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Safety Outcomes in High Risk Patients Receiving Triple Therapy after Percutaneous Coronary Intervention

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BACKGROUND

- Patients who undergo percutaneous coronary intervention (PCI) with drug eluting stents (DES) require dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for at least 12 months to prevent stent thrombosis.
- These patients may also have an indication for warfarin therapy, such as atrial fibrillation (AF) or a mechanical heart valve and thus could require triple therapy (TT) with aspirin, clopidogrel, and warfarin due to their high risk of thrombosis.
- The benefits of TT must be carefully balanced against the risks of bleeding.
- No randomized controlled trials have evaluated the safety and efficacy of the combination of TT.
- There is no consensus on how to best manage these patients, other than a careful individualized approach.
- This ongoing observational study evaluates safety outcomes in patients receiving TT with warfarin, clopidogrel, and aspirin concomitantly.

PURPOSE

- To evaluate the safety outcomes of TT in patients post PCI at the VA Medical Center (VAMC) in Memphis, TN.
- To determine differences between patients who experienced a bleeding episode and those who did not.

METHODS

- This study was approved by the VAMC IRB.
- A retrospective analysis of computerized medical records from veterans undergoing PCI on concomitant anticoagulation and antiplatelet therapies was performed.
- Bleeding was classified according to the TIMI and GUSTO criteria (Table 1).
- Comparisons were made between those patients who experienced a bleed vs. those who did not.

RESULTS

Table 1: Bleeding Classifications

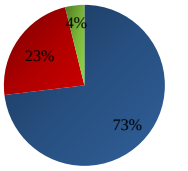
GUSTO	TIMI
Severe: Intracranial bleeding or bleeding that causes hemodynamic compromise requiring treatment	Major: Intracranial bleeding or ≥5 g/dL decrease in Hgb or a ≥15% absolute decrease in Hct
Moderate: Bleeding requiring blood transfusion but does not result in hemodynamic compromise	Minor: Observed blood loss: ≥3 g/dl decrease Hgb or ≥ 10% decrease in the Hct No observed blood loss: ≥ 4 g/dl decrease in the Hgb or ≥ 12% decrease in the Hct
Minor: Bleeding that does not meet the criteria for severe or moderate bleeding	Minimal: Any clinically overt sign of bleeding (including imaging) that is associated with a ≤3 g/dl decrease in Hgb or < 9% decrease in Hct

RESULTS

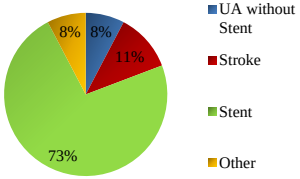
Table 2: Demographics N=26

Age		69.6 ±8.2
Race	African American	9 (34.6%)
	Caucasian	16 (61.5%)
	Unknown	1 (3.8%)
Concomitant Diseases	Diabetes	13 (50%)
	Heart Failure	9 (35%)
	Hypertension	26 (100%)
	Stroke/TIA	9 (35%)
	AF	19 (73%)
	CHADS ≥ 2 (in AF pts)	17 (89.5 %)

Indications for Warfarin



Indications for Clopidogrel



- The majority of patients had indications for warfarin or clopidogrel due to AF or stent placement, respectively.
- DES was placed in 100% of patients receiving stents despite indications for concomitant warfarin.

Table 3: Triple Therapy Observations N=26

Number of Patients with a Bleeding Episode	14 (53%)
Number of bleeds within 90 days of TT start	16 (62%)
Major Bleeds within 90 days of TT start	2 (8%)
Average INR during TT	2.5 ± 0.8
TT Length (months)	9.8 ± 8.2
Baseline Hgb	12.3 ± 1.7
Follow up Hgb*	11.4 ± 2.3
Baseline Hct	36.7 ± 4.8
Follow up Hct*	3.4 ± 6.4

*Follow up Hemoglobin and Hematocrit was the nadir during TT or the result at time of the bleeding event.

- Sixty-two percent of bleeds occurred within 90 days of initiating TT. Forty-six percent were GI bleeds, of which 2 were in patients without GI prophylaxis.
- Average INR was 2.5 ± 0.8. In those who bled, INR range was 1.5 – 3.9 at the time of bleeding.
- Seventy-two percent of patients receiving stents bled.

Table 4: Bleeding Descriptions N=26

TIMI Bleeds	Major 4	Minor 6	Minimal 16	26
GUSTO Bleeds	Severe 1	Moderate 1	Mild 24	26

- In those that bled:
  - Fourteen patients (53.8%) met one or both bleeding criteria, and combined for a total of 26 bleeds.
  - Ten (40%) met TIMI major or minor and 2 (8%) met GUSTO severe or moderate criteria.
  - Fifty percent of bleeds occurred when drugs were given that can interact with warfarin and cause the INR to increase including: levothyroxine, moxifloxacin, amiodarone, phenytoin, enoxaparin, and trimethoprim/sulfamethoxazole.
  - Nineteen percent of bleeds resulted in hospital visits.

Table 5: Bleeders Vs. Non-Bleeders N=26

	Bleeders N=14	Non- Bleeders N=12	P-Value
Age	70.36 ± 8.9	68.75 ± 7.66	NS
ASA Dose*	186 mg ± 125	122 ± 95	NS
Baseline Hgb	11.7 ± 1.7	13.2 ± 1.5	0.022
Baseline Hct	34.9 ± 4.6	39± 4.3	0.029
Length of TT (months)	11.8 ± 10.3	8.2 ± 5.1	NS
CHADS-2-Score Median	3.5	3	NS
HAS-BLED Score Median	4	3	NS
Warfarin Dose*	32.9 ± 8	40.7 ± 20.1	NS
Average INR during TT	2.4 ± 0.7	2.6 ± 0.8	0.005
PPI/H2 (Y)	12	11	NS
Elective Cath (Y)	7	10	NS

*Dose at discharge. NS is p > 0.05.

- Non-bleeders average INR was higher than those who bled, 2.6 ± 0.8 vs. 2.4 ± 0.7, (P = 0.005).
- In patients who bled, the average dose of ASA was higher 186 mg ± 125 vs. 122 mg ± 95, and the average length of TT was longer 11.23 months vs. 8.2 months than the non-bleeders (P = NS).
- $CHADS_2$ and HAS-BLED scores were higher in bleeders than in non-bleeders.
- Baseline Hgb and Hct were lower in bleeders (11.7 ± 1.7 and 34.9 ± 4.6) vs. (13.2 ± 1.5 and 39 ±4.3), P = 0.022 and 0.029 respectively. However, the bleeders received a lower total weekly dose of warfarin (32.9 ± 8) vs. (40.7 ± 20.1), P = NS.

CONCLUSION

- In this cohort, TT was associated with a 53% bleeding risk and a 19% re-hospitalization rate.
- A significantly higher bleeding risk was found in those patients with a lower baseline Hgb and Hct, and lower INR.
- Despite the need for warfarin therapy in patients receiving stents, DES were placed in 100% of cases. The choice to use a bare metal stent should be explored further as it has the potential to decrease time required on TT and thus bleeding risk.
- Balancing the risks and benefits of TT is extremely important, given that in this observation, 62% of patients bled within the first 90 days of TT initiation.

Jacob Marler, Dr. Shannon Finks, and Dr. Kelly Rogers have no conflicts of interest to disclose.