Comparison of Routine Versus Selective Glycoprotein IIb/IIIa Inhibitors Usage in Primary Percutaneous Coronary Intervention (from the British Cardiovascular Interventional Society)

Mateusz Orzalkiewicz, MD[a,b], James Hodson, BSc[b], Chun Shing Kwok, MSc[c], Peter F. Ludman, MD[a], Joel P. Giblett, MD[d,e], Sudhakar George, MD[a], Sagar N. Doshi, MD[a], Sohail Q. Khan, MD[a], Timothy Kinnaird, MD[f], David Hildick-Smith, MD[g], Jonathan N. Townend, MD[a,b], Mamas A. Mamas, DPhil[c], and Patrick A. Calvert, PhD[d,e,*]

The role of glycoprotein IIb/IIIa inhibitors (GPI) in primary percutaneous coronary intervention (PPCI) remains uncertain. Previous analyses compare PPCI outcomes with clopidogrel plus GPI, versus without GPI. This does not reflect modern contemporary PPCI practice with ticagrelor or prasugrel. Nor does it answer the important question faced daily by PPCI operators: should GPI be used routinely or selectively? We aim to determine whether a strategy of routine use of GPI in contemporary PPCI practice is superior to selective GPI use. A total of 110,327 consecutive PPCIs performed in England were prospectively recorded in the British Cardiovascular Intervention Society Database (2009 to 2015). The cohort was divided into routine and selective GPI usage groups based on the PPCI operator's strategy, defined as GPI used in >75% and <25% PPCIs, respectively. Overall, GPI use declined from 73.1% to 43.3% of PPCIs. Routine compared with selective GPI usage was associated with lower all-cause 1-year mortality: 9.7% versus 11.0%, $p < 0.001$. There was a consistent survival benefit for routine GPI usage as compared with selective GPI usage: univariable analysis (hazard ratio = 0.88 [95% confidence interval 0.83 to 0.93], $p < 0.001$), multivariable analysis (hazard ratio = 0.82 [0.77 to 0.88], $p < 0.001$). For survival, there was no interaction between GPI usage and the type of P2Y12-inhibitor used. In conclusion, a strategy of routine GPI usage in patients who underwent PPCI was associated with lower all-cause mortality as compared with selective GPI usage. This benefit was maintained despite 44.3% of patients receiving prasugrel or ticagrelor. **(Am J Cardiol 2019;124:373−380)**

Glycoprotein IIb/IIIa-inhibitors (GPIs), potent parenteral antiplatelet agents, have been used as adjunctive therapy during primary percutaneous coronary intervention (PPCI) for many years with documented efficacy in randomized controlled trials.[1−4] Current European Society of Cardiology guidelines on the treatment of STEMI recommend bailout use of GPI in PPCI (class IIa, level of evidence C), but recently removed a IIb B recommendation for routine use of GPI in PPCI due to the "lack of evidence" to support it.[5] The American College of Cardiology/American Heart Association guidelines from 2013 recommend GPI usage in selected patients (class IIa, level of evidence A for abciximab and B for tirofiban or eptifibatide) with no updates since.[6] The role of GPI as bailout treatment of PPCI is established in clinical practice, with little supporting evidence. Previous studies have compared routine versus no GPI.[1−8] To date, there has been no direct comparison between strategies of routine versus selective or bailout GPI use in PPCI. Such confusion has led to an inconsistent approach to GPI usage among PPCI centers in the United Kingdom (UK) as seen by the apparently random spread of GPI usage in PPCI (Figure 1). From the published data, it is clear that wide variation in international practice exists, with GPI use ranging from <10% to around 90% of PPCIs.[9,10] The optimal strategy of GPI usage (routine vs selective), especially in the context of the constantly changing and contentious field of antithrombotic medications, remains uncertain. We therefore compare patient outcomes between PPCI operator strategies of routine versus selective GPI use in contemporary practice in England.

METHODS

The British Cardiovascular Intervention Society Database database records data from every PCI procedure in the

[a]Department of Cardiology, Queen Elizabeth Hospital, University Hospitals Birmingham, Birmingham, UK; [b]Institute of Translational Medicine, Queen Elizabeth Hospital, University Hospitals Birmingham, Birmingham, UK; [c]Keele Cardiovascular Research Group, Centre for Prognosis Research, Keele University, Keele, UK; [d]Department of Cardiology, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK; [e]Division of Cardiovascular Medicine, University of Cambridge, Cambridge, UK; [f]Department of Cardiology, University Hospital Wales, Cardiff, UK; and [g]Sussex Cardiac Centre, Brighton and Sussex University Hospital NHS Trust, Brighton, UK. Manuscript received January 27, 2019; revised manuscript received and accepted May 6, 2019.

Funding: PAC receives funding from the Academy of Medical Sciences.

See page 379 for disclosure information.

*Corresponding author: Tel: +44 14808364353; fax:+44 1480831315.
E-mail address: patrick.calvert1@nhs.net (P.A. Calvert).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.05.010

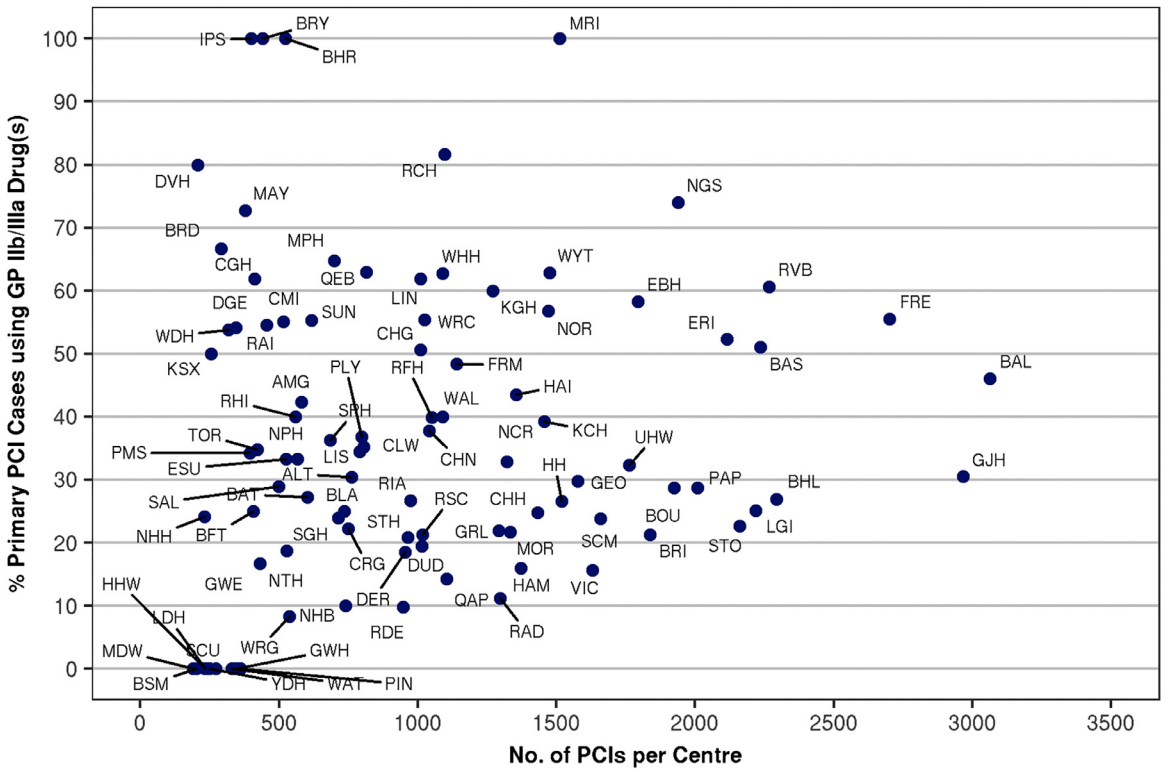

Figure 1. Proportion of PPCIs in which GPI is used at each PPCI Center in the UK in 2016. Each dot and three letter code correspond to a different PPCI center in the UK. (with thanks to Peter Ludman, British Cardiovascular Intervention Society, and National Institute for Cardiovascular Outcomes Research https://www.bcis.org.uk/resources/audit-results/).

UK, including patient characteristics, procedural details, and outcome data.[11] The data collection is overseen and managed by the National Institute for Cardiovascular Outcomes Research. We extracted data of all PPCIs for STEMI performed between January 2009 and April 2015 in England. Patients were identified by pseudonymized unique National Health Service and hospital numbers. The consultant (attending physician) responsible for the PPCI procedure (PPCI operator) was identified by pseudonymized General Medical Council number. For patients with more than one PPCI in the study period, only the first presentation was included. Exclusion criteria were those patients where the first presentation during the period was for a repeat PPCI, PPCI for STEMI with restenosis or in-stent restenosis and/or stent thrombosis (as operators are more likely to use GPI in this setting). In years where a consultant performed less than ten PPCIs, that year was excluded. The study was approved by the National Audit PCI Steering Group. The study complies with the declaration of Helsinki. The primary clinical outcome was all-cause mortality, determined from deaths reported to the Office of National Statistics, a statutory requirement in England.

Since the aim was to compare whether a PPCI operator strategy of routine versus selective GPI usage resulted in better patient outcomes, patients who underwent PPCI were divided into 3 groups according the PPCI operators GPI usage rate in the year of the PPCI. The GPI usage rate of each PPCI operator was evaluated on a yearly basis (GPI usage strategies of each PPCI operator may vary over time). In the absence of existing criteria for defining routine and selective GPI use, by consensus of the authors and taking into account the quartiles of the GPI usage distribution, we divided the population into the following 3 groups: routine GPI use (patients who had PPCI undertaken by an operator who used GPI in >75% of PPCIs in that year), intermediate GPI usage (patients who had PPCI undertaken by an operator who used GPI in 25% to 75% of PPCI in that year), and selective GPI usage (patient who had PPCI undertaken by an operator who used GPI in <25% of PPCI in that year). The GPI usage category was redefined for each year. As such, an operator could move between the 3 groups over time, depending on their GPI usage preferences in a specific year, that is, one operator could appear as routine user 1 year and a selective user in another year if they changed GPI usage strategy. The analyses compared those patients in the routine and selective GPI usage groups.

Initially, comparisons were made between the routine and selective GPI groups, in order to assess whether the patient characteristics were similar. Normally distributed variables were reported as mean ± standard deviation (SD) and compared using independent samples *t* tests. Variables that followed log-normal distributions were $\log_{10}$-transformed, and also compared using independent samples *t* tests, but reported as geometric means with 95% prediction intervals. Nonparametric data were compared using Mann-Whitney tests and categorical variables were compared using Chi-square tests. Time-to-event outcomes were assessed using univariable and multivariable Cox regression analysis models. We used Stata 14 (Stata Corp., College Station, Texas) to perform multiple imputations with

chained equations (mi impute chained command in Stata) in order to generate 10 complete datasets with imputed data for missing baseline variables. Cox regressions were performed on the imputed dataset to estimate the hazard ratios for mortality according to routine or selective GPI use with and without adjustments for baseline variables.

We considered whether the effectiveness of routine GPI usage differed across the P2Y12-inhibitors (clopidogrel, ticagrelor, and prasugrel). A set of Cox regression models were produced in which the GPI usage strategy, P2Y12-inhibitor used and an interaction term were entered. These were then extended to multivariable analysis. Analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, New York), with $p < 0.05$ deemed to be indicative of statistical significance throughout.

RESULTS

Between January 1st, 2009 and April 30th, 2015, 110,327 PPCIs were performed in England. Cases excluded from analysis are shown in Figure 2. The GPI usage rates were calculated for a total of 96,981 PPCIs performed under the care of 690 PPCI operators (a total of 2,409 consultant-years). The GPI usage rate followed a bimodal distribution (Figure 3), with a tendency for PPCI operator to use GPI either routinely or infrequently. The twenty-fifth percentile of this distribution was 23%, and the seventy-fifth was 80%. The selective GPI group (<25% usage) consisted of 28,417 procedures and the routine GPI group (>75% usage) consisted of 26,909 procedures.

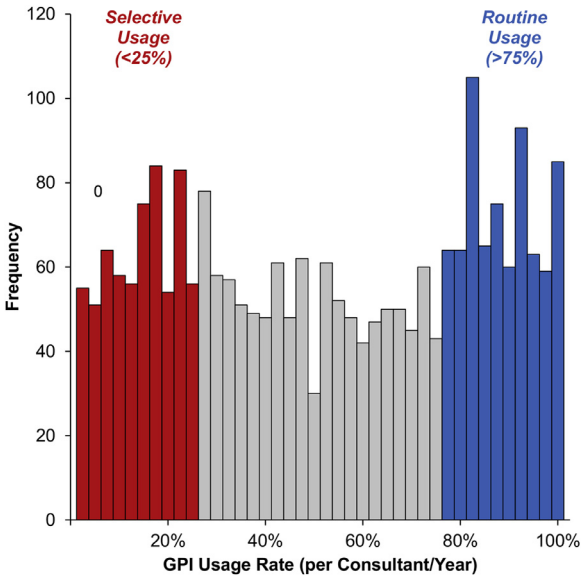

Figure 3. Distribution histogram of glycoprotein IIb/IIIa inhibitors (GPI) usage rates per consultant-year.

The overall GPI usage rate declined from 73.1% of PPCIs in January 2009 to a nadir of 34.2% in March 2013, before increasing slightly to 43.3% of PPCIs in April 2015 (Figure 4). Correspondingly, there was a shift in the GPI usage strategies of the PPCI operators over the period of the study in favor of selective usage (Figure 5).

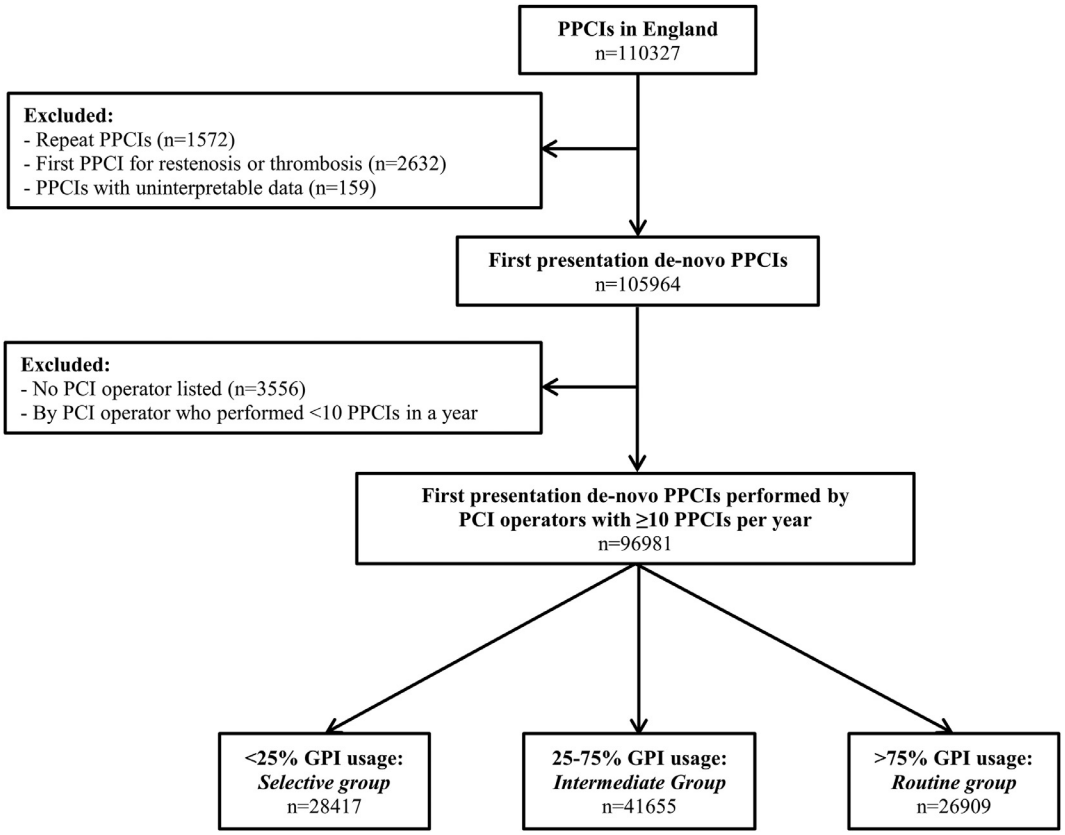

Figure 2. Study profile. GPI = glycoprotein IIb/IIIa inhibitors; PCI = percutaneous coronary intervention; PPCI = primary PCI.

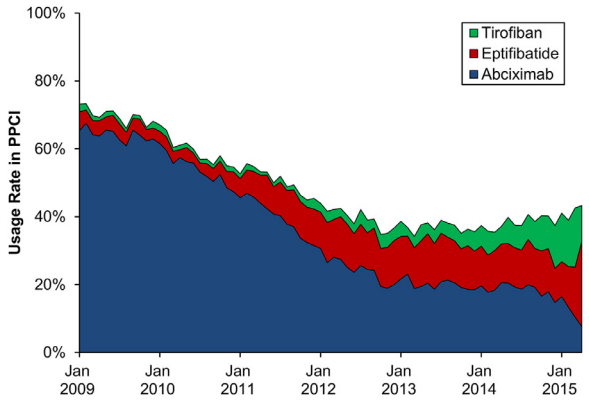

Figure 4. Total glycoprotein IIb/IIIa inhibitor (GPI) usage rates over the study period.

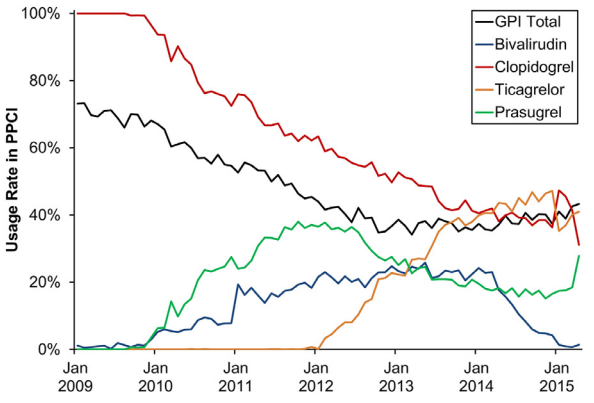

Figure 6. Glycoprotein IIb/IIIa inhibitor (GPI) and additional medications (P2Y12 inhibitors and bivalirudin) usage rate over the study period.

The use of additional medications also varied over the study period (Figure 6). Trends in bivalirudin usage opposed those of GPIs, rising from 1.1% in the first month of the period, to a peak of 25.8% in May 2013, before falling back to 1.4% of procedures by April 2015. The preference for the various P2Y12-inhibitors also varied over time, with clopidogrel used exclusively in procedures between January and August 2009, before usage began to decline in favor of alternatives (prasugrel and ticagrelor). By April 2015, clopidogrel was only used in 31.1% of procedures, with ticagrelor (41.0%) and prasugrel (27.9%) making up the remainder.

Table 1 compares selected baseline demographics and procedural characteristics between the routine and selective GPI usage groups. The 2 groups were well matched, with any absolute differences being small, even if statistically significant. The largest difference was detected in the use of additional medications, with the routine GPI group more likely to receive clopidogrel, rather than ticagrelor or prasugrel, and less likely to receive bivalirudin than the selective GPI group (additional patient characteristics are reported in Table S1 of the supplementary appendix).

Abciximab was the most commonly used GPI, making up 62.3% of administrations in the routine GPI group versus 89.8% in the selective GPI group. Eptifibatide was used more commonly in the routine GPI group (31.0%) than the selective GPI group (1.9%), with tirofiban used in the remainder (6.7% and 8.3%, respectively). The median period of follow-up was 18 months (interquartile range 1.2 to 32.4). All-cause mortality on Kaplan-Meier analysis was 6.7%, 10.3%, and 21.7% at 30 days, 1 year and 5 years, respectively in the overall cohort. Upon univariable analysis, the routine GPI usage group was associated with lower all-cause mortality hazard ratio (HR) 0.87 (0.82 to 0.91), $p < 0.001$ (Table 2). The Kaplan-Meier estimated rates of all-cause mortality within 1 year of the index PPCI were 9.7% versus 11.0%, $p < 0.001$ for the routine versus selective GPI groups (Figure 7).

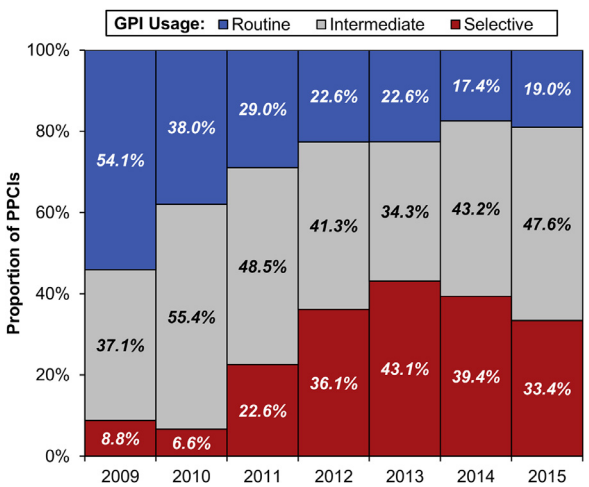

Figure 5. Percentage of primary PCI (PPCI) patients treated by PCI operator with routine, selective, and intermediate use of glycoprotein IIb/IIIa inhibitors (GPI) by year.

The results from multivariable analysis, which adjusted for a range of potential confounding factors, were consistent with those above (full list of covariables in Table S2 of the supplementary appendix). The multivariable analysis was consistent with the assumptions for a Cox proportional hazards model, and showed a consistent survival benefit with lower all-cause mortality in the routine GPI usage group with adjusted HR 0.82 (0.77 to 0.88), $p < 0.001$ (Table 2). Since we noted that there were temporal changes in the use of GPI over time, a post hoc analysis including the calendar year (in which PCI was performed) was undertaken. This showed an adjusted HR 0.93 (0.87 to 0.99), $p = 0.02$.

Since a difference in P2Y12-inhibitor usage had been identified between the GPI groups, a set of analyses considering the interaction between these 2 drug classes, was performed. In analysis of the all-cause mortality, no significant interaction was detected in univariable and multivariable analysis, implying that the degree of survival benefit associated with routine GPI strategy was similar, regardless of the P2Y12-inhibitor administered.

DISCUSSION

Our study shows that a strategy of routine GPI use in PPCI is associated with lower all-cause mortality when compared with a strategy of selective GPI usage. This study is, to our knowledge, the first comparison of routine versus selective usage of GPI in contemporary PPCI for STEMI. Evidence already exists in support of using GPI in PPCI

Table 1
Patient demographics and procedural characteristics in the selective and routine GPI usage groups

	Selective GPI (n = 28,417)	Routine GPI (n = 26,909)	p Value
Age (years)	63.7 ± 13.1	63.2 ± 13.1	<0.001
Male sex	20,918/28,359 (73.8%)	19,881/26,832 (74.1%)	0.377
Body mass index (kg/m^2)	27.5 ± 5.1	27.4 ± 4.9	0.060
Clinical history			
Diabetes			0.211
Non-Insulin dependent	3,021/27,290 (11.1%)	2,801/25,915 (10.8%)	
Insulin-dependent	790/27,290 (2.9%)	809/25,915 (3.1%)	
Smoking history			<0.001
Ex-smoker	6,373/26,199 (24.3%)	6,519/24,083 (27.1%)	
Current smoker	9,736/26,199 (37.2%)	10,125/24,083 (42.0%)	
Family history of CAD	8,595/25,446 (33.8%)	8,735/22,873 (38.2%)	<0.001
Hypertension	10,453/27,166 (38.5%)	10,849/25,680 (42.2%)	<0.001
Previous MI	2,551/27,090 (9.4%)	2,411/24,060 (10.0%)	0.022
PVD	821/27,166 (3.0%)	868/25,680 (3.4%)	0.020
Previous CVA	966/27,166 (3.6%)	1,048/25,680 (4.1%)	0.002
Previous CABG	918/27,962(3.3%)	752/26,035 (2.9%)	0.008
Renal disease*	385/26,458 (1.5%)	406/24,669 (1.6%)	0.085
Cardiogenic shock	2,041/28,331 (7.2%)	1,978/26,766 (7.4%)	0.403
Procedural data			
Femoral access	10,101/28,140 (35.9%)	10,772/26,539 (40.6%)	<0.001
Culprit vessel			<0.001
Proximal LAD	7,452/28,302 (26.3%)	7,230/26,665 (27.1%)	
LAD other / RCA / LCX	18,658/28,302 (65.9%)	17,603/26,665 (66.0%)	
Multivessel PCI	1,459/28,302 (5.2%)	1,232/26,665 (4.6%)	
Left main	361/28,302 (1.3%)	232/26,665 (0.9%)	
Grafts	372/28,302 (1.3%)	368/26,665 (1.4%)	
DES placement	21,569/28,394 (76.0%)	17,926/26,558 (67.5%)	<0.001
No of stents per patient	1.36	1.42	<0.001
Stent length (mm)	22.7 (9.4 - 54.9)	23.7 (10.3 - 54.2)	<0.001
Stent diameter (mm)	3.3 ± 0.6	3.4 ± 0.6	<0.001
Thrombectomy			<0.001
Manual	11,786/25,348 (46.5%)	12,540/24,837 (50.5%)	
Mechanical	923/25,348 (3.6%)	403/24,837 (1.6%)	
IABP	1,120/27,716 (4.0%)	1,214/25,007 (4.9%)	<0.001
TIMI 3 flow after PPCI	21,568/24,313 (88.7%)	20,379/22,871 (89.1%)	0.173
Additional medications			
P2Y12 inhibitor			<0.001
Clopidogrel	10,059/21,253 (47.3%)	11,036/16,626 (66.4%)	
Ticagrelor	5,874/21,253 (27.6%)	1,908/16,626 (11.5%)	
Prasugrel	5,320/21,253 (25.0%)	3,682/16,626 (22.1%)	
Bivalirudin	6,995/23,674 (29.5%)	1,195/20,095 (5.9%)	<0.001

CABG = coronary artery bypass grafts; CAD = coronary artery disease; CVA = cerebrovascular event; DES = drug eluting stent; IABP = intra-aortic balloon pump; LAD/RCA/LCX = left anterior descending/right/circumflex coronary artery; PVD = peripheral vascular disease; TIMI = thrombolysis in myocardial infarction.

* Renal disease definition: functioning transplant, Creatinine > 200 μmol/l, Acute or chronic renal failure on dialysis.

and the bioequivalence between all 3 commercially available agents: abciximab, tirofiban, and eptifibatide in the era of clopidogrel usage.[1–4,12,13] Although important, these trials relate to PPCI in a different era, with different generation stents and P2Y12-inhibitors. Furthermore, these trials compare PPCI results between procedures performed with and without GPI. However, almost all PPCI operators use GPIs in a proportion of patients and very few operators use GPIs in all PPCI patients. Therefore, the "all or nothing" approach of existing trials does not reflect operator practice in the real-world clinical setting. The present analysis comparing operators' outcomes with routine versus selective GPI usage was designed to better reflect the choices faced in everyday clinical practice.

Despite randomized trial and registry data, GPI use has declined over the past decade. The potential reasons are multifactorial, including cost and bleeding risk, but they are not based on firm trial data refuting their utility. In this analysis, the decline in GPI corresponds with increases in use of prasugrel and ticagrelor (newer P2Y12-inhibitors). Despite the strong evidence supporting the use of prasugrel and ticagrelor in PPCI for STEMI,[14,15] there is a paucity of data regarding outcomes of GPI usage in the era of these newer P2Y12-inhibitors. Published subgroup analyses of the PLATO[16] and TRITON-TIMI 38[17] trials compared novel P2Y12-inhibitors versus clopidogrel for those patients that did and did not receive GPIs. Although the conclusions of these studies are not directly comparable to ours as both the PLATO and

Table 2
Univariable and multivariable Cox regression analysis of routine versus selective GPI usage

Outcome	Unadjusted		Fully adjusted*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
All-cause mortality	0.88 (0.83-0.93)	<0.001	0.82 (0.77-0.88)	<0.001

* Missing values imputed with adjustments for age, sex, body mass index, diabetes, smoking, family history, hypertension, previous myocardial infarction, peripheral vascular disease, previous stroke, previous coronary artery bypass graft, renal disease, cardiogenic shock, culprit vessel, drug eluting stent placement, intra-aortic balloon pump, ventilation, thrombectomy, antiplatelet, bivalirudin, vascular access/closure, cardiogenic shock, inotropic support, LV function, cholesterol level and body mass index.

TRITON-TIMI 38 trials represent different patient populations, neither found significant interactions between P2Y12-inhibitor and GPI usage for any of the end points considered. There is little evidence that GPIs are less beneficial when coadministered with prasugrel or ticagrelor than when coadministered with clopidogrel.

The relation between GPI use and bivalirudin in the UK is more complex. Early in the study period there was a general increase in bivalirudin and reduction in GPI usage, likely in response to trials supporting bivalirudin use.[18] However, there was a marked decline in bivalirudin use in 2014, coinciding with publication of the negative HEAT-PPCI trial.[19] The bleeding risks of GPIs may have contributed to their decline in usage. However, many of the trials documenting access site bleeding occurred in an era of routine femoral access. There is strong evidence that many bleeding complications are averted by radial access.[20] In addition the rates of major bleeding were not greater when newer P2Y12-inhibitors were combined with GPI than with clopidogrel and GPI.[16,17]

Firstly, and most importantly, the clinical outcome data to suggest that GPIs are less effective when combined with prasugrel or ticagrelor than with clopidogrel is lacking. Although platelet inhibition may be rapid in control subjects with prasugrel and ticagrelor, in the setting of a myocardial infarction and with the coadministration of opioids, the absorption and therefore efficacy of oral antiplatelets is attenuated.[21] Pharmacokinetic data indicate that there is likely to be a window of ineffective platelet inhibition for some hours after PPCI, during which time patients may be vulnerable to intracoronary and in-stent thrombosis plus microvascular obstruction.[21] Although this may not be angiographically detectable, it may affect coronary flow which is itself a marker of adverse outcomes.[22] Indeed, one of the principle indications for bailout usage of GPI in PPCI is the presence of slow coronary flow with or without

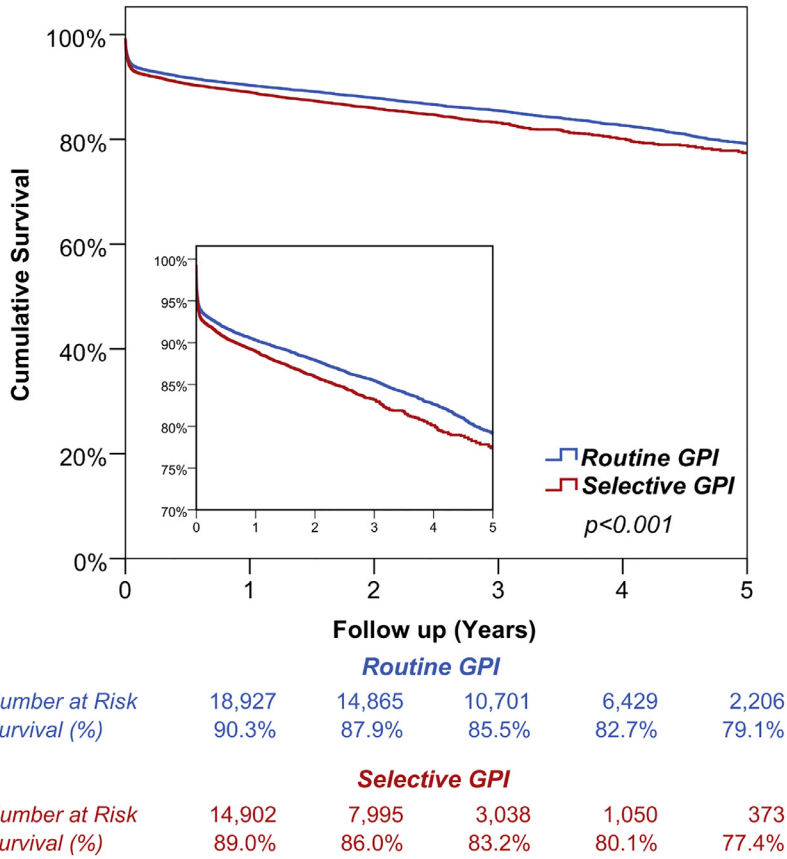

Figure 7. Kaplan-Meier curves of patient survival by glycoprotein IIb/IIIa inhibitor (GPI) usage strategy.

angiographically detectable thrombus.[5] Therefore, parenteral GPI remains the ideal agent to provide rapid, potent, and transient inhibition of platelet function at the time when it is most needed and when other agents cannot act reliably.

Our data, and that of others, suggest a long-lasting survival benefit of a routine GPI strategy despite widespread use of prasugrel and ticagrelor in our study. We hypothesize that a possible mechanism for these findings could be greater myocardial salvage. Infarction size has been shown to be more likely to be "undetectable" on scintigraphy with GPI administration.[3] Despite trial data supporting newer P2Y12-inhibitors, clopidogrel remains the most used P2Y12-inhibitor in PPCI worldwide, perhaps relating to drug costs.[9] The benefit of GPI in patients treated with PPCI and clopidogrel has been demonstrated.[1–4] However, the advent of newer P2Y12-inhibitors have likely resulted in a decline in GPI usage, without supporting evidence for this reduction. A randomized clinical trial examining GPI utility in PPCI patients treated with prasugrel or ticagrelor with modern generation drug eluting stents is needed to address this. The absolute reduction in mortality with GPI use in PPCI is small and may be imperceptible to PPCI operators. However, although rare, bleeding complications of GPI are memorable and may deter PPCI operators from its use, which could be to the detriment of the general population of patients presenting with STEMI. These concerns, alongside the data on bioequivalence among GPIs, mean that use of tirofiban and eptifibatide (with short half-lives) now exceed that of abciximab, which has a longer effect.

As observational data, our study is prone to unmeasured confounders and reports associations, not causal relations. A further limitation of any registry study is data completeness. However, data completeness is constantly monitored by British Cardiovascular Intervention Society Database and overall is good. Uploaded data is subject to a large number of checks including for internal consistency. Missing data and potential data errors are reported to the center regularly and the center is requested to address any issues provide corrected data. In an attempt to account for any selection bias stemming from missing data, we performed multiple imputations which returned a consistent result.

This National Registry Trial, involving all patients who underwent primary PCI for STEMI in England over a 6-year period, demonstrates a survival benefit in those patients treated by PPCI operators with a strategy of routine GPI usage, despite the extensive use of ticagrelor and prasugrel, the advent of which may be responsible for the decline in GPI use. We hope the results of this trial will highlight the enduring efficacy of GPI and its relevance in modern primary PCI practice.

Disclosures

PAC has received lecture fees from Astra Zeneca and Alirocumab Advisory Board Meeting for Sanofi. Other authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.010.

1. Valgimigli M, Biondi-Zoccai G, Tebaldi M, van't Hof AWJ, Campo G, Hamm C, ten Berg J, Bolognese L, Saia F, Danzi GB, Briguori C, Okmen E, King SB, Moliterno DJ, Topol EJ. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J* 2010;31:35–49.
2. Montalescot G, Antoniucci D, Kastrati A, Neumann FJ, Borentain M, Migliorini A, Boutron C, Collet JP, Vicaut E. Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up. *Eur Heart J* 2007;28:443–449.
3. Antoniucci D, Rodriguez A, Hempel A, Valenti R, Migliorini A, Vigo F, Parodi G, Fernandez-Pereira C, Moschi G, Bartorelli A, Santoro GM, Bolognese L, Colombo A. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol* 2003;42:1879–1885.
4. Van't Hof AWJ, Ten Berg J, Heestermans T, Dill T, Funck RC, van Werkum W, Dambrink JH, Suryapranata H, van Houwelingen G, Ottervanger JP, Stella P, Giannitsis E, Hamm C. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008;372:537–546.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini CG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2019;40:87–165.
6. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:e362–e425.
7. Safley DM, Venkitachalam L, Kennedy KF, Cohen DJ. Impact of glycoprotein IIb/IIIa Inhibition in contemporary percutaneous coronary intervention for acute coronary syndromes: insights From the National Cardiovascular Data Registry. *JACC Cardiovasc Interv* 2015;8:1574–1582.
8. Sirker A, Mamas M, Robinson D, Anderson SG, Kinnaird T, Stables R, de Belder MA, Ludman P, Hildick-Smith D. Bivalirudin, glycoprotein inhibitor, and heparin use and association with outcomes of primary percutaneous coronary intervention in the United Kingdom. *Eur Heart J* 2016;37:1312–1320.
9. Kinnaird TD, Ossei-Gerning N, Mitra R, Anderson RA. Interaction between access choice and pharmacotherapy for coronary intervention: the results of a UK survey. *Open Heart* 2014;1:e000094.
10. Golwala H, Pant S, Pandey A, Flaherty MP, Hirsch GA, Kirtane AJ. Heparin versus bivalirudin in ST-segment elevation myocardial infarction: a SCAI-based national survey from US interventional cardiologists. *J Invasive Cardiol* 2016;28:351–356.
11. British Cardiovascular Intervention Society. BCIS Dataset Version 5.6.2. [Internet]. Available from: http://www.bcis.org.uk/pages/page_-box_contents.asp?pageid=693&navcatid=25
12. Zeymer U, Margenet A, Haude M, Bode C, Lablanche JM, Heuer H, Schröder R, Kropff S, Bourkaib R, Banik N, Zahn R, Teiger E. Randomized comparison of eptifibatide versus abciximab in primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction: results of the EVA-AMI Trial. *J Am Coll Cardiol* 2010;56:463–469.

13. Gurm HS, Tamhane U, Meier P, Grossman PM, Chetcuti S, Bates ER. A comparison of abciximab and small-molecule glycoprotein IIb/IIIa inhibitors in patients undergoing primary percutaneous coronary intervention: a meta-analysis of contemporary randomized controlled trials. *Circ Cardiovasc Interv* 2009;2:230–236.
14. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–2015.
15. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–1057.
16. Shimada YJ, Bansilal S, Wiviott SD, Becker RC, Harrington RA, Himmelmann A, Neely B, Husted S, James SK, Katus HA, Lopes RD, Steg PG, Storey RF, Wallentin L, Cannon CP. Impact of glycoprotein IIb/IIIa inhibitors on the efficacy and safety of ticagrelor compared with clopidogrel in patients with acute coronary syndromes: Analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. *Am Heart J* 2016;177:1–8.
17. O'Donoghue M, Antman EM, Braunwald E, Murphy SA, Steg PG, Finkelstein A, Penny WF, Fridrich V, McCabe CH, Sabatine MS, Wiviott SD. The efficacy and safety of prasugrel with and without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) analysis. *J Am Coll Cardiol* 2009;54:678–685.
18. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R, HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;358:2218–2230.
19. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH, HEAT-PPCI trial investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;384:1849–1858.
20. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, Moretti C, Agostoni P, Loschiavo P, Lioy E, Sheiban I, Sangiorgi G. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol* 2012;60:2481–2489.
21. Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, Stavrou K, Migliorini A, Antoniucci D, Tamburino C, Alexopoulos D. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv* 2015;8:e001593.
22. Kammler J, Kypta A, Hofmann R, Kerschner K, Grund M, Sihorsch K, Steinwender C, Lambert T, Helml W, Leisch F. TIMI 3 flow after primary angioplasty is an important predictor for outcome in patients with acute myocardial infarction. *Clin Res Cardiol* 2009;98:165–170.