



Review Article

The use of aspirin for primary and secondary prevention in venous thromboembolism and other cardiovascular disorders



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ABSTRACT

Cardiovascular disease (CVD) includes a number of conditions such as myocardial infarction, coronary heart disease, stroke, and venous thromboembolism. CVD is a leading health problem worldwide and a major cause of mortality, morbidity, and disability; it is also associated with high healthcare costs. The incidence of CVD is predicted to increase in the forthcoming years, and thus it is crucial that physicians are aware of the benefits and limitations of the available therapies to ensure patients receive optimized treatment. Current clinical practice guidelines provide recommendations on the use of anticoagulants and antiplatelets for both the prevention and treatment of CVD. Aspirin is the most studied antiplatelet agent in this context. The benefits of aspirin are well documented and supported by data from robust clinical trials for CVD conditions, such as acute coronary syndrome and stroke prevention in patients with atrial fibrillation. However, the clinical benefits of aspirin are less clear for other conditions, namely for primary prevention of venous thromboembolism after major orthopaedic surgery, particularly in comparison with newer drugs such as the direct oral anticoagulants. This article provides an outline of the current guidelines and a critical assessment of the efficacy and safety data supporting the recommendations for the use of aspirin in the treatment and prevention of venous thromboembolism and other cardiovascular disorders.

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**Abbreviations:** ACS, acute coronary syndrome; AAOS, American Academy of Orthopaedic Surgeons; ACCP, American College of Chest Physicians; AF, atrial fibrillation; APT, Antiplatelet Trialists' collaboration; CAD, coronary artery disease; CAST, Chinese Acute Stroke Trial; CI, confidence interval; CVD, cardiovascular disease; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ESC, European Society of Cardiology; HFS, hip fracture surgery; IST, International Stroke Trial; LMWH, low molecular weight heparin; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PAD, peripheral arterial disease; PE, pulmonary embolism; PEP, Pulmonary Embolism Prevention; RRR, relative risk ratio; SIGN, Scottish Intercollegiate Guidelines Network; THA, total hip arthroplasty; TIA, transient ischemic attack; TKA, total knee arthroplasty; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism; WARFASA, Warfarin and Aspirin study.

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## Introduction

Cardiovascular disease (CVD) comprises a range of disorders affecting the circulatory system, including hypertension, myocardial infarction (MI), atherosclerosis, coronary heart disease, coagulopathies, stroke, and venous thromboembolism (VTE) [1–3]. CVD is the principal cause of death in developed countries [4,5]. It is estimated that by 2020, CVD will be the leading worldwide cause of mortality and disability [5,6]. CVD is a major healthcare burden that is associated with high levels of morbidity, mortality, and disability, and high healthcare costs [2,4,7,8].

The impact of CVD has led to the initiation of numerous clinical trials investigating pharmacological agents, such as antiplatelets and anticoagulants, for both prevention and treatment. This is reflected in clinical practice guidelines [9–17]. Among the antiplatelet agents, acetylsalicylic acid (commonly known as aspirin) has been evaluated extensively for the prevention and treatment of CVD [6]. Aspirin inhibits platelet cyclooxygenase 1 and the synthesis of prostaglandin G<sub>2</sub> and subsequent transformation into prostaglandin H<sub>2</sub>, the precursor of thromboxane A<sub>2</sub>. The result is an inhibition of thromboxane A<sub>2</sub>-induced platelet aggregation and vasoconstriction [6,18].

Evidence gained from the use of aspirin in a wide range of high-risk patients supports its routine prescription by healthcare providers to decrease the risk of subsequent occlusive CVD events. In secondary prevention – among survivors of a MI, occlusive stroke, transient ischemic attack, or coronary artery bypass grafting surgery, or those with stable angina – aspirin significantly reduces the risk of subsequent MI, stroke, and vascular death [19].

The positive impact of aspirin in primary prevention of CVD is less clear [20], particularly when the increased risk of gastrointestinal hemorrhage is taken into consideration [21,22]. In large-scale trials of primary prevention in men and women without established CVD, and subsequent meta-analyses, aspirin produced a significant reduction in the risk of a first MI, but not of stroke or cardiovascular death [20].

Although aspirin is recommended by some current guidelines (Table 1) for VTE prevention, controversy surrounds its effectiveness, particularly after major orthopaedic surgery [17,23]. For VTE primary prevention, current guidelines vary in their recommendations regarding aspirin, making it difficult for physicians to make informed treatment decisions [13–15,17]. For VTE secondary prevention, studies have consistently shown a relatively weak effect of aspirin in this setting (Fig. 1) [24,25].

This situation needs to be addressed and the evidence for aspirin re-evaluated, particularly in light of data from several trials of direct oral anticoagulants (DOACs), such as rivaroxaban, dabigatran, and apixaban, which have demonstrated impressive efficacy for these agents compared with standard of care, with relatively low risks of bleeding in the context of VTE prevention [33–41].

This review will provide a comprehensive overview of the current guidelines and relevant trials in which the efficacy and safety of aspirin have been assessed, and discuss whether there is a sound basis for its recommendation for both primary and secondary VTE prevention, as well as for management of other vascular diseases.

## Use of Aspirin for the Prevention of Venous Thromboembolism

### Primary Prevention after Orthopaedic Surgery

#### Guidelines

The 2012 American College of Chest Physicians-(ACCP) guidelines on VTE prevention in orthopaedic surgery patients (Table 1) provide recommendations on the use of VTE prophylaxis in patients undergoing major orthopaedic surgery, including total hip arthroplasty (THA), total knee arthroplasty (TKA), and hip fracture surgery (HFS) [17]. Aspirin is one of the therapeutic agents recommended. Of note, the recommendations for aspirin were based solely on the evidence presented in the Pulmonary Embolism Prevention (PEP) study [42], the limitations of which will be discussed in detail later. Furthermore, the quality of the evidence

**Table 1**

Summary of the ACCP and ESC guidelines for aspirin use in cardiovascular disorders.

Guideline	Recommendations for aspirin use
ACCP	<ul style="list-style-type: none"> <li>• Primary and secondary prevention of cardiovascular disease [12]</li> <li>• Primary prevention of venous thromboembolism (in any orthopaedic surgery patient) [17]</li> <li>• Primary and secondary prevention of cardiovascular events in peripheral artery disease [10]</li> <li>• Secondary prevention in coronary artery disease and acute coronary syndrome [12]</li> <li>• Secondary prevention in cerebrovascular disease (acute ischemic stroke and transient ischemic attack) [11]</li> <li>• Primary and secondary prevention in non-rheumatic patients with atrial fibrillation at low risk of stroke [26]</li> <li>• Not recommended for primary and secondary prevention in non-rheumatic patients with atrial fibrillation at intermediate and high risk of stroke [26]</li> <li>• Not recommended for primary prevention of venous thromboembolism in medically ill patients [27]</li> <li>• Not recommended for secondary prevention of venous thromboembolism [9]</li> </ul>
ESC	<ul style="list-style-type: none"> <li>• Recommended as part of dual antiplatelet therapy for secondary prevention in acute coronary syndrome and non-cardioembolic transient ischemic attack or ischemic stroke [16]</li> <li>• Not recommended for primary prevention of cardiovascular events [16]</li> <li>• Not recommended for stroke prevention in atrial fibrillation unless oral anticoagulants are refused or not tolerated [28]</li> </ul>

ACCP, American College of Chest Physicians; ESC, European Society of Cardiology.

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