New Oral Anticoagulants in Children: Should They Be Prescribed For Special (Off Label) Situation? No

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Disclosures

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Member of Data Monitoring Boards of clinical trials sponsored by Lilly.
## FDA-approved Antithrombotic Drugs: Pediatric Status

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Generic (Trade)</th>
<th>Pediatric Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumarins</td>
<td>Warfarin (Coumadin)</td>
<td>Routine off-label use</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Unfractionated heparin</td>
<td>Approved</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>Enoxaparin (Lovenox)</td>
<td>Routine off-label use</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin (Innohep)</td>
<td>Routine off-label use</td>
</tr>
<tr>
<td>Indirect Xa inhibitor</td>
<td>Fondaparinux (Arixtra)</td>
<td>Not approved (pediatric use reported)</td>
</tr>
<tr>
<td>Direct Xa inhibitor</td>
<td>Rivaroxiban (Xarelto)</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Apixiban (Eliquis)</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Edoxaban (Lixiana)</td>
<td>Investigational</td>
</tr>
<tr>
<td>Direct thrombin inhibitor</td>
<td>Bivalirudin (Angiomax)</td>
<td>Routine off-label use</td>
</tr>
<tr>
<td></td>
<td>Argatroban (Argatroban)</td>
<td>Not approved (pediatric use reported)</td>
</tr>
<tr>
<td></td>
<td>Dabigatran (Pradaxa)</td>
<td>Investigational</td>
</tr>
</tbody>
</table>

**Routine off-label use:** currently being used routinely in pediatric patients despite lack of pediatric-specific indication.

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**Not approved (pediatric use reported):** no pediatric-specific trials ongoing; at least one pediatric case report published.

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McCrindle et al. *Circulation* 2014;130:1192-1203
# FDA-approved Antithrombotic Drugs: Pediatric Status

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<tr>
<th>Antiplatelet</th>
<th>Generic (Trade)</th>
<th>Pediatric Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclooxygenase (COX)-1 inhibitor</td>
<td>Acetylsalicylate acid (Aspirin)</td>
<td>Routine off-label use</td>
</tr>
<tr>
<td>P2Y$_{12}$ antagonists</td>
<td>Clopidogrel (Plavix)</td>
<td>Routine off-label use</td>
</tr>
<tr>
<td></td>
<td>Prasugrel (Effient)</td>
<td>Not approved (no pediatric use reported)</td>
</tr>
<tr>
<td></td>
<td>Ticagrelor (Brilinta)</td>
<td>Not approved (no pediatric use reported)</td>
</tr>
<tr>
<td></td>
<td>Ticlopidine (Ticlid)</td>
<td>Not approved (no pediatric use reported)</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors</td>
<td>Dipyridamole (Persantine)</td>
<td>Routine off-label use</td>
</tr>
<tr>
<td></td>
<td>Cilostazol (Pletal)</td>
<td>Not approved (no pediatric use reported)</td>
</tr>
<tr>
<td>Glycoprotein IIb-IIIa antagonists</td>
<td>Abciximab (Reopro)</td>
<td>Not approved (pediatric use reported)</td>
</tr>
<tr>
<td></td>
<td>Eptifibatide (Integrilin)</td>
<td>Not approved (no pediatric use reported)</td>
</tr>
<tr>
<td></td>
<td>Tirofiban (Aggrastat)</td>
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<tr>
<th>Thrombolytics</th>
<th>Generic (Trade)</th>
<th>Pediatric Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Streptokinase, Urokinase</td>
<td>Not approved (pediatric use reported)</td>
</tr>
<tr>
<td></td>
<td>Plasminogen activator (Alteplase)</td>
<td>Investigational</td>
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McCrindle et al. *Circulation* 2014;130:1192-1203
New Oral Anticoagulants in Children

- Heparin and warfarin are the traditional anticoagulants used to prevent thrombosis, but both agents are difficult to use effectively in the pediatric population.

- Recently, new oral anticoagulants (NOAC), both direct thrombin inhibitors and direct factor Xa inhibitors, have been developed and approved for multiple indications in adult patients.

McCrindle et al. Circulation 2014;130:1192-1203
New Oral Anticoagulants in Children

**Advantages**

- Oral route of administration
- Rapid onset of action
- Few clinically important interactions with food or other medications
- Standardized dosing with no need for monitoring

McCrindle et al. *Circulation* 2014;130:1192-1203
New Oral Anticoagulants in Children

Pediatric Issues

• Standardized dosing with no need for monitoring has yet to be confirmed for pediatric populations.

• Liquid formulations and their absorption leading to predictable drug levels need to be carefully studied in children.

McCrindle et al. *Circulation* 2014;130:1192-1203
Pediatric Issues (continued)

- The clinical scenario for anticoagulation in children often differs from adults, and frequently includes indwelling catheters or mechanical valves – and none of the NOAC have been shown to effectively prevent thrombosis on these artificial surfaces.

McCrindle et al. *Circulation* 2014;130:1192-1203
Although the use of NOAC is supported by evidence in adult patients, data are needed in children, beginning with appropriate pharmacologic and pharmacodynamic studies in neonates and children, and in pediatric clinical scenarios.

McCrindle et al. *Circulation* 2014;130:1192-1203
New Oral Anticoagulants in Children

Pediatric Issues (continued)

• Extrapolations regarding efficacy and safety from adult studies are not appropriate in most relevant pediatric clinical situations, because of differing developmental aspects of hemostasis and because of the often differing clinical indications in children – although there are considerable challenges to performing pediatric-specific clinical trials.

McCrindle et al. *Circulation* 2014;130:1192-1203
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Pediatric Issues (continued)

• Specific study of the mechanisms of action of NOAC, and their impact on coagulation monitoring assays, are feasible in children and should be performed given the known and suspected developmental differences in the coagulation pathways between children and adults.

• The issues of bleeding and reversibility associated with NOAC will need to be evaluated specifically in pediatric clinical scenarios.

McCrindle et al. Circulation 2014;130:1192-1203
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Pediatric Issues (continued)

• Before NOAC are approved for pediatric use, European and North American regulatory agencies require pediatric investigational programs.

• Although there are multiple pediatric phase 1 studies in progress, recruitment has been very challenging because potential study subjects should be at risk for developing a thrombotic complication and may not directly benefit from participation, despite the advantages of improved convenience and acceptability.

McCrindle et al. Circulation 214;130:1192-1203
Pediatric Issues (continued)

• The potential lack of benefit in the face of unknown risk highlights ethical issues regarding proxy consent for pediatric participation.

• It has also been difficult to conduct appropriate pharmacokinetic and pharmacodynamic pediatric dose-finding studies for NOAC.

McCrindle et al. *Circulation* 2014;130:1192-1203
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Summary

A body of evidence has accumulated over many years for the use of heparin and warfarin anticoagulation in children.

Although NOAC have been successfully introduced in adult patients, these drugs cannot yet be recommended in pediatric patients because of the current lack of data in children.

McCrindle et al. *Circulation* 2014;130:1192-1203