Figure 1

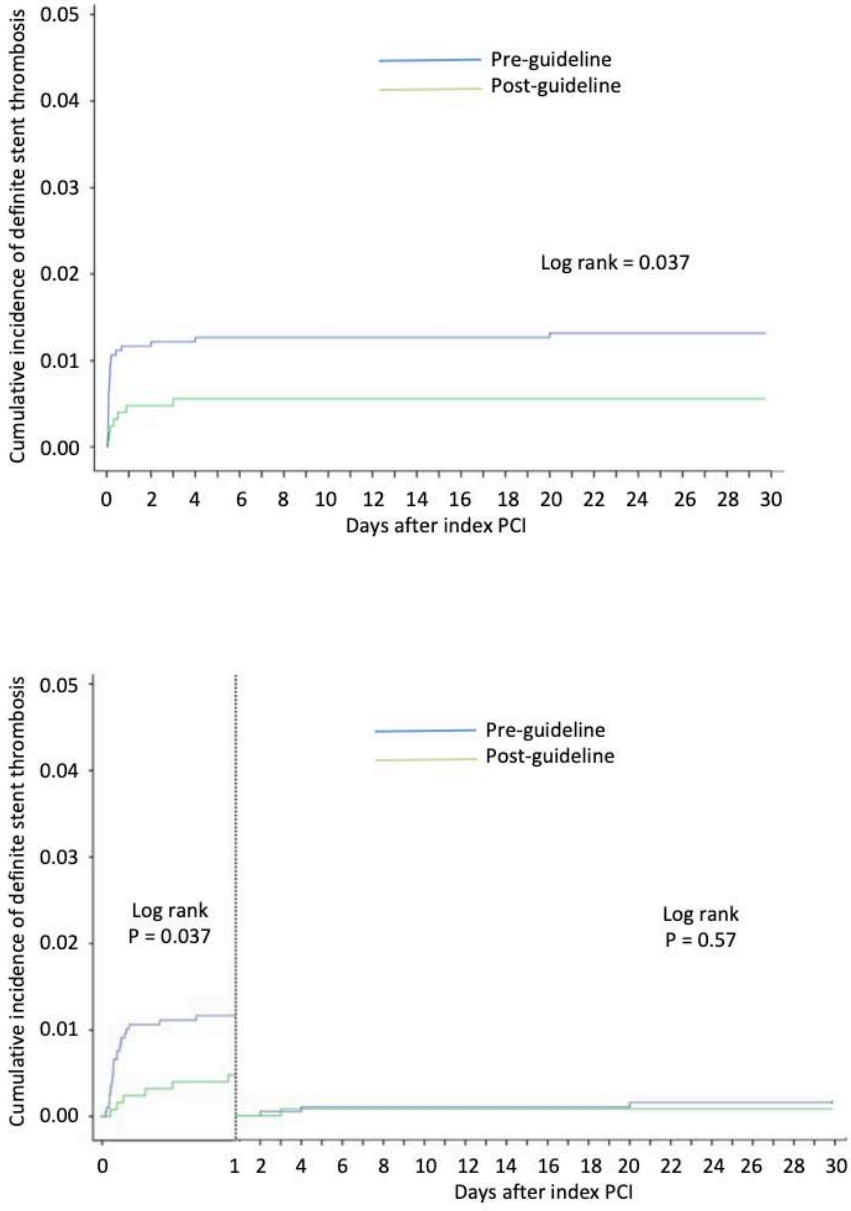
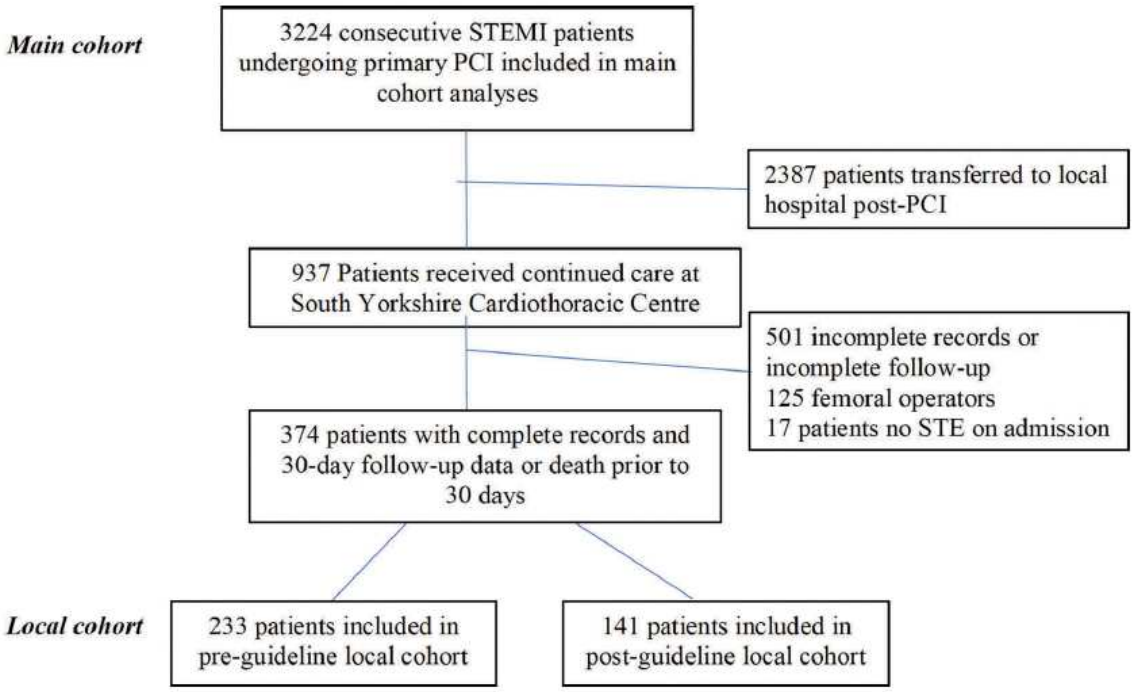

Cumulative incidence of definite stent thrombosis
0.05
0.04
0.03
0.02
0.01
0.00
Pre-guideline
Post-guideline
Log rank = 0.037
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Days after index PCI
Cumulative incidence of definite stent thrombosis
0.05
0.04
0.03
0.02
0.01
0.00
Pre-guideline
Post-guideline
Log rank
P = 0.037
Log rank
P = 0.57
0 1 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Days after index PCI

Figure 2


Main cohort
3224 consecutive STEMI patients undergoing primary PCI included in main cohort analyses
2387 patients transferred to local hospital post-PCI
937 Patients received continued care at South Yorkshire Cardiothoracic Centre
501 incomplete records or incomplete follow-up
125 femoral operators
17 patients no STE on admission
374 patients with complete records and 30-day follow-up data or death prior to 30 days
Local cohort
233 patients included in pre-guideline local cohort
141 patients included in post-guideline local cohort