Surgical Delay for Hip Fracture Clients and the Use of Clopidogrel

An Integrative Review

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# Acceptance of Senior Honors Thesis

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#### Abstract

Hip fractures in elderly patients have very high postoperative mortality rates and the number of hip fractures in the United States is expected to increase exponentially before 2030. Early surgery is essential to improve outcomes, but patients on clopidogrel (Plavix) have a high risk for increased bleeding if surgery is performed within the usual 72 hour window. This paper presents literature and research addressing the dangers of delaying surgery versus undergoing surgery before the effects of the clopidogrel are gone. Based on articles published after 2006, most researchers advocated earlier surgical intervention than previously recommended and emphasized an individualized approached based on the clients' comorbidities and susceptibilities to select postoperative complications.

Surgical Delay for Hip Fracture Clients and the Use of Clopidogrel:

# An Integrative Review

While healthcare is in demand across the country, the area most in need of medical expertise is geriatrics. According to the United States Department of Health and Human Services, people over the age of 65 represented almost 13% of the United States population in the year 2000. By 2030, that number is expected to rise to a total of 19%, an unprecedented increase (Aging Statistics, n.d.). As a result, extensive research should be focused on preparing safe and ethical care for the growing population of elderly patients (Himes, 2001).

Medical professionals and researchers should focus their attention on common issues that arise due to population aging. Aging brings specific changes in the human body. This thesis will specifically address the issues concerning the decrease in bone density and an increased risk for thrombosis. Low bone density can cause pathological fractures in these clients and severely limit their mobility. Hip fractures, or proximal fractures of the femur, are the most debilitating of these fractures with a mortality rate that may be as high as 23% to 32% within a year after surgical repair, especially if surgery is delayed for any reason (Shiga, Wajima, & Ohe, 2008). Mortalities are usually due to the fact that elderly patients present with a variety of comorbidities (Marks, Allergrant, MacKenzie, & Lane, 2003).

Elderly patients usually present a number of risk factors for surgical complications, including cardiovascular conditions. In recent years, the anticoagulant clopidogrel (Plavix) has been increasingly used to treat patients who have undergone a cardiac catheterization, stent placements, and other cardiovascular indications (Chassot,

Delabays, & Spahn, 2007). Clopidogrel is different than other common anticoagulants in that its effects on coagulation are irreversible. The manufacturers of Plavix®, Bristol Myers Squibb, recommend that the medication be discontinued a minimum of seven days prior to any surgery to allow the body to replace affected platelets with new platelets, but this is not specific to the needs of patients with hip fractures (Joseph, Pillai, & Bramley, 2007).

Orthopedic surgeons disagree over which approach is the best for hip fracture patients on clopidogrel. The risks of perioperative bleeding must be weighed against the risk of thrombosis. The risk of thrombotic complications in orthopedic surgeries is higher than most other types (Joseph et al., 2007). Studies have been conducted to determine current practices and compare patient outcomes. The purpose of this review is to examine current literature to determine possible means of improving patient outcome for elderly clients undergoing hip fracture repair while taking clopidogrel.

#### Method

The articles included in this integrated review come from the following databases:

Academic Search Complete, Academic One File, ProQuest Central, ScienceDirect

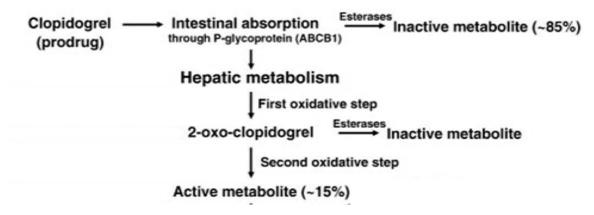
College Edition, CINAHL, Health Source: Nursing/Academic, PubMed and MEDLINE.

Other articles were found by an internet search for scholarly resources. All articles are published in peer reviewed journals within the last five years. The articles consisted of two level III non-experiemental studies describing current practice, eight level III retrospective studies comparing past patients, three level II prospective cohort studies also comparing patints, one literature review, and one level IV letter to the editor.

Issues affecting the mortality rates of patients with fractures were researched and the recent theme of patients on clopidogrel became apparent as a topic worth reviewing. The articles were chosen based on their relevance to the research question. The question that this thesis discusses is what is the safest protocol for patients on clopidogrel who need proximal femur fracture repairs? The articles discussed various aspects of the dilemma including when or if to stop clopidogrel, how long to postpone surgery, and risks associated with each action. Articles not addressing clopidogrel and orthopedic surgeries may be referenced but were not included in the integrative review.

### **Recent Use of Clopidogrel**

When clopidogrel was first developed, it somewhat replaced the other two anticoagulants in its class, ticlopidine and prasugrel, because it was more potent and had fewer side effects. These three medications are known as thienopyridine prodrugs and they deactivate platelets (Becker & Spencer, 2006). Clopidogrel is taken orally and is absorbed in the intestines. The drug must go through a two-step metabolism by the liver (Figure 1), because the agent that actually deactivates the platelets is a carboxylic acid



(Yin & Miyata, 2011) Figure 1 Clopidogrel Metabolism

(Giusti, Gori, Marcucci, Saracini, Vestrini, & Abbate, 2010). The active metabolite peaks in the blood stream in about an hour (Becker & Spencer, 2006) and binds to the

P2Y12 receptor of the platelet to stop the activation process involving adenosine diphosphate (ADP). Once the carboxylic acid has bound to the P2Y12 receptor, it remains there until the platelet enters the spleen to be destroyed (Giusti et al., 2010).

The nature of clopidogrel's mechanism of action makes the therapeutic effect of clopidogrel irreversible and the patient must wait until his or her body manufactures more platelets that have not been chemically altered by clopidogrel. Regular 75 mg doses of clopidogrel inhibit 40-60% of the platelets. The half- life of the metabolite is 7.7 hours and it takes five days for all of the metabolite to be excreted through the kidneys and intestines (Becker & Spencer, 2006, p. 86). Thus, special attention is required when taking patients off clopidogrel therapy to ensure that the effect of the medication is sufficiently cleared (Grujic & Martin, 2009).

Clopidogrel usurps both ticlopidine and prasugrel based on potency (it is 100 times more powerful than ticlopidine) and side effects. The most common side effects are bleeding, bruising, diarrhea, abdominal pain, and dyspepsia. Serious but less common side effects include thrombocytopenia, leucopenia, neutropenia, eosinophilia, thrombotic thrombocytopenic purpura (TTP), aplastic anemia, pancytopenia, agranulocytosis, granulocytopenia, anemia, serum sickness, anaphylactoid reactions, hallucinations, confusion, paresthesia, taste disturbances, vertigo, vasculitis, hypotension, bronchospasm, interstitial pneumonitis, gastric and duodenal ulcers, vomiting, constipation, pancreatitis, colitis, stomatitis, acute liver failure, hepatitis, Stevens Johnson syndrome, arthritis, myalgia, and glomerulonephritis (Plavix 75mg, 2012). Clopidogrel would be contraindicated in patients with hypersensitivity, severe liver impairment, and recent or active bleeding (Plavix 75mg, 2012). Many of the hematological side effects of

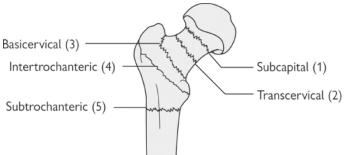
clopidogrel are seen more rarely and less severely than those associated with ticlopidine, which may be due to the fact that the metabolite of clopidogrel does not continue to accumulate in the blood stream like the metabolite of ticlopidine. It also offers fewer gastrointestinal side effects than high doses of aspirin (Becker & Spencer, 2006, p. 87).

According to Becker and Spencer's book (2006), *Fibrinolytic and Antithrombotic Therapy: Theory, Practice, and Management*, studies have shown that clopidogrel is effective in preventing acute coronary syndrome, cerebrovascular accidents, and tissue ischemia related to vascular disease. Clopidogrel therapy, often started with a loading dose of 300 mg after thromboembolitic events, is usually combined with aspirin. This combination was shown to improve outcomes in patients having a coronary artery stent placed more than ticlopidine or clopidogrel alone. Clopidogrel with aspirin reduced the risk of mortality by 20% in patients with unstable angina who received a loading dose and prolonged anticoagulant therapy (Becker & Spencer, 2006, p. 90). The use of clopidogrel is expected to increase due to the accumulation of research showing its therapeutic qualities and due to the rapidly aging population (Butt & Aspros, 2009).

#### **Hip Fractures**

Orthopedic surgery encompasses a vast array of corrective and preventive

(Oxford Medicine Online) surgeries affecting the



**Figure 2 Proximal Femur Fracture** 

musculoskeletal system
(Carmichael, 2003). Joint
replacements, arthritis, and
fractures are all aspects of
orthopedics. Many of the

9

infirmities are not immediately life-threatening and most of the risks are associated with the surgical implications that come about after the hip is repaired and the patient treated. Hip fractures are different, especially in the elderly. An extremely high rate of mortality with one year of surgical correction is associated with elderly patients who sustain a hip fracture (Shiga et al., 2008). Approximately 350,000 hip fractures occur every year in the United States in patients over the age of 65 and that number is expected to double by 2050 (Sterling, 2011). With such remarkable numbers, it is important to understand proper treatment and secure as many positive outcomes as possible (Himes, 2001).

Hip fractures are defined as proximal femur fractures. The femoral neck, trochanters, and the femoral head are all at the proximal end of the femur and considered part of the hip joint (Banik & Dharmarajan, 2006). Fracture can occur in several places (Figure 2) and the location is a factor in the type of internal fixation required. Subtrochanteric fractures are the least common. Blood supply to the femur comes from the femoral circumflex artery, but the head is specifically by the ligamentum teres. The ligamentum teres alone, however, is not adequate to provide blood and oxygen to the head of the femur. If the blood supply is interrupted due to the fracture, the head of the femur may become ischemic, sustaining irreversible tissue damage and increasing local inflammation (Banik & Dharmarajan, 2006).

A hip fracture is diagnosed definitively with an MRI but several assessments and evaluations can be performed to ascertain a probable hip fracture and complications prior to surgery (Banik & Dharmarajan, 2006). It is essential to obtain a thorough patient history, including circumstances surrounding the break, to determine if the fracture is the result of a disease process such as cancer or osteoporosis, if it is the result of accidental

trauma, or if, in some cases, it could be the result of abuse. It is also important to understand the patient's level of mobility prior to the fracture so that rehabilitation goals can help the patient return to his or her baseline. A mental exam is also important because patients, especially elderly clients, may experience an acute change in cognition. Physical signs of a hip fracture include thigh pain when lifting the leg or palpating the femur, deformity, and differing limb lengths. X-rays are helpful when diagnosing hip fractures, but an MRI may show a fracture that was not seen on an X-ray (Banik & Dharmarajan, 2006). After diagnosis, tests should performed to determine possible complications so they can be corrected before surgery if possible. According to Koval (2004), these "include an electrocardiogram (EKG), urinalysis, and basic blood work (complete blood cell count [CBC], electrolyte levels, and coagulation profile)" and more tests should be performed if cardiac or pulmonary risk factors are present (p. 182).

To minimize the possibility of complications before and after the surgery, nursing care should include deep vein thrombosis (DVT) propylaxis, aggressive pain management, and thorough skin care (Koval, 2004). If surgery cannot take place immediately, patients will be put on an anticoagulant that has easily reversible effects and can be discontinued the day before surgery (Banik & Dharmarajan, 2006) such as low molecular weight heparin (Lovenox) (Koval, 2004). Compression stockings or sequential compression devices (SCDs) should be ordered as mechanical DVT prevention and if the doctor has appraised the fracture as stable, the patient should be turned every two hours using the log-rolling method (maintaining skeletal alignment). To prevent skin breakdown, meticulous attention must be given to toileting needs and personal hygiene

(Koval, 2004). Modifiable risk factors individual to each patient should be corrected if possible (Banik & Dharmarajan, 2006).

Major risk factors for hip fractures are associated with bone density. Thin Caucasian women over the age of 80 are at the greatest risk. Patients prone to falls or with a family history of hip fractures are at risk as well. Some of the most common risk factors are smoking, a sedentary lifestyle, alcohol abuse, and a poor diet (Forciea, Schwab, Raziano, & Lavizzo-Mourey, 2004, p. 80). Osteoporosis often causes pathological fractures as well (Forciea et al., 2003, p. 86)

Surgery to correct a hip fracture is either an internal fixation or an arthroplasty. In an internal fixation, surgeons reduce or realign the fracture under fluoroscopic imaging and place screws, and plates to stabilize the fracture. At times, an open reduction is required, but blood loss should be minimized if possible. If the head of the femur is not viable – a common problem in elderly patients – an arthroplasty (or joint replacement) is usually required (Skinner, 2003, p. 146). If the acetabulum (the hip portion of the pelvis) is intact, a hemiarthroplasty is possible, replacing only the head of the femur (Skinner, 2003, p. 394). If the fracture extends and damages the pelvis, however, a total hip arthroplasty is necessary (Skinner, 2003, p. 146).

#### **Special Considerations for Elderly Patients**

Elderly patients are more sensitive to medications and surgical trauma than younger patients. Metabolic changes in the patient can alter the patient's response to medications, requiring differing doses and specific interventions (Forciea et al., 2004, p. 29). Fifty percent of clopidogrel is excreted through the kidneys (Becker & Spencer, 2006, p. 86), but the kidneys are one of many areas that are affected by age (Forciea et

al., 2004, p. 29). Surgical mortality correlated directly to the age of the client as well (Forciea et al., 2004, p. 241).

#### Clopidogrel

Between the age of 30 and 80 years, the kidney loses 20-25% of its mass. Stenosis of the renal blood vessels (considered a normal aspect of aging) leads to loss of pressure regulation in the kidneys which can lead to damage in the nephrons, the functional component of the kidney. The glomerular filtration rate (GFR), used to measure kidney function, decreases gradually throughout adulthood but begins to deteriorate much more rapidly in the later years. If the kidneys are no longer as efficient as they were, clopidogrel will not be excreted from the body as rapidly and the anticoagulant effect will remain longer. The patient's GFR should be measured using creatinine clearance rather than serum creatinine alone due to the fact that elderly patients may have normal levels of serum creatinine but still present with kidney failure (Forciea et al., 2004, p. 29).

Elderly men and women also have changes in liver function which affects the way clopidogrel is metabolized. Because clopidogrel must be metabolized to be effective, decreased liver function could delay or minimize the effect of the medication. The liver shrinks with age and blood supply may decrease by 35-40%. This significantly affects the rate of drug metabolism and will both decrease the potency and prolong the effect of the drug (Forciea et al., 2004, p. 30). More precisely, clopidogrel's half-life may be two to three times longer in elderly patients (Desager, 1994).

### **Surgical Outcomes**

The elderly population is much more likely to require surgical correction of a fracture. Because of common comorbidities, they are also more likely to sustain a

fracture. Sadly, they are more likely to develop complications or die as a result of surgery. The increased morbidity and mortality associated with surgery, however, is due to the high incidence of comorbidities in this demographic (Forciea et al., 2004, p. 241), so this is a vicious cycle that can only be interrupted by careful prevention of modifiable risk factors.

Comorbidities must be identified as soon as possible and treated to prevent complications during and after surgery. Patients with pulmonary conditions should be encouraged to cough and deep breathe before and after surgery. Bronchodilators may be indicated and prescribed to promote oxygenation (Forciea et al., 2004, p. 245). Patients with cardiovascular comorbidities will need special attention to thromboembolism prophylaxis due to reduced circulation and a possible echocardiogram to determine the strength of the heart before surgery (Forciea et al., 2004, p. 246). Antibiotic therapy is recommended due to decreased immunological function secondary to age. An important note must be made concerning anesthesia during the surgery: regional or spinal anesthesia is generally considered the safer procedure. However, certain anticoagulants may cause a spinal hematoma if an epidural is performed. Therefore, based on coagulation studies, general anesthesia may be considered the better choice for certain patients at a high risk for spinal hematomas (Mercado & Petty, 2003). As mentioned before concerning clopidogrel, elderly patients may have a more difficult time metabolizing the medications used for anesthesia and sedation, requiring that they be closely observed (Klotz, 2009).

#### **Surgical Delay**

A clear correlation between surgical delay and morbidity has been established in elderly patients and the morbidities arise primarily due to prolonged immobility (Shiga et al., 2008). Performing early surgery to repair hip fractures decreased the hospital stay, decreased pressure sores (Leung, Lau, Kwan, Chow, & Kung, 2010), resulted in fewer cases of pneumonia (Simunovic, Devereaux, & Bhandari, 2010), and decreased incidence of thromboembolitic complications (Smith, Parvizi, & Purtill, 2011). Surgical delay and mortality has been controversial as many of the mortalities were caused by the comorbidity that delayed the surgery (Vidán, Sánchez, Gracia, Marañón, Vaquero, & Serra, 2011). One of the main causes of descepancy, though, remains the definitely of early surgery versus delayed surgery (Simunovic et al., 2010).

# **Length of Stay**

According to Khan, Kalra, Khanna, Thiruvengada, and Parker (2009), not only does delaying surgery prolong the pain and discomfort of the injury, it most likely prolongs the patient's hospital stay. Naturally, if surgery is delayed a certain number of days, the patient will remain in the hospital for those days, but studies have shown that the recovery time in the hospital is prolonged as well (Leung et al., 2010). The study conducted by Vidan et al. (2010) showed surgical delay longer than five days was associated with a longer hospital stay and Siegmeth, Gurusamy, and Parker (2005) found that patients stayed 10.9 days longer postoperatively if the surgery was postponed longer than 48 hours. Some studies have shown an increase in the length of stay with a delay of only 24 hours (Simunovic et al., 2011). Of the all the complications addressed in the

articles reviewed in this thesis, an increased hospital stay was most consistently correlated with surgical delay.

# **Skin Integrity and Nutrition**

Patients with a hip fracture are placed on bed rest to avoid further displacement of the fracture and to prevent pain. Mobilizing patients with unstable fractures before surgical correction is out of the question due to risk of displacement which may cause death in some elderly patients (Skinner, 2003, p. 146). Immobility places the body weight on body prominences touching the surface of the bed or mattress. Blood flow is pushed out of the tissues and, given enough time, will become necrotic. Skin breakdown is accelerated by moisture and friction. The risk of developing pressure ulcers is significantly decreased by mobilizing the patient, which can only be done after surgery (Leung et al., 2010).

Proper nutrition is essential for healing both the surgical site and the fracture. The patient's diet should be high in protein and vitamin C. Phosphorous, magnesium, and calcium are all essential for bone formation. Fiber and an adequate water intake are also essential while the operation is postponed to prevent constipation which may be a result of immobility and opioid analgesics (Lewis, Heitkemper, O'Brien, Dirksen, & Bucher, 2009). While none of the studies specifically addressed this issue, both Butt and Aspros (2009) and Harty, McKenna, Moloney, D'Souza, and Masterson (2007) documented that the patients participating in the study were fasted several times only to have surgery cancelled the next day. This may contribute to the extended stay in the hospital as well.

# **Postoperative Pneumonia and Urinary Tract Infections**

Surgical delay has also been associated with postoperative pneumonia and urinary tract infections (UTIs). A hip fracture can prevent patients from voiding as often as usual, allowing time for bacterial growth in the urethra. Severe pain can also cause hesitancy and decreased emptying of the bladder. Prevention of pneumonia centers around decreasing patient risk of aspiration and coughing and deep breathing. Coughing with a hip fracture is very painful, though, so the sooner surgery can be performed the less likely the patients are to contract pneumonia postoperatively (Leung et al., 2010). One study found that the number of patients who contracted pneumonia jumped from 12 out of 444 after a 72-hour delay to 50 out of 550 after a 5-day delay, from 2.7% to 11.8%. The same study found that 45 patients developed UTIs after a surgical delay of 72 hours and that number rose to 65 when the patients had a 5-day delay (Vidan et al., 2011). A longer stay in the hospital naturally leads to a higher risk of developing a nosocomial infection, the two most common infections being pneumonia and UTIs (Breathnach, 2009).

# **DVT and Embolism Prophylaxis**

The veins in the legs have the highest risk of developing embolisms. Deep vein thrombosis (DVT) results from immobility and increased platelet aggregation. Veins are not made up of muscles like arteries, but they rely on valves and the muscles surrounding them to move blood toward the heart. When a patient is lying in bed, his or her blood is pooling in his or her veins and beginning to coagulate. Antiembolism stockings (TED hose) apply about 18 mmHg of pressure to push the blood back up to the heart. Sequential Compression Devices are placed on a patient's legs for the same reason. In addition, the patient should be repositioned frequently to encourage blood flow as well.

Hip fractures have been associated with an even higher risk for thrombosis (Lewis et al., 2009).

For patients with proximal femur fractures, anticoagulants are necessary on top of mechanical prevention, especially when surgery will be delayed (Skinner, 2003). In one study, the probability of developing an embolism rose 14.5% if surgery was delayed just one day and 33.3% if it was delayed longer than seven days even if the patients were on prophylactic anticoagulants. The same study found that all 10 of the preoperative DVTs were asymptomatic and not detected by a thorough physical assessment. Smith et al. (2011) recommend that Doppler ultrasound be part of the protocol for all hip fracture patients. These DVTs greatly increase the patient's risk of postoperative thromboembolitic complications and indirectly increase the patient's risk of mortality (Smith et al., 2011).

### Review of Research on Hip fractures and Clopidogrel

Because clopidogrel is a relatively new drug, almost all of the research regarding patients with hip fractures on clopidogrel has been conducted in the last five years.

Clopidogrel created a dilemma for orthopedic surgeons because of its irreversible effects. After clopidogrel was shown to improve patient outcomes in acute coronary syndromes, stent placement, and DVT prophylaxis, doctors began prescribing clopidogrel more frequently. If the patient fell and fractured a femur while taking clopidogrel, surgery was often postponed for up to seven days as recommended by the manufacturers. It had been well established in the literature, however, that hip fracture patients should undergo surgery as soon as possible based on a correlation between surgical delay and morbidity (Shiga et al., 2008). It was also easily established that patients on clopidogrel lost more

blood when surgery was performed within the usual 48 hour window (Chechik et al., 2011). As the matter was further explored, other questions were revealed. Surgeons began to discuss whether oral DVT prophylaxis was required once clopidogrel was discontinued. There was a lack of consensus concerning type of anesthesia to use in order to prevent a spinal hematoma (Lavelle, Demers, & Uhl, 2007). Many physicians disagree on how soon to resume treatment with clopidogrel after surgery is performed (Joseph et al., 2007). Adding to the risk of bleeding associated with clopidogrel, abruptly stopping treatment causes a period of rebound hypercoagulation that further places the patient at risk for a thromboembolism (Collyer, Reynolds, Truyens, Kilshaw, & Corcoran, 2011).

## **Orthopedic Surgeons' Current Protocol**

Recent research shows no protocol in place for standardizing treatment of these patients. Two articles were published in 2007 assessing the disagreement among surgeons. Joseph et al. (2007) sent a survey to 140 orthopedic consultants in Scotland, contacted Bristol-Myers Squibb, and consulted with four hematology departments in an effort to compare practice with evidenced-based recommendations. Bristol –Myers Squibb maintained that clopidogrel should be discontinued seven days before surgery, but only 47.2% of consultants stopped clopidogrel for seven days. Almost 14% did not stop clopidogrel for orthopedic surgeries and the remainder varied, stopping the medication anywhere from 5 to 21 days preoperatively. The hematology departments displayed no consensus regarding urgent orthopedic surgeries, but suggested that perhaps clopidogrel therapy could continue perioperatively as a means of thromboprophylaxis. The authors concluded that patients should be assessed individually to determine the appropriate

emergency care and suggested more research should be conducted in this area (Joseph et al., 2007).

Lavelle et al. (2007) conducted a survey as well to "attempt to ascertain the current standard of care among academic orthopedic centers" as it pertains to patients on clopidogrel who sustain a hip fracture (p. 997). Half of the seventy-four programs that responded stated that they delayed surgery not more than three days for patients on clopidogrel, but 89% stated that surgery was not postponed at all for emergent cases. Several centers responded that there was no protocol, but stated that each surgeon determined what he or she deemed safest. The authors defined their findings as a "complete lack of consensus" (Lavelle et al., 2007, p. 996).

### **Perioperative Blood Loss**

Chechik et al. (2011) focused their study on perioperative blood loss and patients taking clopidogrel. They also narrowed their study to hip fractures over the age of 40. This allowed 88 patients in the study, 44 with continuous clopidogrel therapy and 44 with either aspirin or no anti-platelet therapy. The purpose of the study was to determine the actual risk of blood loss in patients on long term clopidogrel. The amount of blood loss was determined both by measuring intra-operative blood loss and drainage and by preand postoperative hemoglobin levels. Patients who dropped below 9 g/dL were given a blood transfusion. The study showed that while blood loss was significantly higher in patients taking clopidogrel and combined therapy (clopidogrel and aspirin) when surgery was not delayed, short term mortality was unaffected. Probably due to their prior comorbidities, these patients did experience more cardiovascular and cerebrovascular complications. The authors suggest that anticoagulation therapy not be discontinued if

possible, but state that surgeons must determine each patient's individual risks (Chechik et al., 2011).

Johansen, White, and Turk (2008) also focused on perioperative blood loss. This study of 17 clients found that patients' hemaglobin levels fell 1.3 g/dL more if their surgery was not delayed. Of the ten patients whose surgeries were delayed, however, two experienced serious thromboembolitic complications. The authors distinguished between emergency, urgent, and electives surgeries, stating that emergency surgeries were performed immediately and elective surgeries should be performed once the effect of the drug has worn off, but that urgent surgeries were the cause of conflict. Based on their findings, the authors suggested that each patient be evaluated individually for risk of bleeding and risk of thrombosis to determine a time for surgery (Johansen et al., 2008).

#### **Overview of Research**

Most of the remaining research aimed to determine if a correlation existed between patient outcomes and clopidogrel by analyzing time-to-surgery and postoperative complications. Several small scale studies have been conducted on this topic. Butt andAspros (2009) compared comorbidities, surgical delay, type of thromboprophylaxis, hemoglobin levels, and American Society of Anesthesiologists (ASA) scores (which assess patient acuity and comorbidities). They found that patients who underwent hip fracture repair needed more blood transfusions and had a higher mortality when surgery was delayed (Butt & Aspros, 2009).

The study Chechik, Amar, Khashan, and Kadar (2012) conducted had different findings regarding clopidogrel and hip fractures. The average age of the patients in this study was 81.6 years. Based on 30 hip fracture patients whose surgery was delayed and

30 patients who underwent surgery within 48, Chechik et al. found that mortality rates were similar but patients with delayed surgery had longer hospital stays and more complications related to immobility. Bleeding complications, however, were similar in both groups (Chechik et al., 2012).

One study's results showed that there was a significant increase in acute coronary syndrome (ACS) that correlated with the length of time clopidogrel had been withdrawn (Collyer et al., 2011). This study focused on hip fracture patients over the age of 60. Out of 111 patients who had their clopidogrel discontinued for surgery, 23 experienced ACS in 4 to 8 days (Collyer et al., 2011).

Cox, Talbot, Topp, and Templeton (2008) focused on blood loss and hospital stay when studying 20 patients (average age of 81 years) from July 2005 to July 2006. They found that patients had lower postoperative hemoglobin when surgery was immediately performed, but there was no increase in postoperative complications. They also found that length of stay in the hospital after surgery was increased by three days on average when surgery was postponed seven days. Based on that information, the authors suggest early surgical repair. On a related topic, one of the observations the researchers reported was that patients who had delayed surgical intervention also more commonly had spinal anesthesia. The authors attribute this to the risk of a spinal hematoma if surgery is performed immediately (Cox et al., 2009).

Harty et al. (2007) found a significant increase in patient mortality when corrective surgery was delayed for patients on clopidogrel over the age of 65. Comparing 21 patients on clopidogrel to 159 patients in the control group, they found that surgery was performed an average of 7.2 days after the fracture for patients on clopidogrel and

only 2.1 days for patients not on clopidogrel. Twenty-nine percent of patients on clopidogrel died with 30 days of operation and only 4% of patients died within 30 days in the control group. However, because this study did not differentiate between patients on clopidogrel who did get early surgery and patients on clopidogrel who had delayed surgery, the higher mortality could be attributed to the use of clopidogrel rather than the timing of the surgery. The author recommends an experienced surgeon operate and the patient be given platelets two hours before surgery (Harty et al., 2007).

Khatib, Isaacs, Walsh, Walton, and Molnar (2011) conducted a cohort study to "examine the bleeding risk and complication rate of hip fracture surgery without delay in patients who were taking clopidogrel". The authors make the significant observation that hip fracture surgeries generally involve less vascular disruption than cardiothoracic surgeries. This is significant because the seven day delay recommended by clopidogrel manufacturers is based on cardiothoracic literature (Khatib et al., 2011) and therefore may not apply to orthopedic surgery. This study also found that age was a significant factor in postoperative hemoglobin levels (the average age was 84 years). The older the patient was, the greater the drop in hemoglobin. Surgery was not delayed based on clopidogrel and it appeared that it was safe to operate without delay on patients taking clopidogrel (Khatib et al., 2011).

One study analyzed the comorbidities that patients on clopidogrel had prior to surgery on top of assessing the outcome of delayed surgery. For these patients, surgery was delayed for an average of eight days and the average age was 82. Mortality and morbidity were higher in these patients than in the patients in the control group who were not on clopidogrel and had surgery in an average of 2.3 days. As a result of these

findings, the authors suggest having every patient assessed by an anesthetist to determine if general anesthesia is possible over spinal anesthesia and have platelets available in case a transfusion is needed (Leonidou, Cam, & Chambers, 2011).

Maheshwari, Acharya, Monda, and Pandey (2011) conducted research in the United Kingdom to determine correlation between patients over the age of 64 with hip fractures on clopidogrel and one-year mortality. They discontinued clopidogrel at least seven days before the surgery as recommended and no patients needed more than one blood transfusion postoperatively. Unfortunately, 10 out of 30 patients experienced complications related to immobility and 26% died within one year. The researchers recommend that surgery be performed "without undue delay" on "medically fit" patients because surgical delay was the only independent factor to directly correlate with increased mortality (Maheshwari et al., 2011).

Obideyi, Griffiths, and Parker (2008) wrote a short article describing their small scale study. The purpose of the article was to present successful cases of early surgical intervention for hip fracture patients on clopidogrel. Only six elderly patients (average age of 86) were presented and three of those had spinal anesthesia despite clopidogrel therapy. The patients underwent surgery in 27.8 hours on average. The authors feel that this type of patient should not be subjected to protocol. Rather, each case should be carefully considered, with early surgical intervention and spinal anesthesia being viable options (Obideyi et al., 2008).

The last retrospective article reviewed presented evidence that early surgery was a possible alternative for patients on clopidogrel. Gronski and Sim (2009) studied 21 patients on clopidogrel who needed a hip fracture repair and compared them to hip

fracture patients who were not on clopidogrel. Of the patients on clopidogrel, five patients had surgery delayed longer than five days based on concern regarding the use of clopidogrel, which in other studies has been shown to significantly increase the risk of postoperative complications related to immobility. Four patients whose clopidogrel was held for greater than two days needed blood transplants, but the patients whose clopidogrel was held for less than two days (n=8) did not need any transfusions. The authors concluded that operating specifically within the first two to three days was clinically safe but stated that a larger study should be conducted to substantiate their claims (Gonski & Sim, 2009).

#### **Additional Literature**

Haidar and Taher (2010) wrote a Letter to the Editor of *Injury* arguing that two to three days may be the safest time to surgically correct hip fractures in patients on clopidogrel. They based their opinion on clopidogrel's mechanism of action and metabolism. According to the authors, in two to three days, patients may have regained as much as 20% of unaffected platelets which would be sufficient to perform surgery safely (Haidar & Taher, 2010).

Steele, Fox, Fletcher, Grigg, and Bell (2011) compiled a literature review describing recent practice and protocols, blood loss, risks for clopidogrel patients in orthopedic surgeries, and risks of holding clopidogrel before and after surgery. The authors recommended several strategies to prevent poor patient outcomes. Decisions should be made after consulting an anesthetist and the cardiologist who prescribed clopidogrel. Use of clopidogrel alone should not be a reason to postpone surgery and platelet transfusions should be available during surgery. If the patient does not have a

high risk for thrombotic episodes, clopidogrel may be discontinued for a short time. The literature review demonstrates no consensus regarding protocol and states that care must be individualized to the patient (Steele et al., 2011).

#### Conclusion

All of these studies have contributed to the body of knowledge available to orthopedic surgeons in order to assist them in treating hip fracture patients on clopidogrel in the safest way possible. Even though the use of clopidogrel is growing and hip

Table 1				
Study	Total number of patients	Patients on Clopidogrel	Patients in control groups or on other anticoagulants	
<b>Butt &amp; Aspros</b>	15	15	0	
Chechik et al.	60	60	0	
Chechik et al.2	88	44	44	
Collyer et al.	1381	114	1267	
Cox et al.	20	20	0	
Harty et al.	180	21	159	
Johansen et al.	17	17	0	
Khatib et al.	338	39	299	
Leonidou et al.	405	27	378	
Maheshwari et al.	30	30	0	
Sim et al.	135	21	114	

more common due to the aging population of the United States, all of the studies involve a small number of patients (Table 1). Thus, the conclusions reached in these articles may not generalize to all patients

over 65 years old with hip fractures and on clopidogrel. Large scale, randomized experiments should be conducted to determine proper time to withdrawal clopidogrel, the safest preoperative waiting period for the elderly populations, and the adverse effects relating to continued clopidogrel therapy throughout the perioperative period.

However, based on the combined results from these studies, several recommendations can be implemented to help ensure positive patient outcomes. First, a

thorough history and physical should be performed to determine each individual client's risks and comorbidities. Second, anticoagulation therapy should continue throughout the hospital stay even if clopidogrel is discontinued in order to prevent thromboembolitc complications that these patients are prone to. Third, if surgery is being performed while the patient is on clopidogrel or very shortly after, the patient should be prepared to receive a platelet transfusion if blood loss is too high and the surgery should be conducted by an experienced orthopedic surgeon to shorten operative time as much as possible. Last, at the discretion of the surgeon and interdisciplinary team, surgery should be performed at the earliest possible date to prevent complications of immobility and decrease patients 1-year mortality.

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