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Consideration for BID Regimen:
Potential Impact on Adherence and Persistence

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Disclosure

I am a full time employee of WestRock Healthcare, a company specialized in adherence-enhancing packaging.
Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among patients With Atrial Fibrillation

Adherence is Key to Therapeutic Success

Medication adherence: ABC Taxonomy

The process by which patients take their medications as prescribed

A Initiate

Patient does not initiate treatment

Binary (yes/no)

B Implement

Patient delays, omits or takes extra doses

Dosing history

C Persist

Patient discontinues treatment

Time to event

EU-sponsored research

Overview of assessment methods of adherence in ambulatory patients

**Initiate**
- Direct methods (PK/PD): Requires sampling after prescription
- Self-report: Desirability bias
- Pill counts: Easily censored by patient
- Prescription & refill databases: Gold standard
- Electronic monitoring: Gold standard in CT; needs activation

**Implement**
- Direct methods (PK/PD): Sampling is too sparse
- Self-report: Recall bias
- Pill counts: Only an aggregate summary
- Prescription & refill databases: Gold standard
- Electronic monitoring: Gold standard

**Persist**
- Direct methods (PK/PD): Subject to white coat adherence
- Self-report: Desirability bias
- Pill counts: Easily censored by patient
- Prescription & refill databases: Gold standard in CT; needs patient engagement
- Electronic monitoring: Gold standard


Case study

**Dosing History** Data over ~2 years (2011-2012)

- Follow-up: 632 days – 14 days (2%) with double dose
- 115 days (18%) with no doses

→ 84% of prescribed doses taken
Variable adherence creates drug-specific issues of efficacy & safety


Therapeutic Range and Biologic Variability for AntiCoagulants
Half-lives of all NOACs are similar, but dosing regimens in AF differ

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (hrs)</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>12–17</td>
<td>Twice daily (BID)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>12</td>
<td>Once daily (OD)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>10–14</td>
<td>Twice daily (BID)</td>
</tr>
<tr>
<td>Rivaroxaban (adults)</td>
<td>5–9</td>
<td>Once daily (OD)</td>
</tr>
<tr>
<td>Rivaroxaban (elderly)</td>
<td>11–13</td>
<td>Twice daily (BID)</td>
</tr>
</tbody>
</table>

Warfarin (20-60 hrs)

*The approved dosing regimen of rivaroxaban is OD for stroke prevention in patients with nonvalvular AF, prevention of VTE after orthopaedic surgery, and long-term secondary prevention of VTE. Rivaroxaban is administered as a BID regimen for the initial treatment of VTE and secondary prevention after acute coronary syndromes (Xarelto EU SPC 2015)

Heidbuchel et al. Europace 2015

Pharmacokinetic considerations suggest that twice-daily regimen increases forgiveness for single missed doses

Once-daily and twice-daily dosing pharmacokinetic simulations for same agent and the same total daily dose.

With: $T_{1/2}=12\text{h}$ & $T_{max}=3\text{h}$
Trade-off between better daily adherence and remaining in the therapeutic range

Once-daily and twice-daily dosing pharmacokinetic simulations for same agent and the same total daily dose. With: $T_{1/2}=12h$ & $T_{max}=3h$

Twice-daily regimen increases forgiveness for similar deviations in adherence

* Once-daily and twice-daily dosing for same agent and the same total daily dose

- 15% missed doses
- 15 once-daily missed doses vs. 30 twice-daily missed doses over 100 days

Vrijens & Heidbuchel, Europace, 2015
Apixaban has more consistent drug levels, day and night, for twice-daily compared to once-daily

Clinical validation of apixaban twice-daily dosing regimen across indications

Ultimately adherence (persistence) is a measure of patient satisfaction

Yao et al., J Am Heart Assoc. 2016, in press.

Assessment of an education and guidance program for apixaban adherence in non-valvular atrial fibrillation: the AEGEAN study

Implementation of the apixaban dosing regimen

Persistence with apixaban

There was no additional value of a proactive educational program on adherence in the first 6 months of treatment

Elements to change patients’ behaviour

Training

Package

Goals

EDUCATION knowledge

MOTIVATION self efficacy

MANAGEMENT OF ADHERENCE

MEASUREMENT awareness


What Can Be Measured Can Be Managed—Deming, WE

Each of these 6 patients took the same percentage (81%) of prescribed doses

Once daily dosing

Twice daily dosing

Conclusion

• In atrial fibrillation, warfarin is associated with sub-optimal implementation and high discontinuation rates, which affect the level of anticoagulation control\textsuperscript{1,2}

• Clinical trials with NOACs have demonstrated non-inferiority or superiority in efficacy vs. VKA, but adherence to the prescribed regimen is of great importance for translating trial results into clinical practice

• Recent simulated PK modelling data for a theoretical drug (t\(_{1/2}\) \approx 12 h and Tmax = 3 h) has provided reassurance that selection of a twice-daily dose for apixaban rather than a once-daily dose was the correct decision\textsuperscript{3}

• Patient-tailored and measurement-guided intervention are required to achieve sufficient adherence to therapeutic drug regimens\textsuperscript{3}