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Evaluation of bleeding and thrombotic risk in patients receiving triple antithrombotic therapy

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OBJECTIVE

Evaluate bleeding and thrombotic risk of patients receiving triple antithrombotic therapy (TAT) versus dual antithrombotic therapy (DAT) and characterize prescribing patterns.

BACKGROUND

- TAT is used in a subset of patients with indications for both dual antiplatelet therapy (DAPT) and an oral anticoagulant (OAC).
- Indication for TAT is often due to development of acute coronary syndrome with an underlying condition requiring anticoagulation, such as atrial fibrillation, prosthetic heart valve, or venous thromboembolism (VTE).[1]
- Studies have shown an increased risk of bleeding in patients receiving TAT (OAC + DAPT) compared to DAT (OAC + single antiplatelet therapy) with no significant differences in thrombotic events.[2-4]
- Management of patients on TAT is not well addressed in current guidelines, especially regarding duration of therapy.[5-8]

METHODS

- Retrospective chart review of subjects who received percutaneous coronary intervention (PCI) with either TAT or DAT prescribed at hospital discharge. Subjects were then followed for one year post-discharge or end of study period, whichever occurred first.
- Data was included from February 2015 through September 2018.
- Antiplatelet agents: aspirin, clopidogrel, prasugrel, and ticagrelor.
- OACs: warfarin, dabigatran, apixaban, and rivaroxaban.
  - Edoxaban is non-formulary at the study site and was therefore not used in study subjects.
- **Primary outcome**: Incidence of major bleeding within one year as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria
- **Secondary outcomes:**
  - Incidence of any thrombotic event identified using International Classification of Diseases tenth revision (ICD-10) codes
  - Incidence of any bleeding event identified using ICD-10 codes
  - Time to de-escalation of TAT
    - Defined as discontinuation of at least one of the three antithrombotic agents comprising the TAT regimen
- **Subgroup analyses:**
  - Incidence of major bleeding among patients using warfarin versus a direct OAC (dabigatran, apixaban, and rivaroxaban)
  - Incidence of major bleeding categorized by age of the subject
  - Incidence of any gastrointestinal (GI) bleeding among subjects using a proton pump inhibitor (PPI) versus those without a PPI
  - Indication for OAC among subjects with bleeding
  - Bleeding events of various medication regimens

RESULTS

Table 1: Baseline Characteristics

Baseline Characteristics	TAT n = 152	DAT n = 130
Mean age (years ± SD)	63 ± 15	68 ± 13
Number of male subjects	106 (70%)	93 (72%)
Mean CHA_2DS_2-VASc (score ± SD)	1.8 ± 1.6	2.4 ± 1.7
Mean HAS-BLED (score ± SD)	2.3 ± 1	2.7 ± 1

Table 2: Indications for OAC

Indication for OAC	TAT n = 152	DAT n = 130
Atrial Fibrillation/Flutter	67 (44%)	82 (63%)
VTE	30 (20%)	13 (10%)
Mural Thrombus	19 (13%)	9 (7%)
Thromboprophylaxis	19 (13%)	10 (8%)
Valve Prosthesis	1 (1%)	1 (1%)
Multiple Indications	6 (4%)	9 (7%)
Other	9 (6%)	6 (5%)

Figure 1: Drug Regimen by Indication for OAC

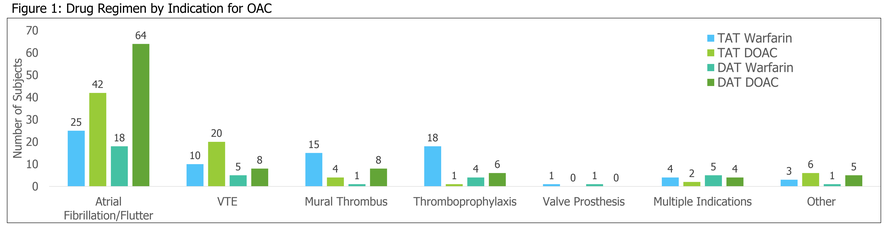


Figure 2: Number of Bleeding and Thrombotic Events

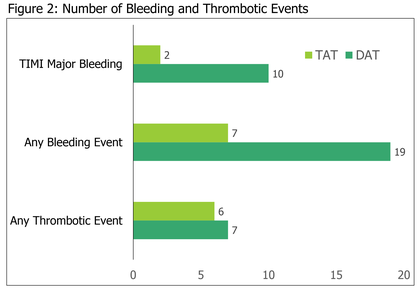


Table 3: Time to De-escalation

Days Post-Discharge	Number of Subjects n = 148
0-30	49 (33%)
31-60	30 (20%)
61-90	15 (10%)
91-120	15 (10%)
121-150	6 (4%)
151-180	6 (4%)
> 180	27 (18%)

Table 4: TIMI Major Bleeding by Age

Age	Number of Subjects	TIMI Major Bleeding
18-30	4	1 (25%)
31-40	13	0 (0%)
41-50	25	0 (0%)
51-60	49	1 (2%)
61-70	72	6 (8%)
71-80	77	2 (3%)
81-90	40	2 (5%)
> 90	2	0

Table 5: Incidence of TIMI Major Bleeding with Warfarin vs DOAC

	Warfarin n = 112	DOAC n = 170
TIMI Major Bleeding	5 (4%)	12 (4%)
HAS-BLED (mean score ± SD)	2.6 ± 1	2.4 ± 1

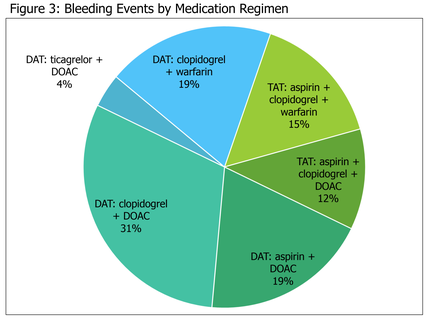
Table 6: Incidence of GI Bleeding

	With PPI n = 119	Without PPI n = 163
GI Bleed	10 (8%)	4 (2%)
HAS-BLED (mean score ± SD)	2.6 ± 1	2.4 ± 1

Table 7: Indication for OAC among subjects with bleeding

Indication for OAC	Subjects with Bleeding n=26	All Subjects n=282
Atrial Fibrillation/Flutter	14 (54%)	149 (53%)
VTE	4 (15%)	43 (15%)
Thromboprophylaxis	4 (15%)	29 (10%)
Multiple Indications	4 (15%)	15 (5%)

Figure 3: Bleeding Events by Medication Regimen



DISCUSSION & CONCLUSIONS

- There is a lack of consistency among providers regarding the management of patients receiving TAT.
- Subjects receiving DAT had a higher incidence of both major and overall bleeding events than patients receiving TAT which is contradictory to previous findings.
  - Patients thought to be at a high risk of bleeding may empirically be prescribed DAT, which is reflected by the higher HAS-BLED score associated with the DAT group.
  - These patients also had an increased risk of clotting as indicated by the higher CHA2DS2-VASc score in this group, but had a similar incidence of thrombotic events between the two groups.
- 82% of subjects on TAT at discharge were de-escalated to at least DAT or DAPT within 6 months, which is in alignment with available guidelines.
  - The timing of de-escalation was often guided by the scheduling of the subject's outpatient cardiology appointments.
- Incidence of GI bleeding events were higher in patients receiving a PPI.
  - These subjects also had a slightly higher risk of bleeding as evidenced by the increased HAS-BLED score in this group.
- There was a higher percentage of bleeding events in subjects using an OAC for thromboprophylaxis or having multiple indications which could be a target area for intervention (16% of the study subjects).
- Of patients with bleeding, 34% used warfarin in alignment with guideline recommendations of use of warfarin + clopidogrel ± aspirin.
  - The majority of bleeding events (66%) were among subjects using a DOAC, which is not a recommended therapy.
- **Limitations**
  - Retrospective chart review with limited documentation of outpatient medication use and compliance.
    - Start/stop dates of agents were updated at appointments and may not reflect exact dates of therapy modification.
  - Inconsistent use of ICD-10 coding for bleeding/thrombotic events.
- **Future Research & Impact on Practice**
  - Creation of a guidance document to encourage consistency in prescribing TAT regimens and appropriate de-escalation.
  - Continued study of this specific patient population to adequately characterize the risks and benefits of various treatment selections.
    - Further analysis of the 18% on TAT de-escalated at > 6 months.

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