Study examines major bleeding risk with low-dose aspirin use in patients with and without diabetes

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Among nearly 200,000 individuals, daily use of low-dose aspirin was associated with an increased risk of major gastrointestinal or cerebral bleeding, according to a study in the June 6 issue of *JAMA*. The authors also found that patients with diabetes had a high rate of major bleeding, irrespective of aspirin use.

"Therapy with low-dose aspirin is used for the treatment of cardiovascular disease. It is recommended as a secondary prevention measure for individuals with moderate to high risk of cardiovascular events (i.e., for patients with multiple risk factors such as hypertension, dyslipidemia, obesity, diabetes, and family history of ischemic heart disease)," according to background information in the article. "Any benefit of low-dose aspirin might be offset by the risk of major bleeding. It is known that aspirin is associated with gastrointestinal and intracranial hemorrhagic complications. However, randomized controlled trials have shown that these risks are relatively small." The authors add that randomized controlled trials evaluate selected patient groups and do not necessarily generalize to an entire population.

In addition, low-dose aspirin use is recommended for certain patients with diabetes. Findings from a meta-analysis suggested that diabetes may increase the risk of extracranial hemorrhage. "These estimates were derived from a limited number of events within randomized trials. Hence, the risk-to-benefit ratio for the use of low-dose aspirin in the

presence of diabetes mellitus remains to be clarified," the researchers write.

Giorgia De Berardis, M.Sc., of Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy, and colleagues conducted a study to determine the incidence of major gastrointestinal and intracranial bleeding episodes in individuals with and without diabetes taking aspirin. For the study, the researchers used administrative data from 4.1 million citizens in 12 local health authorities in Puglia, Italy. Individuals with new prescriptions for low-dose aspirin (300 mg or less) were identified during the index period from January 2003 to December 2008, and were matched with individuals who did not take aspirin during this period.

For the study, the researchers included 186,425 individuals being treated with low-dose aspirin and 186,425 matched controls without aspirin use. During 6 years, 6,907 first episodes of major bleeding requiring hospitalization were registered, of which there were 4,487 episodes of gastrointestinal bleeding and 2,464 episodes of intracranial hemorrhage. Analysis indicated that the use of aspirin was associated with a 55 percent increased relative risk of gastrointestinal bleeding and 54 percent increased relative risk of intracranial bleeding. The authors note that in comparison with other estimates of rates of major bleeding, their findings indicate a 5-times higher incidence of major bleeding leading to hospitalization among both aspirin users and those without aspirin use.

Regarding the use of aspirin being associated with a 55 percent relative risk increase in major bleeding, "this translates to 2 excess cases for 1,000 patients treated per year. In other words, the excess number of major bleeding events associated with the use of aspirin is of the same magnitude of the number of major cardiovascular events avoided in the primary prevention setting for individuals with a 10-year risk of between 10 percent and 20 percent," they write.

The researchers also found that the use of aspirin was associated with a greater risk of major bleeding in most of the subgroups evaluated, but not in individuals with diabetes. Diabetes was independently associated with a 36 percent increased relative risk of major bleeding episodes, irrespective of aspirin use. Among individuals not taking aspirin, those with diabetes had an increased relative risks of 59 percent for gastrointestinal bleeding and 64 percent for intracranial bleeding.

"Our study shows, for the first time, to our knowledge, that aspirin therapy only marginally increases the risk of bleeding in individuals with diabetes," the authors write. "These results can represent indirect evidence that the efficacy of aspirin in suppressing platelet function is reduced in this population."

"In conclusion, weighing the benefits of aspirin therapy against the potential harms is of particular relevance in the primary prevention setting, in which benefits seem to be lower than expected based on results in high-risk populations. In this population-based cohort, aspirin use was significantly associated with an increased risk of major bleeding, but this association was not observed for patients with diabetes. In this respect, diabetes might represent a different population in terms of both expected benefits and risks associated with antiplatelet therapy."

In an accompanying editorial, Jolanta M. Siller-Matula, M.D., Ph.D., of the Medical University of Vienna, Austria, comments on the findings of this study, and writes that "a decision-making process based on balancing an individual patient's risk of bleeding and ischemic events is difficult."

"The study by De Berardis et al underscores that the potential risk of bleeding should be carefully considered in decision making. Assessment of bleeding risk and of net clinical benefit will merit further emphasis as issues inherent to aspirin use also apply to more potent platelet inhibitors and anticoagulants; there is only a thin line between efficacy and safety,

and the reduction in ischemic events comes at the cost of increased major bleedings. Therefore, future studies investigating the risks and benefits for individual patients appear to be mandatory to help physicians appropriately make recommendations about aspirin use for primary prevention."

More information: *JAMA*. 2012;307[21]:2286-2294.
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