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REVIEW TOPIC OF THE WEEK

Aspirin Therapy in Primary Cardiovascular Disease Prevention

A Position Paper of the European Society of Cardiology Working Group on Thrombosis

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ABSTRACT

Although the use of oral anticoagulants (vitamin K antagonists) has been abandoned in primary cardiovascular prevention due to lack of a favorable benefit-to-risk ratio, the indications for aspirin use in this setting continue to be a source of major debate, with major international guidelines providing conflicting recommendations. Here, we review the evidence in favor and against aspirin therapy in primary prevention based on the evidence accumulated so far, including recent data linking aspirin with cancer protection. While awaiting the results of several ongoing studies, we argue for a pragmatic approach to using low-dose aspirin in primary cardiovascular prevention and suggest its use in patients at high cardiovascular risk, defined as ≥2 major cardiovascular events (death, myocardial infarction, or stroke) projected per 100 person-years, who are not at increased risk of bleeding. (J Am Coll Cardiol 2014;64:319–27) © 2014 by the American College of Cardiology Foundation. Open access under CC BY-NC-ND license.

"Natura non facit saltus."
(Nature does not make jumps.)
—Gottfried Leibniz (1)

The recognition that thrombosis plays an important role in acute cardiovascular disease (CVD) (2,3) has resulted in a large number of clinical trials on the effectiveness of antithrombotic drugs in CVD prevention. The benefit of antiplatelet drugs (aspirin and $P2Y_{12}$ inhibitors) in reducing mortality and/or new cardiovascular events in patients with prior CVD (secondary prevention) with an acceptable risk of bleeding has been clearly shown (4,5). However, in patients without prior CVD (primary prevention), the indication for antithrombotic drugs is still unclear. In this population, aspirin—the only antithrombotic drug studied in sufficiently large patient cohorts—produces a statistically significant reduction in the risk of a first myocardial infarction (MI), but increases the risk of both gastrointestinal

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

GI = gastrointestinal

MI = myocardial infarction

PAD = periphery arterial disease

RCT = randomized controlled trial

(GI) bleeding and hemorrhagic stroke (6). As a result, guidelines and other expert opinions differ substantially in their recommendations for primary prevention, reflecting the uncertainty of a precise risk/benefit ratio in this population.

This document, produced by a committee appointed by the European Society of Cardiology (ESC) Working Group on Thrombosis, reviews and discusses the most up-to-date evidence for the safety and efficacy of aspirin use in primary CVD prevention, with the main aim of issuing practical recommendations.

METHODS

We searched the electronic PubMed database for randomized controlled trials (RCTs) or meta-analyses of RCTs using the following terms: anticoagulants OR aspirin OR antiplatelet drugs AND primary prevention AND coronary heart disease OR cardiovascular disease OR coronary artery disease OR peripheral arterial disease (PAD) OR cancer OR all-cause mortality. The last literature searches were performed on February 28, 2014. The authors critically evaluated the evidence, with an assessment of the risk/benefit ratio. The strength of recommendation and level of evidence of particular treatment options were weighed and graded according to the ESC system (7).

ASSESSING BASELINE RISK

In primary CVD prevention, in which the risk of developing atherothrombotic events is generally low, it is essential to estimate the individual baseline risk of such events and carefully balance this against the risk of adverse outcomes related to therapy. Commonly-used tools to assess baseline risk are the Framingham coronary heart disease (CHD) risk score (8), the recently released American College of Cardiology/American Heart Association (AHA/ACC) Task Force risk equations (9), ESC's SCORE (Systematic Coronary Risk Evaluation), or national risk charts. Some tools assess the risk of cardiovascular death, whereas others assess all major cardiovascular events. The Framingham CHD risk score predicts the 10-year risk of developing a coronary event (composite of MI and coronary death), and individuals are categorized as low (<10%), moderate (10% to 20%), or high (>20%) risk. Conversely, the SCORE system, recommended in the ESC guidelines (7), estimates the 10-year risk of a fatal atherosclerotic event: individuals are considered at low risk with a SCORE <1%, at moderate risk with a SCORE ≥1% and <5%, at high risk with a SCORE ≥5% and <10%, and at very high risk with a SCORE ≥10% (7). Clearly, the risk of total fatal and nonfatal events is higher than that of fatal events only. At a 5% risk of fatal events, the total event risk is approximately 15% (7). This 3-fold multiplier is somewhat smaller in the elderly, in whom a first event is more likely to be fatal.

ASPIRIN IN PRIMARY CVD PREVENTION

The only antithrombotic drugs investigated for primary CVD prevention are vitamin K antagonists, which were investigated in only 1 trial and are currently abandoned (Online Appendix), and acetyl salicylic acid (aspirin). Aspirin has been studied in 9 large-scale RCTs (10–18), including more than 100,000 participants (**Table 1**, Online Appendix).

META-ANALYSES OF PRIMARY CVD PREVENTION TRIALS WITH ASPIRIN. The meta-analysis carried out by the ATT (Anti-Thrombotic Trialists) Collaboration in 2009 (6) included the first 6 primary prevention trials (10–15) (n = 95,000) and demonstrated that, over a 10-year period, aspirin therapy was associated with 6 fewer MIs per 1,000 low-risk persons treated (5% CHD risk at 10 years according to the Framingham risk categories). For persons at moderate (15%) and high (25%) CHD risk, aspirin led to a reduction of 19 and 31 MIs per 1,000 patients treated, respectively (8). The downside was that the risk of bleeding events was also higher as a function of cardiovascular risk. Thus, the overall reduction of MIs was almost balanced by the increase in bleeding events throughout baseline risk categories. Aspirin therapy did not seem to have an effect on stroke occurrence. With respect to mortality, there was a small protective effect of aspirin therapy, with 0 to 6 fewer deaths per 1,000 persons treated over 10 years. This protective effect on mortality was found to be of similar magnitude in persons at low

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