BRUISE CONTROL 2
Discussion

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No relevant disclosures for this presentation
Decision Pathway for Peri-procedural Management of Anticoagulation

Major Randomized Controlled Trials on the Management of Perioperative Anticoagulation

- BRUISE CONTROL
  - Continued warfarin vs. heparin bridging for PM, ICD procedures

- BRIDGE
  - Interrupted warfarin, bridging vs. no bridging

- BRUISE CONTROL 2
  - Interrupted vs. continued NOAC for PM, ICD procedures
BRUISE CONTROL

• PM or ICD surgery, est. >5%/yr risk of TE
  – Prosthetic MVR
  – Caged ball or tilting disc AVR
  – Bileaflet AVR and AF/FL, prior CVA/TIA, HTN, DM, CHF, age >75
  – AF/FL ass’d with RHD, CHADS$_2$ >2, or CVA/TIA within 3 mo, plan for DCC
  – Recent (3 mo) venous TE
  – Severe thrombophilia

• Single blind RCT – **continued warfarin vs. heparin bridging**

• Continued warfarin: INR target on DOS ≤3.0, except ≤3.5 for mechanical valves

• Bridging: warfarin held 5d, heparin 3d (IV heparin stopped 4 hrs pre, last LMWH 1d pre), resumed 24 hr post til INR therapeutic

• Primary outcome: clinically significant hematoma

Birnie DH, et al. NEJM 2013;368:2084-2093
### BRUISE CONTROL

**Birnie DH, et al. NEJM 2013;368:2084-2093**

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Heparin Bridge N=338</th>
<th>Continued warfarin N=343</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant hematoma</td>
<td>16.0%</td>
<td>3.5%</td>
<td>0.19 (0.10-0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prolonged hospitalization</td>
<td>4.7%</td>
<td>1.2%</td>
<td>0.24 (0.08-0.72)</td>
<td>0.006</td>
</tr>
<tr>
<td>Interrupted anticoagulation</td>
<td>14.2%</td>
<td>3.2%</td>
<td>0.20 (0.10-0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Required evacuation</td>
<td>2.7%</td>
<td>0.6%</td>
<td>0.21 (0.05-1.00)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1.2%</td>
<td>0.3%</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>0.3%</td>
<td>0</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Lead dislodgement</td>
<td>1.2%</td>
<td>0.3%</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Device system infection</td>
<td>1.8%</td>
<td>0.6%</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Superficial wound infection</td>
<td>0.9%</td>
<td>0.3%</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0.3%</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>0.3%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Non-CNS embolism</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Valve thrombosis</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

**DSMB stopped the trial after the 2nd interim analysis due to a significantly higher rate of clinically significant hematoma in the heparin bridge group**
BRIDGE Trial

- Randomized, DB, placebo-controlled trial during peri-op interruption of warfarin
  - LMWH bridging vs. no bridging
- Warfarin held 5 days pre, resumed within 24 hr post
- Dalteparin 100 IU/kg or placebo – 3d pre to 5-10d post
- Exclusions:
  - Mechanical prosthetic valve
  - Stroke, TIA, systemic embolism within 12 wks
  - Venous thromboembolism (DVT, PE) within 12 wks
  - Major bleeding within 6 wks
  - Severe renal insufficiency (CrCl<30 ml/min)
  - Thrombocytopenia
  - Cardiac surgery, intracranial or intraspinal neurosurgery, high-risk non-surgical procedures (e.g. brain biopsy)

Douketis et al. NEJM 2015;373:823-33
### BRIDGE Trial

<table>
<thead>
<tr>
<th></th>
<th>No Bridge N=918</th>
<th>Bridged N=895</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial TE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.4%</td>
<td>0.3%</td>
<td>0.01 noninferiority</td>
</tr>
<tr>
<td>TIA</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.73 superiority</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.2%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>1.3%</td>
<td>3.2%</td>
<td>0.005 superiority</td>
</tr>
<tr>
<td>Death</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.88 superiority</td>
</tr>
<tr>
<td>MI</td>
<td>0.8%</td>
<td>1.6%</td>
<td>0.10</td>
</tr>
<tr>
<td>DVT</td>
<td>0</td>
<td>0.1%</td>
<td>0.25</td>
</tr>
<tr>
<td>PE</td>
<td>0</td>
<td>0.1%</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Minor bleeding</strong></td>
<td>12.0%</td>
<td>20.9%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Significantly higher major and minor bleeding with bridging compared to no bridging.
- No significantly increased risk of arterial or venous TE without bridging.

Douketis et al. NEJM 2015;373:823-33
BRUISE CONTROL 2

• Inclusion criteria
  – CIED surgery – de novo, PG change, lead replacement or pocket revision
  – Nonrheumatic AF/AFl at mod-high risk of arterial TE
    • $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ or plan for DCC or DFT testing

• Exclusion criteria
  – GFR <30 ml/min
  – Rheumatic valve disease with HD significant valve lesion
  – Mechanical heart valve
  – Active device infection
## BRUISE CONTROL 2

<table>
<thead>
<tr>
<th>Event</th>
<th>Continued DOAC N=334</th>
<th>Interrupted DOAC N=334</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinically significant hematoma</strong></td>
<td>2.1%</td>
<td>2.1%</td>
<td>0.973</td>
</tr>
<tr>
<td>Prolonged hospitalization</td>
<td>0.3%</td>
<td>0.6%</td>
<td>1.000</td>
</tr>
<tr>
<td>Interrupted anticoagulation</td>
<td>2.1%</td>
<td>2.1%</td>
<td>0.973</td>
</tr>
<tr>
<td>Required evacuation</td>
<td>0.6%</td>
<td>0.3%</td>
<td>0.621</td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td>0.6%</td>
<td>0.3%</td>
<td>0.621</td>
</tr>
<tr>
<td><strong>Cardiac tamponade</strong></td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.000</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0.6%</td>
<td>0.0%</td>
<td>0.245</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>0%</td>
<td>0%</td>
<td>--</td>
</tr>
</tbody>
</table>

DSMB and Steering Committee stopped the study at the 2\textsuperscript{nd} interim analysis – no difference in outcomes
Implications of BRUISE CONTROL 1 & 2 and BRIDGE for CIED Procedures

• Continued or interrupted warfarin is preferred over interruption with heparin bridging

• Continued or interrupted NOAC is acceptable
  – No ↑ in CVA/TIA with interrupted NOAC
  – No ↑ in clinically significant hematoma with continued NOAC
  – Possible Exceptions: High thrombotic risk pts excluded from BRUISE CONTROL 2 (HD significant rheumatic valve disease, mechanical heart valve)

• Validated a NOAC holding regimen
  – Rivaroxaban, apixaban – 2 days
  – Dabigatran – based on GFR
  – Resume ≥ 24 hrs after surgery
Implications: Warfarin

• The BRUISE CONTROL and BRIDGE studies support continued or interrupted warfarin for CIED procedures and *interrupted warfarin without bridging for most other procedures*
  – Lack of higher TE risk without bridging in BRIDGE supports this approach for *high bleed risk patients* excluded from BRIDGE
    • Major bleeding within 6 wks
    • Severe renal insufficiency (CrCl<30 ml/min)
    • Thrombocytopenia
    • Cardiac, intracranial or intraspinal neurosurgery

• Bridging may still be advisable for the excluded *higher TE risk pts* (Mechanical prosthetic valve; Stroke, TIA, systemic embolism within 12 wks)
Implications: NOACs

• The absence of differences in CVA/TIA incidence with *holding NOACs for short periods of time* compared to continued NOAC use in BRUISE CONTROL 2 suggests this approach may be used for
  – other surgical procedures
  – High bleed risk pts excluded from BRUISE CONTROL 2 (active device infection/need for lead extraction, GFR<30)

• Exceptions: High thrombotic risk pts excluded from BRUISE CONTROL 2 (Rheumatic valve disease with hemodynamically significant valve lesion; mechanical heart valve)
Limitations and Caveats

• Power was limited for assessment of thromboembolism endpoints, including stroke and TIA, and further limited by the premature stopping of the study
  – Stopping a study early: saves $, but difficulty interpreting 2\textsuperscript{o} endpoints and potential reduction in clinical applicability for these endpoints
  – Futility analysis for CVA/TIA/TE endpoints would be of interest (rates were the same in both BRUISE CONTROL 2 groups)
Thank you

and Congratulations to the

BRUISE CONTROL Investigators