Aspirin Effect...
a new dilemma
Aspirin, the foundation of antiplatelet therapy in cardiovascular medicine, is widely prescribed by physicians to prevent heart attack and stroke. It is estimated that more than 150,000 heart attacks each year could be prevented by the appropriate use of aspirin therapy.1

Recently, physicians discovered that a significant number of individuals taking dosages of aspirin considered therapeutic were experiencing vascular thrombotic events including acute coronary syndromes, transient ischemic attacks, strokes and peripheral vascular events. In addition, clinical researchers, utilizing a variety of laboratory tests, discovered that some patients have a reduced or minimal response to aspirin administration.2

**Aspirin Effect... A New Solution**

The observation that individuals do not respond identically to therapeutic aspirin dosage has been defined as "Aspirin Resistance", a relatively new but well documented concept in the medical literature.3,4

**Aspirin and Thromboxane Generation**

Aspirin’s therapeutic effect inhibits COX-1 and results in decreased production of thromboxane A2 (TXA2), which reduces the ability of platelets to aggregate (figure 1). TXA2 is hydrolyzed in the liver into a number of metabolites including 11-dehydro thromboxane B2 and cleared from circulation by the kidneys (figures 2A and 2B). Thus, high levels of urinary 11-dehydro thromboxane B2 indicate insufficient inhibition of thromboxane A2 production, and a lack of aspirin effect.

Several factors (table 1) have been identified as potential mechanisms for influencing levels of 11-dehydro thromboxane B2.4,5,7

<table>
<thead>
<tr>
<th>Table 1. Mechanisms of Variability in Aspirin Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced aspirin bioavailability</td>
</tr>
<tr>
<td>Competitive interference by other NSAID’s</td>
</tr>
<tr>
<td>Increased platelet turnover</td>
</tr>
<tr>
<td>Generation of thromboxane A2 by COX-2</td>
</tr>
<tr>
<td>Platelet polymorphisms</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Diet and Lifestyle</td>
</tr>
</tbody>
</table>

**Clinical Importance**

In 2002, a clinical outcomes study was published evaluating patients at high risk for cardiovascular events. Urinary 11-dehydro thromboxane B2 was used in the study as a marker for in-vivo platelet activation. Results analyzed by quartile showed that patients in the 4th quartile (lack of aspirin effect) had a 3.5 times greater risk of cardiovascular death than those in the 1st quartile (aspirin effect).4

A second clinical outcomes study evaluating "aspirin resistance" in patients with cardiovascular disease was published utilizing platelet aggregometry. It also demonstrated a greater than 3 times risk of death in those patients not responding to aspirin.3

**Summary**

The ability to monitor aspirin effect allows healthcare providers to provide assurance to patients that their aspirin is working to inhibit platelet function. Dosage is important, as an ineffective response results in adverse events including an increased risk of death.8,9 Other antiplatelet therapy options such as clopidogrel may be utilized.

While there are several different methods available to detect platelet response to aspirin, urinary 11-dehydro thromboxane B2 is a readily available marker that can quantify insufficient inhibition of thromboxane A2 production by the platelets. Some researchers suggest that insufficient inhibition of thromboxane A2 production most accurately represents the definition of true aspirin resistance.4

**Urinary 11-dehydro thromboxane B2 is not subject to the preanalytical variables associated with other blood-based indirect measurements of platelet activation.**

**Laboratory Measurement of Aspirin Effect**

Several tests may be utilized to measure the effect of aspirin on platelets. Urinary 11-dehydro thromboxane is a stable metabolite of thromboxane A2 and an indicator of in-vivo platelet activation. Urinary 11-dehydro thromboxane B2 is not subject to the preanalytical variables associated with other blood-based indirect measurements of platelet activation.

Methods requiring freshly drawn blood measure platelet function resulting from ex-vivo stimulation of the platelet utilizing a variety of platelet activating agents. Tests that require fresh blood are subject to preanalytical variables that can potentially influence patient results including specimen collection, storage and transportation. Inter-laboratory standardization of these tests is difficult.

**Some researchers suggest that insufficient inhibition of thromboxane A2 production most accurately represents the definition of true aspirin resistance.**

![Figure 1. Diagram of the cyclooxygenase platelet activation pathway.](image)

![Figure 2A. Aspirin Effect](image)

**Low**

Urinary 11-dehydro thromboxane B2

Platelets

Kidney

Liver

**High**

Urinary 11-dehydro thromboxane B2

Platelets

Kidney

Liver

**Figure 2B. Lack of Aspirin Effect**

**Figure 2A. Aspirin Effect**

**Diet and Lifestyle**

**Hyperlipidemia**

**Platelet polymorphisms**

**Increased platelet turnover**

**Competitive interference by other NSAID’s**

**Reduced aspirin bioavailability**

**Aspirin**

**PGH2**

**TXA2**

**TXA2**

**TXB2**

**TX-synthase**

**COX-2**

**ARACHIDONIC ACID**

**TXB2**

**Urinary 11-dehydro thromboxane B2**

**Urinary 11-dehydro thromboxane B2 is a stable metabolite of thromboxane A2 and an indicator of in-vivo platelet activation.**

**Table 1. Mechanisms of Variability in Aspirin Effect**

<table>
<thead>
<tr>
<th>Reduced aspirin bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competitive interference by other NSAID’s</td>
</tr>
<tr>
<td>Increased platelet turnover</td>
</tr>
<tr>
<td>Generation of thromboxane A2 by COX-2</td>
</tr>
<tr>
<td>Platelet polymorphisms</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Diet and Lifestyle</td>
</tr>
</tbody>
</table>

---

1. [Reference](#)
2. [Reference](#)
3. [Reference](#)
4. [Reference](#)
5. [Reference](#)
6. [Reference](#)
7. [Reference](#)
8. [Reference](#)
9. [Reference](#)
References


Additional References