ISSUE INTRODUCTION: The Diminishing Role of Aspirin in Cardiovascular Medicine: A Special Supplement to *The American Journal of Cardiology*

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Over the past decade, as the effectiveness of treatment and secondary prevention of cardiovascular disease has steadily improved, and some have speculated we may have reached an efficacy ceiling, many investigators have shifted their work to evaluate opportunities to improve the safety of therapy.[1] As antiplatelet and anticoagulant agents have become more potent and reliable, and other pharmacologic strategies of primary and secondary prevention have emerged, been adopted and been added to evidence-based management, the focus has been sharpened on the inevitable risk of placing patients on antithrombotic therapy—bleeding. The new class of direct oral anticoagulants has earned a dominant role in therapy primarily because of their comparative safety, especially in the risk of intracranial bleeding, to vitamin K antagonists. Early recognition of specifically elevated risk in the elderly, in low-body-weight patients, and in those who had suffered a prior stroke or transient ischemic attack led to labeling restrictions for the potent platelet $P2Y_{12}$ inhibitor prasugrel. Potency of antithrombotic therapy is inextricably linked to risk of bleeding. Interest has therefore evolved to consider withdrawal of previously established agents to minimize bleeding risk while sustaining efficacy.

Interestingly, it seems the most promising candidate for withdrawal from rote inclusion in cardiovascular therapy is aspirin (ASA), which was in every respect one of the true "wonder drugs" of the 20th century.[2] As its effectiveness was increasingly appreciated as an analgesic, an antipyretic, an anti-inflammatory, and ultimately as an antiplatelet, its role as one of the most used drugs in the world became assured. The first crack in ASA's armor was the early recognition of gastrotoxicity, which was accepted as a necessary evil—especially when the nonsteroidal anti-inflammatory drugs developed largely in response to that adverse effect provided only marginal improvement.[3] Recognition of the risk that the use of ASA in pediatric patients with acute viral illness was associated with the development of Reye's syndrome[4] merely served to restrict its use in children[5] and did nothing to impact its use in adults with cardiovascular disease.

The tide began to turn in the first decade of this 21st century, however, spurred by thoughtful articles with such provocative titles as, "What's More Dangerous, Your Aspirin Or Your Car?" in the well-respected journal *Health Affairs*.[6] In the years since, consideration of "addition by subtraction" has led to re-evaluation of the once-unchallenged role of ASA in primary prevention (except for narrowly-defined high-risk cohorts), and in long-term secondary prevention of acute coronary syndrome, stroke, and stent thrombosis. More than one expert has opined that, if submitted for approval today for so many cardiovascular indications, ASA might not receive a favorable review.[7]

Reduction in dose, shortening of course, replacement by other medications, and even replacement with other ASA formulations are all being considered to ensure safer courses of therapy for patients with cardiovascular disease. These strategies and the underlying data are discussed in this special Supplement issue. An international panel of experts reviews the considerations pertinent to today's practice and gives guidance to front-line practitioners as well as to future researchers.

This issue has been accredited in its entirety for continuing education for physicians, nurses, and pharmacists. Instructions for receiving up to 8 hours' credit for reading the entire Supplement appears in the front matter.

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