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## Review article

# Discontinuation of Plavix<sup>®</sup> (clopidogrel) for hip fracture surgery. A systematic review of the literature



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## ABSTRACT

The elderly population is increasing worldwide, associated with an increase in diseases related to aging, such as hip fractures. These patients are sometimes treated with clopidogrel. There are no arguments at present to clearly determine the risk/benefit ratio of early surgical management of traumatic hip fractures in patients treated with clopidogrel (perioperative blood loss, postoperative complications). The goal of this systematic review of the literature was to show that early surgical management (< 48 h) of patients treated with clopidogrel does not increase postoperative morbidity or mortality. Systematic review of the literature: level of evidence IV. A bibliographic search was performed in July 2015 in PubMed, Embase and Cochrane databases using the MeSh keywords "Clopidogrel or Plavix<sup>®</sup>" AND "hip fracture". Two of the authors analyzed 48 articles based on the title and abstract. Twenty-one articles were selected and read completely with an analysis of the references. Nine articles were chosen. Early surgical management (< 48 h) of patients receiving clopidogrel did not increase mortality at 30 days, 3 months or 1 year (between 25 and 30% mortality at 1 year) and did not result in an increase in perioperative bleeding. The risk/benefit ratio of early surgical management of patients with hip fractures receiving clopidogrel is good; morbidity and mortality are not increased in these patients if surgery is performed immediately or less than 48 h after admission.

*Level of evidence:* IV.

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## 1. Introduction

Hip fractures are the most frequent surgical intervention in trauma units and they are a frequent and severe event in the elderly. Death at 1, 3 and 6 months is 5.2, 10.6 and 14.7% respectively [1] and reaches 30 [2] to 46% [3] at one year. The incidence increases exponentially along with socioeconomic costs [4,5]. More than 65% of patients with HF have an ASA score  $\geq 3$  (American Society of Anesthesiologists), which is the sign of significant associated comorbidities [6] and polypharmacy, in particular cardiovascular (60%) [1]. Medical management (internal fixation or arthroplasty, hemi- or total) should be performed as soon as possible and should allow rapid return to full weight-bearing and to the same level of autonomy as before surgery as well as a hospital stay that is as short as possible. Prescription of antiplatelet drugs is frequent in the

elderly to prevent cardiovascular events [7] and can be a contraindication to anesthesia. Clopidogrel (Plavix<sup>®</sup>) is an antiplatelet agent which inhibits platelet function as long as it is active (about 10 days) [8] thus, the effect decreases as platelet function is renewed or recovered (7 to 9 days) [5,9,10]. Despite guidelines for the use of antiplatelet drugs, there is no consensus on the management of clopidogrel during surgery for in semi-emergency traumatic hip fracture [11,12]. Although it is generally agreed that clopidogrel should be discontinued 48 hours before surgery for traumatic hip fracture [13], there is no consensus in the literature and certain surgeons operate patients who are treated with clopidogrel immediately. Delaying surgery by more than 48 hours and a prolonged hospital stay increases postoperative morbidity and mortality [14–16]. Only early physical therapy and return to walking reduces mortality on multivariate analysis [1], while early surgery (< 48 h) reduces the risk of a pulmonary embolism and the length of the hospital stay [17]. This was confirmed by two meta-analyses in 250,000 patients in 2008 [14] then in 191,000 patients in 2012 [18]. Thus, these patients should be managed as early as possible without increasing the perioperative risks, in particular hemorrhagic and cardiovascular.

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The hypothesis of this systematic review of the literature was that early surgical management (a maximum of 48 h after admission) of hip fracture in patients receiving clopidogrel does not increase perioperative complications and decreases postoperative morbidity and mortality. The goal of this study was also to confirm the benefit/risk ratio of early surgery in patients treated with clopidogrel.

## 2. Materials and methods

This review was designed according to the guidelines for systematic reviews of the literature and metaanalyses [19,20].

### 2.1. Search strategy

In July 2015, a bibliographic search was performed in the PubMed, Medline, CINAHL, Cochrane, and Embase databases. The MeSH key words were “clopidogrel” AND “hip fracture”. Two of the authors (LM and TN) independently selected articles that responded to the selection criteria, with no time limit. The selection was made after reading the title and the abstract. The selected articles were read and the references for each article were analyzed to confirm that no major article on the subject was excluded. Use of the keyword “Plavix®” instead of “clopidogrel” resulted in the same number of references.

### 2.2. Selection criteria

The pre-selection criteria were as follows:

- all patients were at least 18 years old;
- a hip fracture was the primary indication for surgery;
- clopidogrel had been prescribed for a chronic disease before the fracture;
- none of the other medications interfered with the platelet half-life;
- peri- and postoperative complications as well as mortality 3 months or 1 year after surgery were mentioned in the study.

The selected studies:

- were not limited in relation to the date of publication;
- were written in French or in English;
- had an abstract that was available on line;
- had a rigorous methodology.

In case of disagreement on the selection of an article, the two authors reached a consensus opinion.

### 2.3. Selection process

A total of 47 articles were examined. An initial selection excluded articles that did not correspond to our criteria (articles on prevention, biomechanical studies, decision trees, technical notes, case reports, language criteria, surgical anatomy articles, non-rigorous methodology). In the second selection process, we chose 9 articles that evaluated the hypothesis. The included articles were randomized controlled trials or observational studies of patients who were receiving clopidogrel at admission and who rapidly underwent surgery (< 48 h).

The selection process is summarized in Fig. 1.

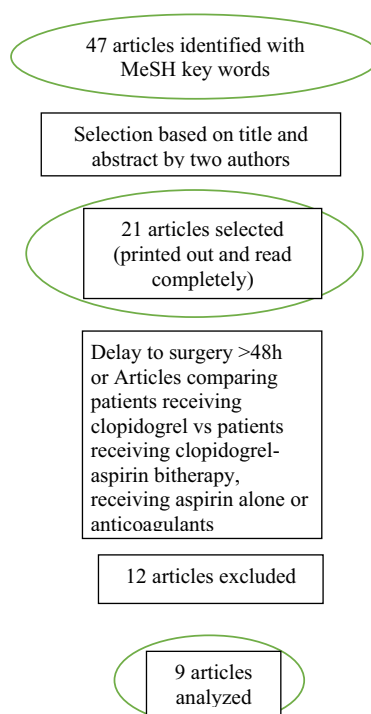


Fig. 1. Selection process.

## 3. Results

Nine articles were selected. Level of evidence of the studies: series of clinical cases, level IV (Table 1).

### 3.1. Mortality

Wordsworth et al. [16] did not report any increased mortality at one year in patients receiving clopidogrel who underwent early surgery (< 48 h) (26.7% mortality at one year). Feely et al. [17] showed that early surgical management (< 36 h) in patients receiving clopidogrel did not result in any increase in mortality at one year. Mortality at one year in this study of 120 patients was 28% in the clopidogrel group and 29% in the control group with a hazards ratio of 1.33.

In the study by Zehir et al. [24], there was no significant increase in mortality at 30 days or at 3 months in patients operated within 48 h who were receiving clopidogrel compared to those who were not receiving antiplatelet drugs (2.7% vs 1.2% mortality at 30 days and 5.4% vs 3.6% mortality at 3 months, respectively). There was an increase in mortality at 30 days and 3 months in patients operated 5 days or more after clopidogrel was stopped (7.2% at 30 days and 12.7% at 3 months).

### 3.2. Complications

Patients operated after prolonged discontinuation of clopidogrel presented with more postoperative complications than those operated within 48 h after clopidogrel discontinuation [21,24]. Complications were mainly due to the supine position including skin ulcers, urinary infections, myocardial ischemia, pulmonary embolisms and acute pulmonary edema.

Zehir et al. [24] reported complications in 10.8% of patients operated within 48 hours after stopping clopidogrel compared to 25.4% in those operated 5 days after discontinuation.

Patients operated within 48 h who were receiving clopidogrel did not present with more postoperative complications (surgical

**Table 1**  
Selected studies; series of clinical cases level IV.

	Type of study	Cases	Groups	Mean age	Type of fracture	Delay to surgery	Management of clopidogrel	Length of hospital stay	Transfusion
Chechik et al. [21]	Cohort	60	Early surgery vs late (> 5d)	82.4	Intra- and extracapsular	Early = 1 day 16 h Late = 7 days 12 h	Continue early surgery; stop at admission for late group	Operated < 48 h: 11 d and 2 h Operated > 5d: 17 d and 17 h	
Wordsworth et al. [22]	Cohort	1225	Clopidogrel vs no clopidogrel	82.3	Intra- and extracapsular	Clopidogrel: 29.4 h Non clopidogrel: 28.8 h	No info		Clopidogrel: 30% Non clopidogrel: 25.9%
Feely et al. [23]	Cohort	120	Clopidogrel vs non clopidogrel	82.2	Intra- and extracapsular	< 36 h for both groups	No info		
Zehir et al. [24]	Cohort	211	G1: clopidogrel operated < 48 h G2: clopidogrel operated > 5d G3 No clopidogrel operated < 48 h	77.3	Intracapsular	G1: 1.79 d G2: 5.82 d G3: 1.68 d	Stop clopidogrel at admission in all Begin again D2 post-op	G1: 8.13 d G2: 14.53 d G3: 7.53 d	G1: 3.16 G2: 2.4 G3: 2.25
Hossain et al. [25]	Cohort	102	Clopidogrel vs no clopidogrel	83	Intracapsular	< 48 h for all	Continue clopidogrel	Clopidogrel: 17.3 d No clopidogrel: 20.5 d	Clopidogrel: 8% No clopidogrel: 3.85%
Wallace et al. [26]	Cohort	110	Clopidogrel vs no clopidogrel	79.8	Intra- and extracapsular	< 48 h	Stop at admission		Clopidogrel: 56% No clopidogrel: 31%
Clareus et al. [27]	Cohort	112	Clopidogrel vs no clopidogrel	85	Intra, extracapsular and on prosthesis	26 ± 19 h	Protocol exacyl for all		Clopidogrel: 3 No clopidogrel: 2
Al Khudairy et al. [28]	Cohort	47	Group 1: stop clopidogrel 3 to 6 days Group 2: stop clopidogrel > 7 days	80.2	Intra- et extracapsular	G1: 4.2 days G2: 8 days	G1: clopidogrel stop between 3 and 6 d G2 clopidogrel stopped > 7d	G1: 21.1 d G2: 28.7 d	

site infections, hematomas, rate of surgical revision) than the control group [25]. Several authors did not find any postoperative increase in bleeding compared to the control group who were not receiving antiplatelet drugs [16,17,26–28].

Clareus et al. [27] did not find any increase in the risk of postoperative transfusions in patients receiving clopidogrel who underwent early surgery (3 transfusions in the clopidogrel group compared to 2 in the non-clopidogrel group). These results were similar to those by Al Khudairy et al. [28].

### 3.3. Perioperative blood loss

Wordsworth et al. [16] did not report any increase in perioperative bleeding in patients receiving clopidogrel who were operated within 48 h after discontinuation (217 ml vs 223 ml).

Clareus et al. [27] and Wallace et al. [20] reported similar results (300 ml vs 350 ml and 142 ml vs 137 ml, respectively).

### 3.4. Duration of hospitalization

The duration of hospitalization was increased in patients who were operated later, due to longer clopidogrel discontinuation [15,28,29].

## 4. Discussion

Early medical management (<48 h) of hip fractures in patients receiving clopidogrel did not increase peri- or postoperative

complications and reduced the hospital stay without increasing mortality at one year.

Fractures of the hip are the most frequent traumatic orthopedic emergency in the elderly. It is a major event in the loss of a person's autonomy and is associated with very high morbidity and mortality at one year. Only one quarter of patients return to their previous level of autonomy and more than 35% are institutionalized the year after surgery [1,30]. In our review of the literature, mortality at one year in patients receiving clopidogrel who underwent early surgery was between 25 and 30%, a rate that is comparable to the mortality at one year observed in most studies, which varies between 12 and 37% [31,32]. The main causes of mortality are cardiovascular and neurological, with at times, a failure to thrive syndrome and lung infections [1,33,34].

Roche et al. [35] reported postoperative complications in 20% of 2448 patients who were operated for a hip fracture with or without comorbidities and a complication rate of 14% in patients without comorbidities. The most frequent complications were pneumopathies (9%) and cardiac complications (5%).

The difficulties of the pre- and postoperative management of this population are the associated comorbidities and the frequent prescription of antiplatelet drugs and anticoagulants. Thus, the goal is to operate these patients as rapidly as possible without increasing the peri- and postoperative risks, while managing acute decompensation of chronic diseases. Nevertheless, there are two explanations to the low risk of hemorrhage in patients receiving clopidogrel: a certain percentage of patients are resistant to this molecule, as many as 40 to 50% [27,36] and there are also numerous

interactions between clopidogrel and other drugs such as proton pump inhibitors which may inhibit the action of clopidogrel and are often prescribed in the postoperative setting.

Clopidogrel is a thienopyridine-class antiplatelet agent that inhibits the adenosine diphosphate platelet receptors. There is no antidote to its antiplatelet action. There is no consensus on the delay to be observed between stopping clopidogrel and surgery (internal fixation or hip replacement). However, surgery should be performed as early as possible to decrease postoperative morbidity and mortality. The goal of this review of the literature was to confirm the benefit/risk ratio of early surgery for hip fracture in patients treated with clopidogrel.

Chechik et al. [37] reported an increase in perioperative bleeding in patients with a more severe fracture hematoma who were being treated by clopidogrel and received early management (1091 ml vs 899 ml) but this did not influence mortality. He also described an increase in perioperative bleeding with the association clopidogrel-aspirin (1312 ml vs 899 ml), a bitherapy that is frequent in these age groups, as well as an increase in the duration of surgery. Certain studies have reported an increase in postoperative transfusions in surgery patients who are receiving clopidogrel, but this did not influence morbidity or mortality [24]. A retrospective study in 8000 elderly subjects with hip fracture showed that perioperative transfusions did not influence mortality in patients with a hemoglobin level of > 8 g/dL [38].

Extending the delay until surgery (> 7 days) in order to manage the discontinuation of clopidogrel results in an increase in mortality at 30 days, 3 months [24,29] and at one year in these patients [39].

Harty et al. [29] showed that mortality at 30 days was markedly higher in 21 patients receiving clopidogrel in whom surgery was delayed for approximately one week, than in the control group (29% vs 4% respectively).

An increasing number of patients are treated with other antiplatelet agents (prasugrel and ticagrelor) which are more effective than clopidogrel. European anesthesia guidelines [40] recommend stopping ticagrelor for 5 days and prasugrel for 7 days before elective surgery. In hip fracture surgery, this delay can be reduced to 3 days to recover 33% of platelet reactivity. The problem is that ticagrelor cannot be reversed with platelet transfusion in case of bleeding. [41].

## 5. Conclusion

Early surgical management (< 48 h) of hip fractures in patients receiving clopidogrel is not associated with increased postoperative morbidity or mortality either for internal fixation or arthroplasty, thus these patients can safely undergo surgery without waiting 48 h.

## Disclosure of interest

The authors declare that they have no competing interest.

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