# Perioperative management of clopidogrel therapy: the effects on in-hospital cardiac morbidity in older patients with hip fractures

T. C. Collyer<sup>1\*</sup>, H. C. Reynolds<sup>2</sup>, E. Truyens<sup>3</sup>, L. Kilshaw<sup>4</sup> and T. Corcoran<sup>3,5</sup>

<sup>1</sup> Department of Anaesthesia, Harrogate District Hospital, Harrogate, UK

<sup>2</sup> Department of Anaesthesia, Leeds General Infirmary, Leeds, UK

<sup>3</sup> Department of Anaesthesia and <sup>4</sup> Department of Geriatric Medicine, Royal Perth Hospital, Perth, Australia

<sup>5</sup> School of Medicine and Pharmacology, University of Western Australia, Australia

\* Corresponding author. E-mail: thomascollyer@gmail.com

# **Editor's key points**

- Clopidogrel increases perioperative bleeding, so surgery is often deferred while therapy is stopped.
- However, morbidity and mortality are known to increase, if hip fracture surgery is delayed.
- In this retrospective series, cessation of clopidogrel therapy was associated with an increased risk of acute coronary events.

**Background.** Increasing numbers of older patients prescribed clopidogrel are presenting for urgent hip fracture surgery. Best practice for the management of clopidogrel therapy is unknown, although delays to surgery are associated with increased mortality. We investigated the influence of perioperative management of clopidogrel therapy on inhospital cardiac morbidity and transfusion in this population.

**Methods.** Retrospective review of all patients aged >60 yr, admitted to a single centre with hip fractures between June 2005 and November 2008. Acute coronary syndrome (ACS) was defined as a raised plasma troponin concentration  $>0.04 \ \mu g$  litre<sup>-1</sup> associated with chest pain, new ECG changes, or both.

**Results.** Of 1381 patients admitted with hip fractures, 114 were receiving regular clopidogrel therapy with a median age of 83.7 (60–98) yr. Clopidogrel was withheld perioperatively in 111 (98%) of these patients. Twenty-three patients (20.2%) suffered an ACS. Risk peaked for ACS [odds ratio (OR) 6.7 (95% confidence interval, CI, 1.7–25.8)] (P=0.006) between days 4 and 8 after clopidogrel withdrawal. The OR for requiring a blood transfusion during or after surgery peaked at day 1 after clopidogrel withdrawal [OR 2.31 (95% CI, 1.02–5.21)] (P=0.044).

**Conclusions.** The length of withdrawal of clopidogrel therapy perioperatively was associated with a significantly increased incidence of ACS. An association between shorter withdrawal and increased blood transfusion requirements was also seen. The study emphasizes the cardiovascular risks of routinely interrupting clopidogrel therapy in this at-risk population and that a more considered, individualized, evidenced-based approach is needed.

**Keywords:** acute coronary syndrome; blood transfusion; clopidogrel; hip fractures; myocardial ischaemia

Accepted for publication: 10 June 2011

Hip fractures are a significant cause of both morbidity and mortality. Estimates of associated mortality are reported between 5% and 10% at 30 days after surgery and 12% and 37% at 1 yr.<sup>1</sup> In the UK, there are around 70 000 hip fractures a year with an associated economic burden of £1.4 billion.<sup>2</sup> This figure will increase with an ageing population, indeed figures estimate that the incidence of hip fracture could reach 21 million worldwide by 2050.<sup>3</sup>

Given this significant morbidity and mortality, considerable effort has focused on identifying best practice in the perioperative management of these patients. Operative delay is one factor that has been clearly shown to influence postoperative morbidity and mortality. Shiga and colleagues<sup>1</sup> demonstrated that operative delay beyond 48 h after admission increased 30 day all-cause mortality by 41% and 1 yr allcause mortality by 32%. A review of 52 published studies claimed a more modest association between operative delay and increased mortality but a clear association with increased morbidity,<sup>4</sup> although the causes of operative delay were not identified. One possible cause was concern regarding bleeding in patients taking antiplatelet therapy, particularly the thienopyridine clopidogrel. Clopidogrel combined with aspirin is of proven benefit in the secondary prevention of cardiovascular and cerebrovascular events.<sup>5 6</sup> It is also the prophylactic regimen of choice in patients taking

© The Author [2011]. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved. For Permissions, please email: journals.permissions@oup.com

aspirin and clopidogrel and presenting with hip fractures has increased.

Withholding clopidogrel perioperatively and delaying surgery is common, although there is a wide variation in practice.<sup>8 9</sup> This practice results in a clinical dilemma: the concerns of perioperative bleeding must be balanced against the cardiovascular risks of stopping antiplatelet medication, particularly when thrombogenesis is likely. We sought to investigate the influence of the perioperative management of clopidogrel therapy on in-hospital cardiac morbidity and the association with in-hospital transfusions.

## **Methods**

Approval was obtained from the Quality Improvement Committee of the Royal Perth Hospital (RPH), Australia, and from the RPH ethics committee as a quality improvement activity.

A retrospective review of all patients aged >60 yr admitted to the RPH, a large tertiary teaching hospital, with hip fractures between June 2005 and November 2008 was conducted. These patients were identified from a contemporaneous database kept by the Department of Orthogeriatrics. Patients prescribed regular clopidogrel therapy on admission were identified and their notes recalled and examined.

Data collected included age, sex, and ASA. Cardiovascular risk factors were hypertension, congestive cardiac failure, ischaemic heart disease, cerebrovascular disease, diabetes mellitus, and myocardial infarction within the previous 6 months. The perioperative management of clopidogrel and any aspirin therapy was recorded. Preoperative blood results including International Normalized Ratio, activated partial thromboplastin time, haemoglobin concentration, platelet counts, and urea were recorded. Days from admission to surgery, total length of stay, and method of anaesthesia were ascertained. Transfusion details included total units transfused before, during, and after surgery. Plasma tropinin concentrations were determined using the ARCHITECT STAT Troponin-I assay (Fisher Diagnostics, Middletown, VA, USA). Coronary ischaemia (acute coronary syndrome, ACS) was defined as an increase in plasma troponin concentrations  $>0.04 \ \mu g$  litre<sup>-1</sup> in association with clinical symptoms or signs of coronary ischaemia, ischaemic ECG changes, or both. Clinical signs included chest pain, breathlessness, and signs and symptoms consistent with congestive cardiac failure (documented as dyspnoea, basal crepitations, or heart failure).

#### Statistical analysis

Reduced cubic spline transformations were applied to logistic regression models to examine the change in risk over time since clopidogrel was withdrawn. Cubic splines are smoothed functions bounded by cut points known as knots. The fit of the cubic spline is largely dependent on the number of knots chosen, with the recommended number relative to sample size. The spline process divides the data into sections based on the number of knots specified, three in this study,

912

fits the best line to the data without requiring the line to be straight, and then smoothes the connections between the sections. The cubic splines were used to identify the pattern of risk (illustrated in plots) and to then inform the choice of categories used in the regression models.<sup>10</sup>

Logistic regression models, including age and sex, were then developed to obtain age- and sex-adjusted estimates of odds ratios (ORs) for time off clopidogrel and the outcome. The study sample size did not facilitate the inclusion of co-morbidities in the regression models. The primary outcome was length of time off clopidogrel and association with ACS; the secondary outcome was association with total blood transfusions.

Data were analysed using the following statistical packages: Stata  $^{11}$  and  ${\rm R.}^{12}$ 

### **Results**

Of the 1381 older patients admitted with hip fractures, 114 were receiving regular clopidogrel therapy (Table 1). The incidence of ACS varied according to the specific cardiac co-morbidities (Table 2). Of these 114 patients, 111 (98%) had their clopidogrel therapy stopped on the day of admission, although the interval to surgery, length of stay, and duration without clopidogrel varied (Table 3). In 104 patients, clopidogrel therapy was indicated for the secondary prevention of cardiovascular events, in four patients, therapy was indicated for the primary prevention of coronary stent thrombosis, and in the remaining six patients, the indication for clopidogrel therapy was unclear from the notes. There were no acute coronary events in the four patients taking clopidogrel for the primary prevention of stent thrombosis. Thirty-four patients were receiving dual clopidogrel and aspirin therapy on admission, 25 of whom also had their aspirin therapy withheld in the perioperative period. Eleven of these 34 patients (32%) suffered an ACS,

 Table 1
 Patient characteristics, anaesthesia technique, incidence of ACS, and total blood transfusion, n (%) unless otherwise stated

Characteristics				
Age (yr) [median (range)]	83.7 (60-98)			
Gender (M/F)	36/78			
ASA score				
II	6 (5)			
III	70 (61)			
IV	38 (33)			
Anaesthetic technique				
General anaesthesia	21 (18)			
General anaesthesia with regional nerve block	65 (57)			
Spinal anaesthesia with or without sedation	25 (22)			
Incidence of ACS	23 (20.2)			
Total blood transfusions				
Number of patients	60 (52.6)			
Total number of units [median (IQR)]	1 (0-2)			

 Table 2
 Prevalence of cardiac specific co-morbidities, column 1, and the incidence of ACS, n (%), within the corresponding subgroup, column 2

Co-morbidity	Prevalence	ACS (percentage of co-morbidity)
Hypertension	97 (85)	19 (20)
Congestive cardiac failure	36 (32)	10 (28)
Ischaemic heart disease	83 (73)	22 (27)
Myocardial infarction <6 months	7 (6)	5 (71)
Cerebrovascular disease	38 (33)	8 (21)
Diabetes mellitus	33 (29)	9 (27)

**Table 3** Duration of withholding clopidogrel therapy in theperioperative period, times from admission to surgery, and totallength of stay (days), presented as median (IQR)

	Duration (days)
Duration withheld before surgery	2 (1-4)
Duration withheld after surgery	3 (1-8)
Total time withheld	7 (3–12)
Time from admission to surgery	2 (1-4)
Total length of hospital stay	18 (13-28)

seven (28%) having stopped both aspirin and clopidogrel therapy.

In the 25 patients who underwent surgery under spinal anaesthesia, the median [inter-quartile range (IQR)] time off clopidogrel was 3 (1–5) days. In addition, eight of these patients were prescribed dual therapy with aspirin on admission. There were no reported cases of spinal haematoma.

Results of the reduced cubic spline transformations investigating the peak risk for an acute coronary event against the length of withdrawal of clopidogrel therapy perioperatively are shown in Figure 1. The reduced cubic spline transformation investigating the odds of requiring a blood transfusion both intraoperatively and after operation, against the length of clopidogrel withdrawal before operation, is shown in Figure 2. The figures demonstrated a peak risk for ACS between days 4 and 8 after clopidogrel withdrawal. Investigation of the risks of clopidogrel withdrawal for 4-8 days perioperatively, compared with all other patients and adjusted for both age and sex, found the OR [95% confidence interval (CI)] for ACS as 6.7 (1.7-25.8) (P=0.006) (Table 4). The risks of requiring a blood transfusion during or after surgery against the length of clopidogrel withdrawal before operation (days) peaked at day 1. Investigation for the risk of blood transfusion between days 0 and 1, compared with all other patients and adjusted for age and sex, found the OR (95% CI) for transfusion as 2.31 (1.02-5.21) (P=0.044) (Table 4).



**Fig 1** Estimated spline transformation showing the log odds for an ACS plotted against number of perioperative days clopidogrel was withheld. The relative odds peak at days 4–8 off clopidogrel therapy.



**Fig 2** Estimated spline transformation showing the log odds for requiring a blood transfusion both intraoperatively and after operation plotted against duration clopidogrel was withheld before surgery (days). The relative odds peak at day 1 off clopidogrel therapy.

## Discussion

In this retrospective, observational study, we found that the management of clopidogrel in older patients with hip fractures was significantly associated with cardiac morbidity, with a peak risk between days 4 and 8 after withdrawal of clopidogrel. There was also a significant association between the length of preoperative withdrawal of clopidogrel and requirements for blood transfusion before and after surgery, with peak risk at day 1.

The association between delays to hip fracture surgery and morbidity and mortality is well established.<sup>1</sup> <sup>4</sup> <sup>13-15</sup>

 
 Table 4 ORs, adjusted for both age and sex, comparing the association between clopidogrel withdrawal perioperatively and risks for ACS and intraoperative or postoperative blood transfusions

	Odds ratio (95% CI)	P-value
ACS		
Withdrawal 4-8 days	6.7 (1.7–25.8)	0.006
Age	1.03 (0.95–1.12)	0.42
Sex (male)	0.46 (0.14-1.49)	0.19
Blood transfusions		
Withdrawal 0-1 days	2.31 (1.02-5.21)	0.044
Age	0.98 (0.93–1.03)	0.47
Sex (male)	2.58 (1.08-6.14)	0.033

Accordingly, national guidelines advise that surgery should be performed as soon as the medical condition of the patient allows. Indeed, operations within 36 h of hip fracture are now markers of best practice in the UK. However, this association between delays to surgery and morbidity and mortality has led many to hypothesize that delays are merely a marker of significant co-morbidity and that increased morbidity and mortality is therefore to be expected. To our knowledge, detailed examination of specific medical causes resulting in operative delays, and their association with postoperative morbidity, has not previously been conducted.

We found that preoperative withdrawal of clopidogrel therapy was commonplace (98%) during the study period, 2005-8. The median duration of cessation of clopidogrel before surgery was 2 days, and the median length of time clopidoarel was restarted after surgery was 3 days. There is little logic in pharmacological terms to this practice. Clopidogrel is a non-competitive, irreversible, inhibitor of platelet ADP P2Y<sub>1.2</sub> receptor, resulting in a 40-70% reduction in platelet aggregation lasting  $\sim$ 7 days.<sup>16</sup> When prescribed at 75 mg once daily, the onset of clinical action ranges from 3 to 5 days, whereas at 400 mg, therapeutic levels are achieved in 2-5 h.<sup>17</sup> Therefore, withholding clopidogrel for 2 days before and 3 days after surgery, then restarting at a dose of 75 mg daily, potentially leaves patients with a peak reduction in the antiplatelet effect between days 5 and 10. We found that cardiac morbidity peaked in those patients off clopidogrel for a duration of 4-8 days. The cause for this peak incidence is likely to be multifactorial: the stress response to both the initial trauma and the corrective surgery resulting in a hypercoagulable state; patient immobility and a rebound increase in platelet function secondary to the abrupt withdrawal of antiplatelet medications.<sup>18</sup>

It has been demonstrated recently that outcome from myocardial infarction is worse in patients recently withdrawn from antiplatelet therapy.<sup>19</sup> It is therefore desirable to maintain antiplatelet therapy during this hypercoagulable perioperative period in patients at risk. However, preparation for intraoperative bleeding is also important. An association between shorter preoperative withdrawal of clopidogrel and

the odds of requiring an intraoperative or postoperative blood transfusion was demonstrated. However, it is important to note that despite the increased odds of requiring a blood transfusion in those patients operated on early, the median number of units transfused per patient was 1, with no adverse transfusion reactions noted. Given that the plasma half-life of clopidogrel is 4 h, after 24 h cessation, the plasma concentration of clopidogrel has decreased to <2% and any platelets transfused are unaffected by</p> clopidogrel. The authors' own practice, in line with recent guidance,<sup>20</sup> is to perform surgery 24 h after stopping clopidogrel with platelets available for transfusion if required. Clopidogrel is restarted 12 h after surgery, after discussion with the orthopaedic team and inspection of the wound site and drains. Unfortunately, there are currently no routine methods for the perioperative assessment of platelet function to help inform transfusion requirements; however, novel methods, including the Thrombelastography<sup>®</sup> Platelet Mapping<sup>TM</sup> Assay, are under investigation.<sup>21</sup>

It is interesting to note that 25 patients received spinal anaesthesia, with no reported cases of spinal haematoma. The median (IQR) time off clopidogrel in these patients was 3 (1–5) days. Eight of these patients were also prescribed dual therapy with aspirin on admission. Until recently, most authorities have advised stopping clopidogrel 7 days before neuroaxial anaesthesia,<sup>22</sup> yet little or no evidence exists that clopidogrel alone increases the risks of vertebral canal haematoma.<sup>20</sup> Furthermore, a recent case series reported the uneventful performance of neuroaxial techniques in patients taking clopidogrel, with no associated complications<sup>23</sup> and new guidelines suggest that epidural or spinal anaesthesia is not contraindicated in patients receiving clopidogrel monotherapy.<sup>20</sup> However, dual antiplatelet therapy with aspirin and clopidogrel remains a contraindication.

There are several limitations to this study. Despite identifying 1381 older patients with hip fractures over a 3 yr period, only 114 patients were on clopidogrel therapy on admission. The small sample size dictates that these results must be interpreted with caution, and the CIs for the risk of ACS are wide. A larger study would have facilitated the inclusion of co-morbidities in the regression models. Recording of preoperative creatinine would have allowed calculation of Lee's Revised Cardiac Risk Index; the association with ACS could then have been investigated. Significantly, the study is retrospective and does not necessarily prove that clopidogrel discontinuation causes ACS. There may be other reasons for the associations seen including differences between the populations discontinuing clopidogrel for shorter and longer periods of time. It is possible that patients restarting clopidogrel earlier had fewer medical problems and were operated upon earlier, but this does not explain why the risk peaked at days 4-8. The investigators were also unblinded when interrogating the notes for evidence of acute coronary events, risking the possibility of recall bias. The prescription of thromboprophylaxis was also not recorded; however, hospital policy advised the prescription of enoxaparin in all hip fracture patients, unless specifically contraindicated. Finally, a comparator group, not on clopidogrel therapy on admission, is planned for future analysis.

In conclusion, we found that withholding antiplatelet therapies during the perioperative period was associated with an increased risk of ACS. The data support a change in practice towards continuing antiplatelet therapy perioperatively, unless clearly contraindicated.

## Acknowledgements

The authors wish to thank Mrs Sally Burrows and Dr Michael Phillips at the University of Western Australia for their help with statistical analysis. We also wish to thank Dr Katherine Smither for her help with data collection.

## **Conflict of interest**

None declared.

## References

- 1 Shiga T, Wajima Z, Ohe Y. Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression. *Can J Anaesth* 2008; **55**: 146–54
- 2 The National Hip Fracture Database. *Preliminary National Report*, 2009. Available from http://www.ccad.org.uk/nhfd.nsf/ Preliminary\_National\_Report.pdf
- 3 Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. Osteoporos Int 1997; 7: 407–13
- 4 Khan SK, Kalra S, Khanna A, Thiruvengada MM, Parker MJ. Timing of surgery for hip fractures: a systematic review of 52 published studies involving 291,413 patients. *Injury* 2009; **40**: 692–7
- 5 CAPRIE Steering Committee. A randomised, blinded, trail of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329–39
- 6 Steinhubl SR, Berger PB, Mann JT III. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. *J Am Med Assoc* 2002; **288**: 2411–20
- 7 Mehta SR, Yusof S, Peters RJG, *et al.* Effects of pretreatment with clopidogrel and aspirin followed by long term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**: 527–33
- 8 Inman DS, Michla Y, Partington PF. Perioperative management of trauma patients admitted on clopidogrel (Plavix). A survey of orthopaedic departments across the United Kingdom. *Injury* 2007; 38: 625–30

- 9 Palan J, Odutola A, White SP. Is clopidogrel stopped prior to hip fracture surgery—a survey of current practice in the United Kingdom. *Injury* 2007; **38**: 1279–85
- 10 Harrell FE, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst 1988; 80: 1198–202
- 11 StataCorp. Stata Statistical Software: Release 10. Stata 10.1. College Station, TX: StataCorp LP, 2007
- 12 R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing, 2008. ISBN 3-900051-07-0. Available from http://www.R-project.org
- 13 Novack V, Jotkowitz A, Etzion O, Porath A. Does delay in surgery after hip fracture lead to worse outcomes? A multicentre survey. *Int J Qual Health Care* 2007; **19**: 170–6
- 14 Bottle A, Aylin P. Mortality associated with delay in operation after hip fracture: observational study. Br J Anaesth 2006; 332: 947–51
- 15 Moran CG, Wenn RT, Sikand M, Taylor AM. Early mortality after hip fracture: is delay before surgery important? J Bone Joint Surg Am 2005; 87: 483-9
- 16 Weber AA, Braun M, Hohfeld T, Schwippert B, Tschope D, Schror K. Recovery of platelet function after discontinuation of clopidogrel treatment in healthy volunteers. Br J Clin Pharmacol 2001; 52: 333–6
- 17 Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Hemost 1999; 25 (Suppl. 2): 15–9
- 18 Lordkipanidzé M, Diodati JG, Pharand C. Possibility of a rebound phenomenon following antiplatelet therapy withdrawal: a look at the clinical and pharmacological evidence. *Pharmacol Ther* 2009; **123**: 178–86
- 19 Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004; **110**: 2361–7
- 20 Scottish Intercollegiate Guidelines Network (SIGN). Management of hip fracture in older people. No. 111, June 2009. Available from http://www.sign.ac.uk/pdf/sign111.pdf
- 21 Collyer TC, Gray DJ, Sandhu R, Berridge J, Lyons G. Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by Thrombelastography Platelet Mapping. *Br J Anaesth* 2009; **102**: 492–8
- 22 Llau J, De Andres J, Gomar C, et al. Anticlotting drugs and regional anaesthetic and analgesic techniques: comparative update of the safety recommendations. Eur J Anaesthesiol 2007; 24: 387–98
- 23 Osta WA, Akbary H, Fuleihan SF. Epidural anaesthesia in vascular surgery patients actively taking clopidogrel. Br J Anaesth 2010; 104: 429–32