Combination Aspirin & DOAC Therapy Increases Bleeding Risk

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Moderator:
Arthur Allen, PharmD, CACP | Andrea Van Beek, RN, DNP, AGPCNP-BC

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Disclosures & Notification of Support

The speakers have the following relevant financial relationships with commercial interests:

**Jordan Schaefer, MD**
None

**Geoffrey Barnes, MD, MSc**
Pfizer/Bristol-Myers Squibb | Janssen | AMAG

**Arthur Allen, PharmD, CACP**
Alexion Pharmaceuticals | BMS/Pfizer Alliance | Boehringer-Ingelheim Pharmaceuticals | Janssen Pharmaceuticals | Roche Diagnostics

**Andrea Van Beek, RN, DNP, AGPCNP-BC**
None
Background- Aspirin Indications

- **Primary prevention of cardiovascular disease**
  - 25-45% of adults over 40

- **Stable ischemic heart disease**

- **Peripheral arterial disease, cerebrovascular disease**

- **Secondary prevention**
  - Non-cardioembolic ischemic stroke
  - Transient ischemic attack
  - Venous thromboembolic disease

- **Thromboprophylaxis**
  - Myeloproliferative disorders
  - Antiphospholipid syndrome

- **Pain**

- **Colorectal cancer**

- **Preeclampsia**

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\(a\) Off label use

Aspirin and Anticoagulation

- Mechanical heart valves
- Acute coronary syndromes with indication for anticoagulation
- Some cardiac devices
  - Left ventricular assist devices
- Others
Risks Versus Benefits

- Combination therapy increases bleeding\(^4-6\)
  - Data mostly for warfarin+aspirin, atrial fibrillation>venous thromboembolic disease

- Combination therapy is common\(^4,7\)

- Low dose direct oral anticoagulant therapy with aspirin
  - Better cardiovascular outcomes but more major bleeding events\(^8\)

Direct Oral Anticoagulants

- **DOACs**
  - Apixaban
  - Dabigatran
  - Edoxaban
  - Rivaroxaban

- **Better safety profile compared to warfarin**
  - Lower rates of fatal bleeding, cardiovascular mortality, and all cause mortality
  - Higher rates of gastrointestinal bleeding

Study Questions

▪ How often are patients anticoagulated with a DOAC for Afib or VTE, without a recent myocardial infarction or heart valve replacement, treated with concomitant aspirin?

▪ How does this impact bleeding outcomes?
  ▪ Major bleeding (fatal, life-threatening, central nervous system)
  ▪ Nonmajor bleeding
  ▪ ER visits for bleeding
  ▪ Hospitalizations for bleeding
  ▪ Thrombotic outcomes
Methods: Michigan Anticoagulation Quality Improvement Initiative

- 4 of 6 anticoagulation clinics participated
- Patient enrollment:
  - Jan 2015 - December 2019
- Analysis:
  - 2020
- Trained data abstractors
- Predefined forms
- Random chart audits
DOAC for Afib or VTE, w/ 3+ months of follow-up

Valve replacement or recent MI

NO valve replacement or recent MI
n=3,280

Propensity match

Enrollment

ASA, N=1,047

No ASA, N=1,047

Primary Analysis
Methods: 1:1 Propensity Match

- **Demographics**
  - Age, sex, weight, alcohol/tobacco use

- **Indication**
  - Atrial fibrillation, venous thromboembolism

- **Co-morbidities**

- **Coagulation History**
  - History of recent bleeding (≤ 30 days)
  - Remote bleeding (>30 days)
  - History of stroke/TIA
  - History of venous thromboembolism
  - History of gastrointestinal bleeding
  - Remote myocardial infarction

- **Medications**
  - Estrogen/progesterone
  - Antiplatelet therapy
  - NSAIDs
  - DOAC
    - High or low dose

- **Duration of follow-up**

- **HAS-BLED (modified)**

- **Charlson Comorbidity Index**
Outcomes

- Rate of aspirin use without a clear indication

- Thrombosis
  - Stroke/TIA
  - Pulmonary embolism
  - Deep vein thrombosis
  - Myocardial infarction

- Bleeding
  - Major bleeding
    - Fatal
    - Life threatening
    - Intracranial or intraspinal
  - Non-major
  - Any bleeding

- Emergency room visits
- Hospitalizations
Study Schema
Results- ~1/3 of Patients on Combination Therapy
### Results—Propensity Matched Cohort

<table>
<thead>
<tr>
<th></th>
<th>After Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOAC n=1047</td>
</tr>
<tr>
<td><strong>DOAC (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>61.7</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>8.9</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.1</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>29.3</td>
</tr>
<tr>
<td><strong>DOAC dose</strong></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>19.7</td>
</tr>
<tr>
<td>High dose</td>
<td>80.3</td>
</tr>
<tr>
<td><strong>Age, y (mean ± SD)</strong></td>
<td>71.9 ± 12.0</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>57.6</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² (%)</td>
<td>53.9</td>
</tr>
<tr>
<td><strong>Indication n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>AF/Aflutter</td>
<td>78.5</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>22.5</td>
</tr>
<tr>
<td>Both</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Follow-up Median (IQR)</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Results-Propensity Matched Cohort

<table>
<thead>
<tr>
<th>Co-Morbidities (%)</th>
<th>After Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOAC n=1047</td>
</tr>
<tr>
<td>CAD</td>
<td>28.1</td>
</tr>
<tr>
<td>Cancer</td>
<td>24.6</td>
</tr>
<tr>
<td>CHF</td>
<td>22.0</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>3.5</td>
</tr>
<tr>
<td>CKD</td>
<td>21.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30.4</td>
</tr>
<tr>
<td>History of falls</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>0.6</td>
</tr>
<tr>
<td>HTN</td>
<td>65.8</td>
</tr>
<tr>
<td>PAD</td>
<td>6.9</td>
</tr>
<tr>
<td>Prior PCI/CABG</td>
<td>11.5</td>
</tr>
</tbody>
</table>
Results-Bleeding/Thrombosis

Limitations

▪ Registry data
▪ Not able to fully match on all variables
  ▪ Residual differences included in regression models
▪ Both atrial fibrillation and venous thromboembolic disease
▪ Key subgroups underrepresented
  ▪ Vascular stents
  ▪ Poorly controlled risk factors
  ▪ High thrombotic risk
  ▪ Myeloproliferative neoplasms
  ▪ Thrombophilias
▪ Geographically limited
▪ Underpowered for thrombotic outcomes
▪ Largely (71.2%) patients newly started on DOACs
Conclusions

- DOACs and Aspirin
  - Increase bleeding for patients w/ Afib and/or VTE without a recent heart valve replacement or ACS
  - More research is needed for high-risk subgroups
  - Consider deprescribing aspirin when risk>benefit

Used with permission. 2 minute medicine: https://www.2minutemedicine.com/visualabstract-aspirin-treatment-without-indication-in-patients-on-direct-oral-anticoagulants-may-increase-the-risk-of-bleeding-events/
Questions?
How to Claim Credit

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- Launched July 1st
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  - Abstract can be read on site
  - View by date range
  - Includes ACF authored papers
- Links to our new Rapid Recap Newsletter
- This curated literature overview is game changing!
- Thank you Dr. Bishoy Ragheb and Elaine Whalen for this vision

The Anticoagulation Forum’s Literature Update includes citations identified from PubMed, curated and chosen by our Centers of Excellence team based on their utility for anticoagulation practitioners and then categorized by topic. This list is updated twice a month by Dr. Bishoy Ragheb, Pharm.D. Our database is searchable by date, author, title, and keywords and the most impactful articles are highlighted with a star.

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**Articles**

**When to use anticoagulation in COVID-19**

**Abstract**

Early in the COVID-19 pandemic, infection with SARS-CoV-2 was noted to be associated with a coagulopathy and high rates of VTE observed in ICU patients, leading many to escalate doses of anticoagulants in infected ICU patients, as described by Kolias and colleagues. Many single and multi-institutional analyses found increased VTE rates in ICU patients, based in part on how aggressively patients were assessed for VTE. In the first 210 patients with COVID-19 admitted to our institution, we found a 3-4 fold increase in cumulative incidence of VTE in the ICU patients compared to those on the ward, resulting in a change in institutional practice to increased "intermediate" dose LMWH for thromboprophylaxis. Using propensity score matching, we found no difference in VTE or mortality with "intermediate" doses compared to standard LMWH, although with no concerning increase in major bleeding.

Review of past data on the effectiveness of standard dose VTE practice in ICU patients also factored into our decision making, as VTE rates were higher in this population than those on the ward.

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**Frequency of Thrombocytopenia and Platelet Factor 4-Antiplatelet Antibodies in Patients With Central Venous Stents**

**Abstract**

Frequency of thrombocytopenia and platelet factor 4-antiplatelet antibodies in patients with central venous stents prior to the COVID-19 pandemic.
Where are these resources?

- Literature update created 1st & 3rd Mondays, monthly
- Rapid Recap one month following by several editorial teams
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