Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Aspirin Resistance Testing

Description/Background

Aspirin is a mainstay in the prevention of atherosclerotic events. Physicians have other drugs available to replace or supplement aspirin, principal of these being clopidogrel (Plavix®). It is fortunate that there are aspirin alternatives because recent research indicates that there are patients who are resistant to aspirin, and even to clopidogrel.

Both aspirin and clopidogrel inhibit the ability of blood platelets to aggregate, or clump. Clumping is one of the early steps in producing a blood clot, which is, under ordinary circumstances, a beneficial effect. Inappropriate clot formation, however, in the arteries supplying blood to the heart or brain, impairs blood flow, leading to damage or death of tissue.

Aspirin is an antiplatelet drug that works to prevent heart attacks and strokes by reducing the production of thromboxane, the chemical that makes platelets sticky. Although thromboxane cannot be measured directly, its chemical biomarker, 11-dehydro-thromboxane B_2, can. A low level of this biomarker in the urine means that aspirin is working as it should to reduce thromboxane production. High levels of the biomarker in the patient's urine may mean that the dosage of aspirin is not effective for decreasing the risk of a heart attack or stroke for that particular patient.

Aspirin's ability to suppress the production of prostaglandins and thromboxanes (both of which are produced during the metabolism of aspirin or clopidogrel) is due to its irreversible inactivation of the cyclooxygenase (COX) enzyme. Cyclooxygenase is required for prostaglandin and thromboxane synthesis. Low-dose, long-term aspirin use irreversibly blocks the formation of thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation. This anticoagulant property makes aspirin useful for reducing the incidence of heart attacks. A dose of 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostacyclin synthesis being little affected. However, higher doses of aspirin are required to attain further inhibition.

Despite aspirin's remarkable benefits, approximately 10-20% of aspirin-treated patients will have a cardiovascular event within five years of initiating therapy. This led to the concept that there is a subset of "aspirin resistant" patients who do not respond to aspirin's anti-clumping therapy and are therefore at persistent risk of future cardiovascular events. The term "aspirin resistance" has been used to describe the occurrence of occlusive cardiovascular disease (CVD) events despite regular intake of this agent at recommended doses. True biochemical aspirin resistance must be differentiated from non-compliance, a more common reason for therapy failure.

It is difficult to assess the clinical importance of aspirin resistance since there is currently no consensus on how to define, measure, and treat aspirin and clopidogrel resistance. Laboratory tests are just becoming available, and test results can vary depending on the laboratory performing the test and which test system is used. As a result, the incidence of 'resistance' has been estimated to be as low as 5% in some studies, and as high as 60% in others. This variation probably also reflects differences in treatment dosage and duration, as well as the existence of other conditions and/or medications that might influence drug action.

The lack of standardized measures of platelet function makes estimation of the prevalence of aspirin resistance difficult. Mounting evidence suggests that aspirin resistance is associated with adverse clinical outcomes, which have been assessed in patients with coronary artery disease, myocardial infarction, cerebrovascular disease and peripheral vascular disease. Patients with aspirin resistance have significantly more adverse vascular events than patients without such resistance. However, there are no guidelines for the treatment of aspirin resistance.

The AspirinWorks® Test measures the thromboxane metabolite, 11-dehydro thromboxane B2 in a urine sample (to aid in the qualitative detection of aspirin effect).

Regulatory Status

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.

Medical Policy Statement

The clinical utility of aspirin resistance testing by measurements of thromboxane metabolites has not been demonstrated. The peer reviewed medical literature has not shown that aspirin resistance testing will alter patient treatment or outcomes. Therefore, aspirin resistance testing is experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

84431

Rationale

There is no universally accepted definition of aspirin resistance. In pharmacological terms, this means insufficient pharmacological inhibition of platelet cyclooxygenase-1 (COX-1)-derived thromboxane formation, with subsequent insufficient inhibition of platelet function, by standard antiplatelet doses of aspirin (75–300 mg/day).

Adjusting aspirin drug therapy on the basis of individual response is an appealing proposition but is presently not evidence-based. Identifying those with a suboptimal response to aspirin may also influence other aspects of their management such as the choice of a drug-eluting or bare metal stent for percutaneous revascularization. An individualized approach may reduce the adverse consequences of aspirin therapy, allow more cost-effective use of expensive medication and improve patient outcomes.

In addition to the uncertainty regarding setting normal values and confidence intervals to define aspirin resistance, another major problem is the selection of appropriate methods for its determination. Measurement of inhibition of serum thromboxane quantitatively determines the pharmacological potency of aspirin to block the platelet COX-1 as seen from reducing the capacity of formation of an end product, i.e., thromboxane B_2. However, serum thromboxane has no direct equivalent in terms of platelet aggregation or total body thromboxane generation. Further, serum thromboxane has no physiological or clinical correlate *in vivo* because the locally generated amounts of thromboxane at a site of thrombus formation *in vivo* are several

orders of magnitude lower. In fact, in about 99% of cases aspirin does effectively block platelet COX-1, and thus pharmacological resistance does not account for clinical resistance.

A study by Valgimigli et al reported on a double-blind, prospective, randomized tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to Clopidogrel study.[1] One thousand two-hundred and seventy-seven patients who had undergone elective coronary angioplasty in 10 European sites were screened by a point-of-care assay. Some were determined to be aspirin-resistant (93), clopidogrel resistant (147) or dual poor responders (23). The patients were randomly assigned in a double-blind manner to receive tirofiban (Aggrastat®) or placebo. The primary end point, consisting of troponin I/T elevation at least three times the upper limit of normal, was attained in 20.4 percent in the tirofiban group compared with 35.1 percent in the placebo group. The conclusion reached was that in low-risk patients according to clinical presentation who had poor responsiveness to standard oral platelet inhibitors via a point-of-care assay, intensified platelet inhibition with tirofiban lowers the incidence of myocardial infarction after elective coronary intervention. According to the authors, the study provides proof of concept for a new treatment strategy in patients with coronary artery disease that assessing response to standard antiplatelet agents by a point-of-care assay modulates the intensity of treatment accordingly. However, this theory has yet to develop into a standard patient-selection criteria guideline. In addition, the author of the article had received honoraria for lectures for or served on advisory boards for Merck, the manufacturer of Aggrastat®.

In 2008, Krasopoulos et al performed a systematic review of literature to determine if there is a relation between aspirin "resistance" and clinical outcomes in patients with cardiovascular disease.[2] Twenty studies totaling 2930 patients with cardiovascular disease were identified. Most studies used aspirin regimens, ranging from 75-325 mg daily, and six studies included adjunct antiplatelet therapy. Compliance was confirmed directly in 14 studies and by telephone or interviews in three. Information was insufficient to assess compliance in three studies. Overall, 810 patients (28%) were classified as aspirin resistant. A cardiovascular related event occurred in 41% of patients (odds ratio 3.85, 95% confidence interval 3.08 to 4.80), death in 5.7% (5.99, 2.28 to 15.72), and an acute coronary syndrome in 39.4% (4.06, 2.96 to 5.56). Aspirin resistant patients did not benefit from other antiplatelet treatment.

In 2012, Ferraris et al published a review article which stated, “Currently, extensive literature exists about aspirin resistance, its mechanisms, detection and its treatment.[7] Existence of a link between high on -treatment platelet reactivity and atherothrombotic events suggests common mechanisms for atherosclerosis progression and thrombotic complications, with the platelets being a key cellular interface between coagulation and inflammation. A change in the approach to prevention of other thrombolic events may ultimately include all the components of atherothrombogenesis, including platelets, monocytes and endothelial cells. Nonetheless, tailoring antiplatelet therapy in accordance with the presence of aspirin resistance is one possible solution. However, the evidence in favor of this strategy is insufficient.” The author concludes that the optimal treatment, if any, of aspirin resistance is unknown.

Insufficient pharmacological inhibition of platelet COX-1 by aspirin may exist but it is likely to be very rare (about 1%). The term aspirin “resistance” does not adequately explain treatment failures with low-dose aspirin which occur more often but have no direct pharmacological relationship to COX-1 inhibition by the drug. ‘Treatment resistance’ is a frequently used term for this phenomenon but of greater relevance in this context are patient adherence and "residual” platelet reactivity. Aspirin “resistance,” however it is defined, is not a matter of

concern and – except individual cases of aspirin intolerance – has no clinical consequences since no appropriate alternatives are available. Moreover, even if platelet function is incompletely inhibited, the drug may have effects on autocrine and paracrine functions of platelet-derived thromboxane. Thus, there is no reason to withhold aspirin alone or in dual antiplatelet therapy because of concerns regarding possible “resistance.”

In a 2015 update reported in UpToDate, Hennekens et al reviewed a number of case series that were useful to formulate, but not test, hypotheses concerning aspirin nonresponse.[3] They concluded that the totality of clinical evidence does not support routine testing of patients for "aspirin resistance," whether by in-vitro testing of platelet function or by genetic testing. They state that the first step in management of a patient with apparent nonresponse to aspirin is to address issues of compliance. Additional options for patients who have had a clinical event on aspirin may include using a non-enteric formulation, increasing the dose, or adding another antiplatelet agent, depending on the clinical scenario.

Guirgis et al (2017) performed a review giving context to the clinical role and implications of antiplatelet resistance in peripheral arterial disease (PAD).[4] A review of English-language literature on aspirin resistance (AR) and clopidogrel resistance (CR) in PAD involving human subjects using PubMed and MEDLINE databases was performed in April 2017. A total of 2075 patients in 22 relevant studies were identified. To give this issue context, a review of the larger, more established literature on antiplatelet resistance in coronary disease was undertaken, identifying significant research associating resistance to major adverse cardiovascular events (MACEs). Studies in the coronary arterial disease literature have strongly associated antiplatelet resistance with increased MACE. Prevalence of AR or CR in coronary disease appears to be >55% for each in some studies. Meta-analyses of >50 studies revealed that AR and CR are significantly associated with MACE (relative risk of 2.09 and 2.8, respectively). This adds further weight to the literature reporting antiplatelet resistance as an independent predictor of and a threefold risk factor for major adverse cardiovascular events. The prevalence of resistance in PAD in this review was comparable to that in the coronary disease literature, with AR and CR prevalence up to 60% and 65%, respectively. There is evidence that the adverse effects of antiplatelet resistance are significant in PAD. In fact, research directly studying stent thrombosis populations with either coronary arterial disease or PAD revealed more significantly impaired platelet responsiveness to clopidogrel and aspirin in PAD compared with similar individuals with coronary disease. AR in PAD was found in studies to be a significant risk factor for iliofemoral stent reocclusion ($P = .0093$) and stroke in patients with symptomatic carotid disease ($P = .018$). CR was found to be a significant, independent risk factor in predicting ischemic outcomes in several recent PAD studies ($P < .0001$). Loss-of-function carriers of enzyme CYP2C19, important in clopidogrel metabolism, have a 30% greater risk of ischemic events ($P < .001$). Importantly, less antiplatelet drug resistance may be encountered with newer antiplatelet agents, including ticagrelor and prasugrel, because of reduced enzymatic polymorphisms. The limited research addressing AR and CR in PAD suggests that further research is required to clarify the role of platelet assays and potential for individualized antiplatelet therapy.

Bij de Weg et al. (2020) evaluated the changes in aspirin resistance during and after pregnancy.[5] The study focused on “obstetric high risk women with an indication for aspirin usage during pregnancy to prevent placenta mediated pregnancy complications”; in all, 23 pregnant women were included. Four complementary aspirin resistance tests (“PFA-200, VerifyNow®, Chronolog light transmission aggregometry (Chronolog LTA) and serum thromboxane B2 (TxB2) level measurement”) were used to measure aspirin resistance in each

trimester of pregnancy, as well as 3 months post-partum. The tests identified aspirin resistance at the following: PFA-200: 30.4%, VerifyNow: 17.4%, Chronolog LTA: 26.1%, and serum TxB2, 23.8%, respectively. The authors also identified that aspirin resistance tended to be more frequency during pregnancy compared to after pregnancy. However, the authors also acknowledged that there was "weak" correlation between tests and recommended more research on aspirin resistance as well as obstetric outcome.

Summary of Evidence
It is not currently recommended to test for aspirin resistance in patients or to change therapy based on this testing in routine clinical practice. Therefore, this testing is considered experimental/investigational.

Ongoing and Unpublished Clinical Trials
There are no clinical trials in assessing aspirin resistance or AspirinWorks testing that could potentially affect this review.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma[6]

This Task Force includes representatives from six different societies: The European Society for Trauma and Emergency Surgery (ESTES), the European Society of Anaesthesiology (ESA), the European Shock Society (ESS), the European Society for Emergency Medicine (EuSEM), the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) and the European Society of Intensive Care Medicine (ESICM). Although this guideline focuses on trauma settings, there are some comments on point-of-care (POC) platelet function tests, such as VerifyNow. The Task Force remarks that:

- "The role of POC platelet function devices in guiding haemostatic therapy is not established."
- "Currently, there is no agreement on the optimal assay for platelet function (see R11) and controversy exists as to whether bleeding in the setting of APA [aspirin] use warrants platelet transfusion", although the Task Force acknowledges that "that reliable measures of platelet function would be useful to guide reversal therapies in the setting of the bleeding trauma patient".
- The Task Force also states that due to the "lack of congruency" demonstrated by studies focusing on these platelet function assays, there is a need for future studies to investigate the potential benefit of these platelet function monitoring assays. The Panel remarks that "their [platelet function assays]' role in identifying trauma-induced platelet dysfunction and in guiding haemostatic therapy remains unclear and their use can only be recommended as an adjunct to standard laboratory monitoring."

Overall, the following recommendation of "We suggest the use of POC platelet function devices as an adjunct to standard laboratory and/or POC coagulation monitoring in patients with suspected platelet dysfunction" was given a grade of "2C", which was defined as "Very weak recommendation; other alternatives may be equally reasonable".

Society of Thoracic Surgeons

In 2012, the Society of Thoracic Surgeons released an updated practice guideline suggesting that, because of their high negative predictive value, preoperative point-of-care testing to assess bleeding risk may be useful in identifying those patients with high residual platelet reactivity after usual doses of antiplatelet drugs that can undergo operation without elevated bleeding risk. Point-of-care testing to assess perioperative platelet function may be useful in limiting blood transfusion. Both of these recommendations were based on evidence from a single randomized controlled trial or several large nonrandomized studies.[7]

Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association and the Working Group on Thrombosis of the European Society of Cardiology[8]

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 $P2Y_{12}$ 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.

Government Regulations National/Local:

No NCD or LCD on this topic. There is a Medicare fee listed for code 84431.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through June 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/10	3/16/10	2/16/10	Joint policy established
9/1/12	6/12/12	6/19/12	Routine maintenance. References added, policy reformatted.
1/1/14	10/17/13	10/25/13	Routine maintenance. Additional rationale added.
11/1/15	8/24/15	9/14/15	Routine maintenance.
11/1/16	8/16/16	8/16/16	Routine policy maintenance. Added supplemental information. Updated references.
11/1/17	8/15/17	8/15/17	Routine policy maintenance. No change in policy status.
11/1/18	8/21/18	8/21/18	Routine policy maintenance. No change in policy status.
11/1/19	8/20/19		Eliminated Medicaid section. No change in policy status.
11/1/20	8/18/20		Routine policy maintenance, added reference # 39. No change in policy status.
11/1/21	8/17/21		Routine policy maintenance, added information on AspirinWorks testing. No change in policy status.
11/1/22	8/16/22		Routine policy maintenance, no change in policy status.
11/1/23	8/15/23		Updated rationale, added reference 5,6 and 8. No change in policy status. Vendor Managed: Avalon. (ds)

11/1/24	8/20/24		Routine policy maintenance, no change in status. Vendor managed: Avalon (ds)

Next Review Date: 3rd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ASPIRIN RESISTANCE TESTING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A