Bridging with Tirofiban during Oral Antiplatelet Interruption: A Single-Center Case Series Analysis Including Patients on Hemodialysis

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INTRODUCTION Patients requiring an interruption in dual-antiplatelet therapy (DAPT) within 6 months of cardiac stenting are at risk for thrombotic events. Bridging with short-acting intravenous antiplatelet agents has been proposed to minimize the risk of thrombotic and hemorrhagic complications.

METHODS This retrospective analysis of a tirofiban bridging strategy did not use an initial bolus loading dose. Tirofiban infusions were initiated 24–48 hours after the last oral antiplatelet dose at a rate of 0.1 µg/kg/min (or 0.05 µg/kg/min if renal dysfunction) and continued until 4–8 hours before surgery or until DAPT could be resumed. Coprimary end points were occurrence of major adverse cardiac events (MACE) and bleeding.

RESULTS Twenty patients requiring DAPT interruption within 6 months of cardiac stenting for either a surgical procedure or who were unable to take any medications by mouth were included. The median time from stent implantation to DAPT interruption was 33 days (range 3–146 days). Two patients experienced a MACE during their hospital stay. No major bleeding events occurred; minor bleeding occurred in four patients during tirofiban therapy. Five patients in this analysis had end-stage renal disease requiring hemodialysis. Of these patients, no MACE or major bleeding events occurred.

CONCLUSIONS This analysis observed that a tirofiban bridging strategy without an initial bolus loading dose has comparable efficacy and safety as previously published reports. A tirofiban infusion without bolus dosing may be a safe option for antiplatelet bridging in patients with a recent cardiac stent implant to prevent stent thrombosis.

KEY WORDS tirofiban, perioperative, bridging, hemodialysis, antiplatelet agents, cardiac stents.


Dual-antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 platelet receptor inhibitor (e.g., clopidogrel, prasugrel, or ticagrelor) is recommended for up to 12 months and in some cases longer after cardiac stent implantation to prevent stent thrombosis and recurrent myocardial infarction.1–5 Interruption of DAPT for surgical procedures within the initial high-risk 3- to 6-month time frame after cardiac stent placement is associated with increased rates of ischemic complications. In contrast, continuing oral DAPT, where effects can be sustained for 3 or more days after ingestion, increases the risk of surgical-related hemorrhage. As such, sustaining antiplatelet effects can be a challenge in patients with recent cardiac stent placement who require interruption of oral DAPT.6

One proposed strategy to sustain antiplatelet effects when holding the longer acting oral P2Y12 inhibitors is to use parenteral short-acting antiplatelet agents as a bridge therapy. Small
studies have shown that use of the intravenous glycoprotein IIb/IIIa inhibitors, tirofiban or eptifibatide, is an effective strategy to prevent perioperative thrombotic events with minimal increased risk of bleeding.7–11

At the University of California Davis Medical Center (UCDMC), tirofiban is the intravenous antiplatelet agent used for antiplatelet bridging because it is available in premixed bags and at the time offered, it was the least expensive approach. The dosing strategy at UCDMC differs from previously published reports8 in that an initial bolus loading dose of tirofiban is not administered because onset of activity is rapid, and the process is easier to order and implement at the bedside. The purpose of this analysis was to evaluate the efficacy and safety of a tirofiban bridging strategy.

Methods

Study Population and Design

This single-center retrospective observational analysis was conducted at UCDMC. Consecutive adult patients (older than 18 years) who required a hold of their DAPT within 6 months of cardiac stenting for either an urgent or planned surgical procedure, for gastrointestinal work-up, or who were otherwise unable to take any medications by mouth and received tirofiban bridging therapy were included. Data were manually collected from the electronic medical record. This analysis was approved by the institution's investigational review board.

Bridging Protocol

At UCDMC, a tirofiban bridging guideline is used for patients who require holding of their P2Y12 inhibitor therapy during the first 6 months after cardiac stenting (Appendix 1). Decisions to implement a parenteral antiplatelet bridge were at the discretion of the attending physician, typically a cardiologist, that continued antiplatelet therapy with a rapid offset was necessary. The oral P2Y12 inhibitor was discontinued 5 days before scheduled interventions or surgery, and tirofiban was started 24–48 hours after the last dose of a P2Y12 inhibitor. Aspirin continuation was at the discretion of the physician.

The tirofiban bridge was initiated at an infusion rate of 0.1 μg/kg/min without an initial bolus. A 50% renal dose adjustment (0.05 μg/kg/min) was used in patients with creatinine clearances (Clcr) lower than 30 ml/min. The tirofiban bridge was discontinued at either 4 or 8 hours before surgery based on a Clcr of 30 ml/min or higher or lower than 30 ml/min, respectively. In cases of very high-risk bleeding procedures and lower perceived stent thrombosis risk, a longer hold for 12 hours was an option.

Postoperatively, practitioners had the option to restart the P2Y12 inhibitor alone or resume the tirofiban therapy after adequate hemostasis was achieved and continue for up to 6 hours after administration of the P2Y12 inhibitor.

Study Outcomes

Coprimary end points of this analysis were the incidence of major adverse cardiac or bleeding events associated with tirofiban therapy. Major adverse cardiac events (MACE) were screened until hospital discharge and included death, repeat myocardial infarction, stent thrombosis, or target lesion/vessel revascularization.7 Bleeding events were collected until tirofiban discontinuation and classified by their location and severity as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria and whether a blood transfusion was required. The TIMI criteria classifies bleeding into minimal, minor, and major categories based on hemoglobin/hematocrit decreases, need for intervention, or intracranial hemorrhage.12

Results

Study Population Characteristics

A total of 20 patients received tirofiban bridging therapy between October 2011 and May 2016. The study population included 11 men and 9 women with a median age of 72 years (range 44–82 years). Table 1 lists the characteristics of their recent cardiac stenting history. All patients had at least one drug-eluting stent, and one patient had both a drug-eluting and a bare metal stent. The median time from stent implantation to P2Y12 inhibitor interruption was 33 days (range 3–146 days).

Planned surgical procedures accounted for 14 (70%) of the cases of tirofiban bridging. Cardiac surgeries, including four cardiac valve replacements and five coronary artery bypass graft (CABG) operations, accounted for most of the surgical procedures. Other procedures included three percutaneous endoscopic gastrostomy
placements, one pancreatic mass biopsy, one axillobifemoral bypass, and one video-assisted thoracoscopic lobe resection. The remaining indications for tirofiban bridging included post-catheterization vomiting precluding oral administration (one patient), presentation with gastrointestinal bleeding (two patients), and new ileus or obstruction prohibiting oral medication administration (three patients).

Bridging

The median time between the last dose of a P2Y12 inhibitor and initiation of tirofiban infusion was 36 hours, with a range of 5 hours to 9 days. Most of the patients (65% [13]) also had aspirin therapy held. Tirofiban dosing was reduced for Clcr lower than 30 ml/min in seven patients. Of those who required dose reduction for a Clcr less than 30 ml/min, five patients had end-stage renal disease dependent on hemodialysis.

The median duration of tirofiban bridge before surgical intervention was 70 hours, with a range of 30 hours to 7 days. Two patients resumed tirofiban for 9 and 21 hours after surgery before P2Y12 inhibitors were restarted. The remaining patients without planned surgical intervention received tirofiban for a median of 48 hours, with a range of 17 hours to 12 days.

Outcome Events

Two patients experienced a MACE during their hospital stay. One event occurred in a patient who experienced a cardiac arrest and died shortly after transcatheter aortic valve replacement. The other event occurred in a patient who was admitted for in-stent thrombosis and planned CABG. During the time period tirofiban was stopped before surgery, this patient had recurrent chest pain and electrocardiogram changes suggestive of rethrombosis.

No major TIMI bleeding events occurred during tirofiban therapy. Minimal or minor TIMI bleeding events occurred in four patients during the tirofiban therapy as displayed in Table 2. Two of these patients experienced recurrent gastrointestinal bleeding as evidenced by melena. One case occurred in a patient with known gastritis, whereas no source of bleed was identified in the other case. An additional two cases of new bloody secretions and hemoptysis were reported, only one of which required a blood transfusion and discontinuation of tirofiban. Three of the bleeding events that developed during tirofiban therapy occurred in patients who were receiving the lower dose of tirofiban and also continued on aspirin therapy.

Discussion

Although DAPT is recommended for up to 12 months after cardiac stent implantation, emergent surgical procedures, significant bleeding, or prolonged nothing by mouth status may result in oral DAPT interruption during this initial high-risk time period. Clinicians must balance the risks of in-stent thrombosis and recurrent myocardial infarction associated with oral DAPT withdrawal against the risks of surgical-related bleeding with prolonged antiplatelet effects in this patient population. Available evidence-based guidelines recognize the utility of antiplatelet bridging in this setting but generally conclude that evidence is insufficient to provide specific guidance or details supporting the efficacy of this strategy. Therefore, clinicians currently have to weigh patient-specific clinical factors to assess thrombosis versus bleeding risk when deciding whether to use an antiplatelet bridge. Some of these factors include the time lapse since the most recent stenting, stent type and location, and extent of stenting performed.

Once the decision to use a bridging strategy during oral DAPT interruption is made, treatment options include the intravenous glycoprotein IIb/IIIa inhibitors, tirofiban or eptifibatide, or cangrelor, the P2Y12 platelet receptor inhibitor. A 2014 systematic review of the literature included eight case series and one randomized

### Table 1. Cardiac Stenting History

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for stent implantation, n (%)</td>
<td></td>
</tr>
<tr>
<td>STEMI or cardiac arrest</td>
<td>3 (15)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>9 (45)</td>
</tr>
<tr>
<td>UA</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Stable CAD</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Type of stent, n (%)</td>
<td></td>
</tr>
<tr>
<td>Drug eluting</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Bare metal</td>
<td>1 (5)</td>
</tr>
<tr>
<td>No. of stents per patient, median (range)</td>
<td>2 (1–8)</td>
</tr>
<tr>
<td>P2Y12 inhibitor, n (%)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Days between stent implantation and P2Y12 inhibitor interruption, median (range)</td>
<td>33 (3–146)</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.
control trial of antiplatelet bridge therapy in cardiovascular and noncardiovascular surgeries. The reported success rates, defined as freedom from cardiac adverse events, were 100% with tirofiban, 93.8% with eptifibatide, and 96.2% with cangrelor when used as a bridging strategy.\(^{13}\) Despite the difference in initial dosing strategy, our analysis had similar outcomes compared with these published experiences and found tirofiban was an effective agent in preventing MACE during DAPT interruption.

The tirofiban bolus was not considered necessary for several reasons: patients were not experiencing an acute thrombosis, were not undergoing a procedure at the time of tirofiban initiation, maintained residual effects from the withheld oral antiplatelet therapy, and had no perceived need for achieving higher antiplatelet effects emergently within the next 1–2 hours. A bolus might have been considered if emergent antiplatelet effects were necessary on clinical assessment and no antiplatelet effects were present. Given tirofiban's rapid onset of activity, beginning the infusion without an initial bolus dose also facilitated easier initiation of therapy at the bedside by nursing staff who typically were less familiar with the agent outside of cardiac catheterization and probably had limited experience administering tirofiban. Thus starting the infusion without the bolus would have the additional benefits of avoiding delays with implementing the therapy and reducing the potential for error.

The single death in this retrospective review could not be confirmed as a tirofiban failure because the underlying cause of cardiac arrest postoperatively was not further investigated or determined. As for the case of suspected rethrombosis before CABG, this patient had originally presented with in-stent thrombosis despite DAPT as an outpatient and was likely at high risk for events during antiplatelet withdrawal.

Our experience with bleeding events during tirofiban therapy is also comparable with previously published reports that observed bleeding in 11–41% of the studied populations bridged with tirofiban, eptifibatide, or cangrelor in the perioperative setting.\(^{13}\) In the present analysis, no patient experienced a major bleed as defined by TIMI criteria. Of the four bleeding events observed during therapy (20% of the population), only two were new instances of bleeding, whereas the other two patients had previously experienced gastrointestinal bleeding during the same hospitalization before tirofiban therapy.

Notably, five patients in this analysis had end-stage renal disease requiring hemodialysis. To date, no published literature has evaluated the use of tirofiban as a bridge in the hemodialysis-dependent population. Tirofiban can be removed during hemodialysis. In an assessment of tirofiban administration in eight patients requiring intermittent hemodialysis lasting ~4 hours, tirofiban clearance during the second dialysis period was 73.14 ± 19 ml/min compared with 513 ± 183 ml/min in individuals with normal renal function. Although tirofiban was removed by dialysis, patients remained on the infusion without a dosage adjustment during dialysis because it was considered a transient short-term period, and the level of tirofiban was expected to increase shortly after hemodialysis completion.\(^{14}\) Effectiveness or requirements for adjusting the tirofiban dose in the setting of continuous renal replacement therapy, however, have not been established. In the present analysis, no MACE were observed in the patients dependent on hemodialysis. However, the bleeding event of new-onset hemoptysis and bloody respiratory secretions requiring blood transfusion and discontinuation of tirofiban occurred in a patient dependent on hemodialysis. Three of the four bleeding events occurred in patients with reduced renal function despite the tirofiban dose adjustment.

Interpretation and application of the results of this analysis are limited by the retrospective single-center assessment that relied on accurate documentation within the electronic medical record. To minimize this limitation, objective definitions of efficacy and safety end points were

<table>
<thead>
<tr>
<th>Bleeding event</th>
<th>Bleeding location</th>
<th>Tirofiban dose, (\mu g/kg/min)</th>
<th>TIMI severity</th>
<th>Aspirin held</th>
<th>Blood transfusion</th>
<th>Tirofiban stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gastrointestinal</td>
<td>0.05</td>
<td>Minimal</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Respiratory</td>
<td>0.05</td>
<td>Minimal</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Respiratory</td>
<td>0.05</td>
<td>Minimal</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Gastrointestinal</td>
<td>0.1</td>
<td>Minor</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

TIMI = Thrombolysis in Myocardial Infarction.
used. The results of this analysis are also specifically limited to tirofiban and do not offer a comparison with the other available intravenous glycoprotein IIb/IIIa inhibitor, epifibatide, or the intravenous P2Y12 platelet receptor inhibitor cangrelor, recently approved by the U.S. Food and Drug Administration. Cangrelor presents an attractive bridging option because it shares the same mechanism of action as the oral agent being interrupted. However, data evaluating cangrelor bridging are limited to a single dose-finding study that does not provide enough data to support enhanced effectiveness over other available agents (tirofiban or epifibatide) to counteract the increased cost of therapy.15

Conclusion
In this retrospective analysis, a tirofiban dosing strategy without an initial bolus loading dose showed comparable efficacy and safety outcomes as previously published reports of tirofiban bridging in patients with recently implanted cardiac stents who require an interruption in DAPT. A tirofiban infusion without bolus dosing may be considered a safe antiplatelet bridging approach in patients with a recently implanted coronary drug-eluting stent: a phase II study of “bridging” antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. Br J Anaesth 2010;104(3):285–91.

References

Appendix 1. UCDMC Tirofiban Bridging Guideline
Tirofiban:
• Discontinue the oral P2Y12 inhibitor (e.g. clopidogrel, prasugrel, or ticagrelor) 5–7 days before surgery. At the discretion of the physician, aspirin therapy can be continued before, during, and after the procedure.*
• Start tirofiban 24–48 hrs after the last oral P2Y12 inhibitor dose
• Tirofiban dosing:
  o No bolus needed.
  o $Cl_{cr} \geq 30 \text{ ml/min}$: 0.1 µg/kg/min, stop infusion 4 hrs before surgery.
  o $Cl_{cr} < 30 \text{ ml/min}$: 0.05 µg/kg/min, stop infusion 8 hrs before surgery.
• Restart infusion 2 hrs after the end of surgery if deemed safe and continue for up to 6 hrs after the resumption of oral P2Y12 inhibitor therapy (option to reload on day 1) and aspirin.
*Aspirin typically held in situations such as neurosurgical and spinal procedures.
Adapted from reference 8.
UCDMC = University of California Davis Medical Center.