Measurement of Thromboxane Metabolites for ASA Resistance

Policy Number: APEA – G2107 – Measurement of Thromboxane Metabolites for ASA Resistance
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Policy Description

Thromboxane (TXA2) is a prostaglandin metabolite that causes platelet aggregation and vasoconstriction (Lopez, et al, 2014). Aspirin (ASA) is an acetylated salicylate and is classified as a nonsteroidal anti-inflammatory medication (Abramson, 2017). Aspirin resistance is the inability of aspirin to decrease platelet production of thromboxane A2 and, thereby, platelet activation and aggregation.

Related Policies

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Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

1. The measurement of thromboxane metabolites in urine (e.g. AspirinWorks) to evaluate aspirin resistance DOES NOT MEET COVERAGE CRITERIA for all indications.

Scientific Background

Aspirin acts primarily by interfering with the biosynthesis of cyclic prostanoids, including thromboxane (Abrams, 2018). It irreversibly inhibits COX-1, resulting in an antithrombotic effect due to a decrease in production of thromboxane. Low doses of aspirin (typically 75 to 81 mg/day) have antiplatelet properties (Abramson, 2019) and are indicated for the primary and secondary prevention of cardiovascular disease. However, aspirin has been noted to occasionally fail to provide any significant benefit in patients with cardiovascular disease.
Several possible explanations can account for this phenomenon, including genetic variability, nonadherence, or a pharmacological interaction with another drug (Zehnder, Tanty, & Gurbel, 2018).

Numerous studies show that aspirin resistance affects 15% to 25% of individuals (Alberts, 2010). A systematic review and meta-analysis on aspirin resistance indicated that patients who are resistant to aspirin are at a greater risk (odds ratio [OR]: 3.85) of clinically important cardiovascular morbidity than patients who are sensitive to aspirin (Krasopoulos, Brister, Beattie, & Buchanan, 2008). The effect of aspirin administration varies considerably among patients at high risk for cardiovascular events. Gum and coworkers found insufficient inhibition of platelet aggregation by aspirin in 6 to 24 percent of patients with stable coronary artery disease (Gum et al., 2001) while other estimates range from 5 to 60 percent (Martin & Talbert, 2005).

Many biochemical tests and several commercially available products have been developed to detect aspirin resistance. Tests used in research laboratories include aggregometry, tests based on activation-dependent changes in platelet surface, and tests based on activation-dependent release from platelets. Point-of-care tests include PFA-100, IMPACT, and VerifyNow, which can detect platelet dysfunction that may be due to aspirin effect (Paniccia, Priola, Liotta, & Abbate, 2015).

It has been proposed that aspirin resistance can also be detected by thromboxane metabolites in urine. Aspirin inhibits platelet activation through the permanent inactivation of the cyclooxygenase (COX) activity of prostaglandin 
H synthase-1 (referred to as COX-1), and consequently inhibits the biosynthesis of thromboxane A2(TXA2), a platelet agonist (Abramson, 2019). The urinary concentrations of the metabolite 11-dehydrothromboxane B2 (11 dhTxB2) is proposed to indicate the level of TXA2 generation (Smock & Rodgers, 2010).

The AspirinWorks Test Kit is an enzyme-linked immunoassay test that can be used to determine levels of 11 dhTxB2 in human urine (Geske, Guyer, & Ens, 2008). The AspirinWorks Test Kit was compared to the Accumetrics VerifyNow Aspirin Assay as the predicate device. The manual AspirinWorks Test Kit measures urinary 11 dhTxB2, a metabolite of TXA2, a direct inducer of platelet aggregation while the automated Accumetrics VerifyNow Aspirin Assay is a turbidimetric-based optical detection system, which measures platelet-induced aggregation in whole blood. Both analyze aspirin's effect through the reduction of TXA2 production or the resulting inhibition of platelet aggregation (FDA, 2015).

A major limitation of this test is that while serum TxB2 comes primarily from platelets, urinary 11dhTxB2 is not a specific measure of platelet thromboxane formation. Urine 11dhTxB2 reflects systemic thromboxane formation, and up to 30% or more can derive from extra-platelet sources, including monocytes, macrophages, atherosclerotic plaque, and other tissues that contain nucleated cells capable of regenerating functional COX-1, or that contain COX-2 (Smock & Rodgers, 2010).

Clinical Validity and Utility

The FDA noted that results from two different clinical studies established a cutoff for aspirin effect at ≤1500 pg 11d hTxB2/mg creatinine. Further analysis revealed that 180/204 (88.2%) of samples from individuals not taking aspirin were above the cut-off value. Analysis of samples from individuals taking various doses of aspirin revealed that 7/163 (4.3%) of 81 mg/day aspirin users indicated a lack of aspirin effect (greater than 1500 pg 1 ldhTxB2/mg creatinine) and 4/38 (10.5%) of the 325 mg/day aspirin users indicated a lack of aspirin effect. In total, 11/201 (5.5%) of all aspirin users tested indicated a lack of aspirin effect (FDA, 2007).

Lordkipanidze et al (2007) compared the results obtained from six major platelet function tests in the “assessment of the prevalence of aspirin resistance in patients with stable coronary artery disease.” 201 patients receiving 80 mg of aspirin were evaluated. Two of the tests used
to measure platelet aggregation were VerifyNow and urinary 11-dehydro-thromboxane B(2) concentrations. Prevalence of aspirin resistance for VerifyNow was measured to be 6.7% and 22.9% for urinary 11-dehydro-thromboxane B(2) concentrations. The prevalence of aspirin resistance varied according to the assay used. Results from these tests showed “poor correlation and agreement between themselves.” The authors concluded that “platelet function tests are not equally effective in measuring aspirin’s anti-platelet effect and correlate poorly amongst themselves and that the clinical usefulness of the different assays to classify correctly patients as aspirin resistant remains undetermined” (Lordkipanidze et al., 2007).

Dretzke et al (2015) examined “whether or not insufficient platelet function inhibition by aspirin (‘aspirin resistance’), as defined using platelet function tests (PFTs), is linked to the occurrence of adverse clinical outcomes, and further, whether or not patients at risk of future adverse clinical events can be identified through PFTs.” The authors reviewed 108 studies, with 58 on patients on aspirin monotherapy, and found that some PFTs may have prognostic utility. However, the authors noted that many of the studies found contained significant “methodological and clinical heterogeneity”. No cost-effectiveness studies were found.

Wang et al (2018) evaluated the association between stable urine metabolites of thromboxane (TxA2-M), prostacyclin (PGI2-M), levels of cellular adhesion molecules, chemokines, C-reactive protein, and the incidence of major adverse cardiovascular events (MACE). 120 patients with stable atherosclerotic cardiovascular disease on aspirin therapy were examined. The authors found that urinary TxA2-M levels were “significantly” correlated with circulating P-selectin and E-selectin levels, and associated with higher risk of MACE. The authors concluded that “these results provide insight into the contribution of TxA2 biosynthesis to ASCVD progression in humans, and suggest that patients with elevated TxA2-M levels may be predisposed to advanced platelet and endothelial activation and higher risk of adverse cardiovascular outcomes (Wang et al., 2018).”

Harrison et al compared 9 platelet function tests to assess responsiveness to three ASA dosing regimens in 24 type 2 diabetes patients randomized to ASA 100 mg/day, 200 mg/day, or 100 mg twice daily for 2 weeks. Of these 9 tests, three were VerifyNow, urinary 11-dehydro-thromboxane B2 (TxB2) and serum TxB2. The investigators evaluated VerifyNow as a “very good” measure, serum TxB2 as a “good” measure, and urinary TxB2 as a “moderate” measure. The authors concluded that “the platelet function tests we assessed were not equally effective in measuring the antiplatelet effect of ASA and correlated poorly amongst themselves, but COX-1-dependent tests performed better than non-COX-1-dependent tests (Harrison et al., 2018).”

Guidelines and Recommendations

International Society on Thrombosis and Haemostasis

The Working Group on Aspirin Resistance (Michelson et al., 2005) published a position paper which concluded that other than in research trials it is not appropriate to test for aspirin resistance or change therapy based on such tests. There are no published studies which address the clinical effectiveness or data linking aspirin dependent laboratory test to clinical outcomes in patients.

Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association and the Working Group on Thrombosis of the European Society of Cardiology (2015)

This study group was convened to assess the utility of platelet function testing in acute cardiac care for predicting adverse events and guiding antiplatelet therapy. The panel lists recommended assays for assessment of platelet activity during P2Y12 inhibitors, which are “the VASP-P® assay, the VerifyNow® device and the Multiplate® analyser”. Although VerifyNow is
the precursor to AspirinWorks, AspirinWorks itself was not mentioned as a recommended assay (Aradi et al., 2015).


The ACCP states “In patients who are receiving antiplatelet drugs, we suggest against the routine use of platelet function assays to monitor the antithrombotic effect of aspirin or clopidogrel” (Douketis et al., 2008).

**State and Federal Regulations, as applicable**

AspirinWorks received 510(k) marketing clearance from the FDA in May 2007 and is intended to aid in the qualitative detection of aspirin in apparently healthy individuals post ingestion. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Applicable CPT/HCPCS Procedure Codes**

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<tr>
<td>82570</td>
<td>Creatinine; other source</td>
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<tr>
<td>84431</td>
<td>Thromboxane metabolite(s), including thromboxane if performed, urine</td>
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*Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*

**Evidence-based Scientific References**


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Policy Implementation/Update Information
7/1/20 New Policy

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational
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