Bleeding Risks Associated with the Use of Aspirin, a Thienopyridine and Warfarin Therapy

Elizabeth Gardner
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Warfarin is the fifth most prescribed cardiovascular agent and the thirteenth most prescribed drug in the United States (Ansell, Oertel and Wittkowsky, 2005, p. xiii.). There were 31 million prescriptions for warfarin dispensed in 2004 (Wysowski, Parivash and Swartz, 2007). Its use has prevented thousands of strokes and the sequela of disability and death since its widespread use, and its indications are increasing. It also has a narrow therapeutic index. Warfarin’s most common side effect, and potentially most dangerous, is bleeding. Percutaneous coronary intervention with stenting (PCI-S) has also saved thousands of lives and reduced disability from coronary artery disease. Aspirin and a thienopyridine are indicated post-procedure for up to a year. Both these drugs have associated bleeding risks. Clinicians are concerned that the combination of these three drugs will increase the risk of bleeding to the point it will preclude the patient from undergoing PCI-S. This paper is an exploration of bleeding risks in populations taking these three agents: warfarin, aspirin and a thienopyridine.

**Purpose**

The purpose of this project is to determine bleeding risk in persons taking a combination of warfarin, aspirin and a thienopyridine (usually ticlodipine or clopidogrel). Warfarin is a commonly prescribed drug used to prevent thrombosis and stroke, and carries with it well-known bleeding risks. Percutaneous coronary intervention with stenting (PCI-S) is also a widely used procedure, whose number is expected to increase as the population ages. Patients require treatment with two antiplatelet agents-aspirin and a thienopyridine post PCI-S. Both of these medications carry with them a risk for bleeding. A perfect storm of bleeding risk exists for persons requiring therapy with all three agents. The question to be answered by this literature review is: What is the incidence of bleeding in patients taking warfarin, aspirin and a thienopyridine?
Justification

Warfarin Therapy: Reasons and Risks

Warfarin is an oral anticoagulant that interferes with the synthesis of Vitamin-K dependant clotting factors II, VII, IX and X, thereby inhibiting thrombus formation. It is most often used to prevent stroke in patients with atrial fibrillation (AF). AF is one of the most common abnormal heart rhythms and strong independent risk factor for stroke. Singer (2005) reports AF as the cause 14% of all strokes in the US and that the Framingham Heart Study estimated the prevalence of AF to be 2% at age 60 and 10% at age 80. The risk of stroke in this population is five times higher across all age groups. Anticoagulation with warfarin is very effective in reducing the risk of stroke, with the pooled results of five randomized studies showed a relative risk reduction rate of 68%. It is also the most effective therapy for stroke prevention in patients with mechanical prosthetic heart valve replacement, severe left ventricular dysfunction, intracardiac thrombi, deep vein thrombosis, pulmonary embolus, and antiphospholipid antibody syndrome. Bleeding is the most common side effect of warfarin therapy. Ryan (2005, p.13.3) reports that in one study, 12% of patients started on anticoagulation at time of hospital discharge had an episode of major hemorrhage. Wysowski et al. reported that data from hospital emergency departments for 1999 through 2003 indicated that warfarin was associated with about 29,000 visits for bleeding complications per year and it was among the drugs with the most visits. This data was consistent with other reports of major bleeding frequencies for warfarin as high as 10% to 16%.

Coronary Stenting and Associated Bleeding Risks

Coronary artery disease (CAD) remains the leading cause of death in the U.S. It is estimated that 10 million people have symptomatic disease. (Becker and Spencer, 2005). Acute
coronary syndrome (ACS) occurs blood flow to the heart muscle is critically compromised, leading to ischemia and necrosis. Fenton (2009) found that there were 1,680,000 hospital discharges for ACS in 2001. One of the treatment options for ACS is percutaneous coronary intervention with stent placement (PCI-S). Two types of stents are used: bare metal (BMS) or drug–eluting (DES). The recommendations for management post-PCI-S placement are two antiplatelet agents: aspirin and a thienopyridine (usually clopidogrel or ticlodipine) to prevent thrombosis and occlusion of the stent. They inhibit thrombosis by reducing platelet aggregation. Length of therapy depends on the type of stent: BMS requires one month of dual therapy (DT) with two antiplatelet agents, while the DES requires at least one year per ACC/AHA recommendations (Holmes et al. 2009). Both aspirin and thienopyridines have bleeding risks.

Mcquaid and Laine (2006) conducted a review and meta-analysis of adverse events using low-dose aspirin and clopidogrel in randomized controlled trials. They concluded that overall the annual incidence of major bleeding due to low-dose aspirin was modest—only 1.3 patients per thousand higher than what is observed with placebo treatment (p.624). Holmes et al., in their 2009 JACC white paper, found that DT carries with it a variable but overall increased frequency of bleeding events.

**Practice Implications**

As the population ages, there will be an increasing number of patients requiring concomitant warfarin therapy and treatment with two antiplatelet agents. These patients may be managed by an advanced practice nurse (APN) in a variety of settings: primary health care, anticoagulation management services, geriatric practice, inpatient or outpatient specialty services or emergency services. It is imperative, therefore that the APN recognize the indications for these therapies and their associated bleeding risks, and develop a risk reduction strategy.
Methodology

An English-language literature search was conducted using Texas Woman’s University library database. Sources included MEDLINE with Full Text, Cochrane Library, Scopus, Science Direct, CINAHL with Full Text, and PubMed Remote. Best Practices electronic database was accessed via Parkland Hospital. Literature publication dates were between January 2004 and August 2009. Search terms included “aspirin,” “warfarin,” “thienopyridine,” “clopidogrel,” “antiplatelet therapy,” and “anticoagulant.” The initial search yielded hundreds of articles. Twenty-two articles were identified when the search included the all the terms “aspirin,” “warfarin,” and “thienopyridine.” Additional references were located by examining the citations of the retrieved articles. Articles that did not reference cardiac disorders were excluded.

Definition of Terms

Acute Coronary Syndrome (ACS). This is an umbrella term used to cover any group of clinical symptoms compatible with acute myocardial ischemia. Acute myocardial ischemia is chest pain due to insufficient blood supply to the heart muscle that results from coronary artery disease. Acute coronary syndrome thus covers the spectrum of clinical conditions ranging from unstable angina to non-Q-wave myocardial infarction and Q-wave myocardial infarction. Coronary heart disease is the leading cause of death in the United States. Unstable angina and non-ST-segment elevation myocardial infarction are very common manifestations of this disease (American Heart Association, 2009).

Acute Myocardial Infarction (AMI) is defined as death or necrosis of myocardial cells. It is a diagnosis at the end of the spectrum of myocardial ischemia or acute coronary syndromes. Myocardial infarction occurs when myocardial ischemia exceeds a critical threshold and
overwhelms myocardial cellular repair mechanisms designed to maintain normal operating
function and hemostasis. Ischemia at this critical threshold level for an extended period results
in irreversible myocardial cell damage or death (Bolooki and Bajzer, 2009).

Anticoagulant. An anticoagulant is a substance that prevents coagulation; it stops blood from
clotting (Wikipedia, 2009).

Antiplatelet. An antiplatelet drug is a member of a class of pharmaceuticals that decreases
platelet aggregation and inhibit thrombus formation. They are effective in the arterial circulation,
where anticoagulants have little effect (Wikipedia, 2009).

Atrial fibrillation (AF or afib) is the most common cardiac arrhythmia and involves the two
upper chambers (atria) of the heart. Its name comes from the fibrillating (i.e. quivering) of the
heart muscles of the atria, instead of a coordinated contraction. It is diagnosed by the absence of
P waves on an electrocardiogram (Wikipedia, 2009).

Bleeding Risk. Bleeding is the major complication of warfarin therapy. The most common sites
of anticoagulation- related bleeding is the gastrointestinal tract, the genitourinary tract and soft
tissues (Beyth, 2005 p.32.2). Intracranial bleeding is the most deadly complication, with a
mortality rate of up to 60%. No consistent criteria exist to define bleeding severity. In some
studies, bleeding was classified as major if it was intracranial or retroperitoneal, if it led directly
to death, or if it resulted in hospitalization or transfusion. In other studies, major bleeding only
included “fatal or life-threatening bleeding.” “Bleeding requiring blood transfusions” was, in
some studies based on a minimum requirement of a certain number of units, in others, a
reduction of the hemoglobin level (Schulman, Beyth, Kearon, and Levine, 2008). Minor
bleeding can be defined as an event as simple as a nosebleed or a cut after shaving to a bleeding
Incident requiring transfusion of one unit of blood (which, it may be noted, is not minor to patient or insurance company).

Coronary Artery Stent. An intraluminal coronary artery stent is a small, self-expanding, stainless steel mesh tube placed within a coronary artery to keep the vessel open. It may be used during a coronary artery bypass graft surgery to keep the grafted vessel open, after balloon angioplasty to prevent reclosure of the blood vessel, or during other heart surgeries (Medline Plus, 2009).

International Normalized Ratio (INR). A system established by the World Health Organization (WHO) and the International Committee on Thrombosis and Hemostasis for reporting the results of blood coagulation tests. Results are standardized using the international sensitivity index for the particular thromboplastin reagent and instrument combination utilized to perform the test (Mednet, 2009).

Percutaneous coronary intervention (PCI), also known as coronary angioplasty, is a therapeutic procedure used to treat stenotic coronary arteries of the heart found in coronary heart disease (Wikipedia, 2009).

Thienopyridine: One of a group of compounds, including ticlopidine and clopidogrel, which prevent platelet aggregation (Medlexicon, 2009).

Warfarin: A drug that decreases blood coagulation by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidated vitamin K to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. For this reason, drugs in this class are also referred to as vitamin K antagonists (Wikipedia, 2009).
A literature search resulted in total of 17 studies. Of these, five were commentaries, summaries or consensus opinions. In Rubboli and diPasquale’s 2007 abstract, they concluded that there was a substantial increase in bleeding observed with the administration of triple therapy but noted the studies were few, observational and retrospective. Eikelboom and Hirsch (2007), referencing five studies, assessed the clinical risks and benefits of combined antiplatelet and anticoagulant therapy. They conferred that triple therapy was a rationale approach in patients with atrial fibrillation with a coronary stent, but recommended that randomized studies be conducted to determine if the risks outweigh the benefits. Rubboli, Halperin, Airaksinen et al. (2008) conducted a systematic review of the literature assessing the safety and efficacy of antithrombotic regimens in populations undergoing PCI with stent placement. The most common indication for warfarin in this group was AF. TT was the most commonly prescribed regimen. They concluded that TT is currently recommended in this population but is also associated with major bleeding. Holmes, et al., in their June 2009 White Paper, reviewed nine studies. They noted that the studies were mostly single-center registries, small case controlled series or ad-hoc prospective studies. Up to 21% of patients receiving TT needed a blood transfusion, and the relative risk of major bleeding was three to five times higher than that observed in the groups receiving DT. They noted that many factors confounded their analysis, including variation in medication doses and length of therapy, and different definitions of bleeding events.

Hermosillo and Spinler (2008) comprehensively analyzed the results of twelve studies. The results of their analysis is as follows:
Two of these (Orford, 2004 and Porter, 2006) are case series. Orford’s population consisted of 66 patients undergoing PCI with stent placement receiving TT. No information is available regarding the length of therapy or medication doses. Bleeding episodes occurred in 9.2% of patients (95% CI), and 3% of patients had major bleeding (defined as needing two or more units of packed red blood cells (PRBC). Bleeding only occurred in patients who had INRs above the recommended range or pre-existing GI lesions. Porter evaluated 180 patients undergoing PCI with stent placement who received TT for 30 days. Minor bleeding developed in 18 (10%) of those patients, and major bleeding in 1 (1%). Level of evidence-2c3a.

Buresly’s 2005 case-control study evaluated bleeding complications associated antithrombotic treatment regimens. The study population was 21,443 elderly patients with a history of AMI. They had received either warfarin, ASA and warfarin, ASA plus a thienopyridine, or TT (141 patients). Average length of treatment was 654 days. The TT cohort had a higher bleeding risk (0.09 per patient year) than the other groups. One patient receiving TT had a bleed (1/141). The sample size precluded calculation of a HR. Level of evidence-4.

One study is a randomized, open label, multi-center trial. Anand, in the 2007 WAVE study, evaluated patients with peripheral artery disease with ACS or stent placement. The average length of treatment was thirty-five months. Of 2,161 patients, 1,080 received TT, 1,081 received DT. Outcome measured was life-threatening bleeding. The TT bleeding rate was 4.0%, DT; 1.2% (RR of 3.41, 95% CI 1.84 to 6.35, p<0.001). TT was permanently discontinued in 29.5% of patients s. 4.9% of DT. Level of evidence 1-b.
The other eight studies analyzed by Hermosilla and Spindler were retrospective cohort studies. (level of evidence- 2b). Their results are reiterated as follows:

Mattichek’s, et. al(2005) population was patients who underwent stent placement for AMI. They examined the 6 month and 12 month GI bleed rates in patients receiving DT (n=42) or TT (n=40). At six months, GI bleeding rate was 9% for TT vs. 0.0% for DT (p=ns). Blood transfusions for GI bleeding were required by 12.5 % of TT group vs. 3.5% of DT ( p=ns). At twelve months, GI bleeding was 15 % for TT vs. 0% DT, (p=ns), transfusion need was 21% vs. 3.5% ( p=0.028).

Konstantin, et al. (2006) surveyed a database of, 2737 Israeli patients discharged from hospital after AMI. The purpose was to determine the incidence, complications and outcomes from TT. Two thousand six hundred and sixty one patients received DT, 76 (2.8%) patients received TT. During hospitalization, the TT group experienced more complications such as heart failure, tachyarrhythmias, reinfarctions, and major bleeding (2.6 vs. 0.6%, p = 0.03) .No information was available about minor bleeding rates and no bleeding outcomes were assessed at thirty day and six month follow-up. The post-hospitalization mortality rate did not significantly differ.

Khurram, et al. (2006) compared the risk of bleeding in patients requiring TT (n=107) vs. DT(n=107) in patients undergoing PCA with coronary stent placement. The average length of follow-up was 211 days. Major bleeding was defined as bleeding that was significantly disabling, intraocular, or requiring two or more units of PRBCs. Major bleeding was reported in 6.6% of the TT group vs. 0.0% in the DT group; p=0.014. Minor bleeding was defined as other bleeding events that led to disruption of therapy. This occurred in 14.9% of TT group vs. 3.8%
of DT group; p=0.01. Adjustment for confounding variables showed TT was an independent predictor of bleeding (HR 5.44, 95% CI 2.03 to 14.53; p=0.001).

DeEugenio, et al. (2007) assessed the bleeding risk in 97 patients receiving TT who had undergone stent placement or brachytherapy. They were matched 1:1 with patients on ASA and clopidogrel. Sex and stent type were controlled for. Of the 97 patients receiving TT, 14% had major bleeding vs. 3% in DT group. TT was an independent predictor of bleeding (HR 5.0 (95% CI 1.4 to 17.8); p=0.012. Incidence of minor bleeding was collected but not reported.

Karjalaine, et al. (2007) compared the results of a warfarin-containing antithrombotic regimen (n=219) with a control group that contained antiplatelet therapy only (n=227). The study group was post-PCI with a long-term indication for warfarin. Of these, 106 patients (48.4%) received TT. The remainder received either warfarin alone or warfarin with one antiplatelet agent. The control arm received a combination of antiplatelet agents (94.3%) or a single antiplatelet agent (5.7%). Major bleeding was reported as being three times higher in the TT group (8.2% vs 2.6: OR 3.3, 95% CI 1.3 to 8.6; p=0.014).

Nguyen’s et al. (2007) patients had acute coronary syndrome followed by coronary stenting (n=800). In hospital, 580 (73%) received TT, 220 (27%) received DT. Major bleeding was recorded in 5.9% of patients on TT and 4.6% of patients on DT; p=.46. Only 24% of patients remained on TT. No information on bleeding outcomes at six months was available.

Nguyen, Murphy and Mega (2007) studied a group of 19,315 patients diagnosed with STEMI and treated with fibrinolytic therapy. Outcomes were assessed after thirty days. Eighty-six patients received TT, 4497 received DT and the remainder monotherapy or another combination. Major bleed rate was 1.16% in TT and 0.31% in DT, p=.25. Minor bleed rate was
0.0% in TT and .042 % in DT; p=1.0. Combined major and minor bleed was 1.16 % in TT and 0.73 % in DT (p=.48).

Ruiz- Nodar, et al. (2008) analyzed the outcomes of 426 patients with AF who had undergone PCI. There were 213 in TT group, 174 in DT group and the remainder on other combinations of oral anticoagulant and antiplatelet therapy. Major bleeding occurred in 14.9% of the patients receiving a warfarin–containing regimen vs. 9.0% of the non-anticoagulated patients (p=0.19). Minor bleeding occurred in 12.6% of TT vs 9.0% of DT; p=0.32.

Five more studies were published since Hermosillo and Spinlers analysis.

Johnson’s retrospective cohort study (2008) from Kaiser Permanente involved patients enrolled in their anticoagulation management service as of September 2005. In this study the thienopyridine was either clopidogrel or dipyridamole. One thousand six hundred and twenty three received TT, 2,560 received warfarin only. In six months, the TT cohort was more likely to have had anticoagulation –related hemorrhages (4.2% vs. 2.0%, p <0.001). An independent association was found between hemorrhagic events and TT (OR=2.75:95% CI 1.44 5.28). Level of evidence-2b.

Manzano-Fernandez, et al. (2008) assessed the safety of anti-thrombotic therapies in 104 patients with AF undergoing PCI-S. Fifty one patients received TT, 53, non-TT. The endpoints were early major bleeding (EMB), defined as events that occurred less than 48 hours after PCI), or late major bleeding, (LMB), events occurring more than 48 hours after PCI. The incidence of LMB in TT was 21.6%, non-TT 3.8%; p=0.006. Incidence of EBM was not significant (5.8% in TT, 11.3% in non TT, p=.33). Use of intraprocedure anticoagulants and multivessel, left main
artery disease were independent predictors for EMB. TT use, occurrence of EBM and baseline anemia were independent predictors for LBM. Level of evidence-2b.

Rogacka, et al. (2008) studied 127 consecutive patients post stent placement who had been discharged on TT. DES were placed in 71 patients, BMS in 56. The average age was 69.9 years and 86.6% were men. The mean amount of time on TT was 5.6 months. During this time, 4.7% (six patients) developed major bleeding complications, three of these lethal. Sixty-seven percent of bleeds occurred in the first month. There were was no significant differences between DES and BMS in respect to major and minor bleeding rates the first month of study. Level of evidence-2c3a.

Rossini, et al. (2008) prospectively studied 102 consecutive patients for 18 months undergoing coronary stenting on TT. The INR was kept between 2.0-2.5. The control group received DT only (n=102). The average amount of time on TT was 157 +/- 134 days. At 18 months, a non -significant increase in bleeding was observed in the two groups (10.8% vs. 4.9%, p=0.1). The risk of bleeding was significantly lower in the group of patients on warfarin whose INR was within the target range (4.9% vs. 33%, p=0.00019). Level of evidence- 2b.

Olson, Delate, Johnson, Wilson and Witt (2009) compared major hemorrhagic rates among patients receiving TT (n=175) vs. those receiving DT (n=339) after PTCA with stent placement. Patients were matched by age, sex and stent types and followed for up to 12 months. The TT group had 25 (14.3%) major hemorrhages and the DT group ten (3.0%) (OR 2.0; 95% CI,1.1-3.8). Level of evidence-2b.

**Conclusion**
The review of the literature reveals that there is no clear answer to the research question. The only randomized study did find a significant difference in bleeding rates (4.1% for TT vs. 1.2% for DT). In the other studies, results ranged from no significant bleeding to rate as high as 33%. With the exception of the randomized trial, the level of evidence is no greater than 2-b. Other limitations include differing criteria to define severity of bleeding, which accounts in part for the variation in the rates of bleeding. Many of the studies had small sample sizes. This literature review did not address the differences in bleeding rates with different indications for warfarin, nor the influence of other risk factors. It can be concluded, however, that based on the weight of evidence, patients who take triple therapy have increased risk for bleeding events. More specific answers are to be found in future randomized studies that utilize standardized definitions of bleeding events. WAR-STENT (Rubboli, Bolognese, Di Pasquale, et al. 2009) is currently in progress and may address some of the issues. Until then the following recommendation can be considered when managing these patients: Restrictive use of DES to reduce exposure time to triple therapy, and research to determine if clopidogrel and warfarin would be as an effective alternative with less bleeding risk. Khurram et al. (2009) thought that patients with a high risk of bleeding should receive BMS to reduce time of exposure to TT. Holmes, et al.(2009) recommended careful follow-up, low dose aspirin, (<100mg/day) and a lower target INR. Most patients would require an INR of 2.0 to 2.5. The exception would be those with mechanical valve replacement, who would require an INR of 2.5-3.0. Holmes also recommended adding a proton pump inhibitor. The APN should provide vigorous patient education, assess for signs and symptoms of anemia, consider following stool guiac, hematocrit, hemoglobin and RBC indices, and maintain a high level of suspicion.
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