Acetylsalicylic acid resistance and clinical outcome – the Hobikoglu study is worth noting

Michael R Buchanan PhD FAHA

The *Canadian Journal of Cardiology* editors have facilitated our understanding of current cardiovascular issues with a varied collection of studies, including solid, evidence-based and up-to-date consensus articles by individuals in collaboration with the Heart and Stroke Foundation of Canada. But equally as important, the editors also provoke our thoughts with articles that may not appear as 'rigorous' as we are taught to expect, but ones conveying messages that could significantly impact clinical practice and, therefore, should merit serious consideration. The study by Hobikoglu et al in the current issue of the *Journal* (pages 201-206) is one of these.

Hobikoglu et al followed 140 patients with acute coronary syndrome, first by determining their acetylsalicylic acid resistance status – ie, their platelets responded to acetylsalicylic acid as expected (acetylsalicylic acid-sensitive) or the platelets were not inhibited by acetylsalicylic acid as expected (acetylsalicylic acid-resistant) – and then documenting the risk of adverse clinical events. The study was small – only 140 patients. They did not measure a biomarker of compliance, such as serum salicylate or thromboxane A_2 . They assessed acetylsalicylic acid resistance using only one assay, namely, the platelet function analyzer PFA-100 (Dade Behring, USA). However, Hobikoglu et al found that acetylsalicylic acid-resistant patients had more than a threefold increased risk of suffering a clinically important event than did acetylsalicylic acid-sensitive patients (OR 3.03; 95% CI 1.06 to 8.62).

In 2003, Gum et al (1) reported that among 326 patients with stable cardiovascular disease, acetylsalicylic acid-resistant patients had a 2.9-fold increased risk of suffering a clinically important event (OR 2.86; 95% CI 0.88 to 9.33).

Poston et al (2) reported that among 225 patients after coronary artery bypass grafting, acetylsalicylic acid-resistant patients had more than a 2.5-fold increased risk of suffering a clinically important event (OR 2.54; 95% CI 0.89 to 5.17).

Chen et al (3) reported that among 117 patients after percutaneous coronary intervention, acetylsalicylic acid-resistant patients had more than a threefold increased risk of suffering a clinically important event (OR 3.82; 95% CI 1.42 to 10.29).

Zhang et al (4) reported that among 256 patients after percutaneous coronary intervention, acetylsalicylic acid-resistant patients had more than a 2.8-fold increased risk of suffering a clinically important event (OR 2.87; 95% CI 1.62 to 5.10).

Andersen et al (5) reported that among 71 patients after myocardial infarction, acetylsalicylic acid-resistant patients had a 1.8-fold increased risk of suffering a clinically important event (OR 1.79; 95% CI 0.62 to 5.17).

Others (6-8) have reported that acetylsalicylic acid-resistant patients have more than a fivefold increased risk of suffering an adverse cardiovascular-related event.

All these studies were small. There is no consensus about which acetylsalicylic acid-resistant assay is the most reliable; consequently, the assay varies from one study to the next. The acetylsalicylic acid dose also varies from one study to the next. But wait – despite the obvious limitations of these studies, the message of each is consistently clear and always the same. Regardless of the number of patients studied, the assay used, the dose of acetylsalicylic acid ingested, the clinical entity investigated and the country of study origin, acetylsalicylic acid resistance was found to be associated with a significant increase in risk of adverse events. Specifically, if real, the impact of acetylsalicylic acid resistance on clinical outcome is global and adversely affects all cardiovascular-related disease entities. Moreover, the concept of acetylsalicylic acid resistance has been with us for the past two decades; in other words, the concept of acetylsalicylic acid resistance has stood the test of time.

A quick review of the data in the study by Hobikoglu et al and the other studies cited above also provides additional insight: there is a significant dose-response effect. The lower the dose of acetylsalicylic acid, the higher the incidence of acetylsalicylic acid resistance (Table 1).

These results are consistent with those of a previous study that reported on an acetylsalicylic acid dose effect, which, incidentally, was shown to be independent of the inhibition of thromboxane A_2 (9). Specifically, acetylsalicylic acid doses of 75 mg/day or more maximally inhibit cyclo-oxygenase activity, thereby blocking thromboxane A_2 synthesis, but acetylsalicylic acid resistance can still be detected. The results of a more recent study (10) of 700 patients were consistent with this premise.

Thus, the study by Hobikoglu et al remind us once again that we must seriously consider the impact of acetylsalicylic acid resistance on clinical outcome.

We may not agree with the assay used, but should we not take steps to ascertain which assay may be better? It is easy for us, as reviewers, to reject studies such as the one by Hobikoglu et al as too small and fraught with limitations. But thanks to the editors at the *Journal* for allowing the work of Hobikoglu et al to provoke us once again on this important and timely issue. Literally millions of patients throughout the world chronically ingest acetylsalicylic acid to decrease the risk of future untoward cardiovascular events. Clearly, many, and perhaps most, benefit significantly from the acetylsalicylic acid therapy. However, it is difficult to deny the existence of acetylsalicylic acid resistance and its adverse clinical outcome when studies such as the one by Hobikoglu et al repeatedly come to our attention. Is now not the time for industry or academia, as well the Heart and Stroke Foundation of Canada or the Canadian Institutes of Health Research, to facilitate the funding of larger and more rigorous

Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario

Correspondence: Dr Michael R Buchanan, Department of Pathology and Molecular Medicine, 2N22C, McMaster University, 1200 Main Street West, Hamilton, Ontario L8N 3Z5. Telephone 905-525-9140 ext 22930, e-mail mbuchan@mcmaster.ca

TABLE 1
Dose-related incidence of acetylsalicylic acid (ASA)
resistance

	75 mg	100 mg	160 mg to 200 mg	325 mg
ASA-resistant*, %	85	61	36	16

* $r = -0.9128$, $P < 0.025$

evidence-based studies on acetylsalicylic acid resistance to determine the best way to assess acetylsalicylic acid resistance and its impact on clinical outcome in patients with assorted cardiovascular disease entities? Or can we be assured that acetylsalicylic acid resistance is simply 'an interesting academic phenomenon with no clinical relevance', which I have been told on occasion? Tell that to the 16% to more than 30% of patients who do not benefit from acetylsalicylic acid therapy. If acetylsalicylic acid resistance is real, those patients number in the millions per year. Now is the time for us to find out for sure.

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