Section Editor: Peter Sandercock, MA, DM, FRCPE, FMedSci

Antiplatelet and Anticoagulant Agents for Secondary Prevention of Thromboembolic Events in People With Antiphospholipid Syndrome

Malgorzata M. Bala, MD, PhD; Magdalena Celinska-Lowenhoff, MD, PhD; Wojciech Szot, MD, PhD; Agnieszka Padjas, MD, PhD; Mateusz Kaczmarczyk, MD; Mateusz J. Swierz, MD; Anetta Undas, MD, PhD

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the presence of antiphospholipid antibodies and subsequent arterial or venous thrombosis or pregnancy morbidity. Individuals with a definite APS diagnosis have an increased lifetime risk of recurrent thrombotic events.

Objectives

The aim of this systematic review was to assess the effects of antiplatelet or anticoagulant agents, or both, for the secondary prevention of recurrent thromboembolism, particularly ischemic stroke, in people diagnosed with APS.

Search Methods

We searched several electronic databases up to February 2017 and supplemented them by searching several ongoing trials registers, checking the reference lists of included studies, systematic reviews, and practice guidelines, and contacting experts in the field.

Selection Criteria

We included randomized controlled trials that evaluated any anticoagulant or antiplatelet agent, or both, in the secondary prevention of thromboembolism among patients with APS diagnosed according to the criteria valid when the study was performed. Studies specifically addressing women with obstetric APS were excluded.

Main Results

Our review included 5 randomized controlled trials involving 419 individuals with APS. The results are presented in form of comparisons identified by the review.

1. Nonvitamin K antagonist oral anticoagulants (rivaroxaban) versus standard vitamin K antagonist (VKA; warfarin) treatment (1 study): no thrombotic or major bleeding events observed during 210 days, but the study was not powered to detect such differences (low-quality evidence), the rates of clinically relevant nonmajor bleeding were similar (relative risk [RR], 1.45; 95% confidence interval [CI], 0.25–8.33; moderate quality of evidence);
2. High-dose warfarin versus moderate/standard intensity VKA (2 studies): during 2.7 and 3.4 years of follow-up, there was a similar risk of any thromboembolic event (RR, 2.22; 95% CI, 0.79–6.23; low-quality evidence) and major bleeding (RR, 0.74; 95% CI, 0.24–2.25; low-quality evidence), but the risk of any bleeding and minor bleeding was increased in the high-dose warfarin (hazard ratio, 2.03; 95% CI, 1.12–3.68; low-quality evidence, and RR, 2.55; 95% CI, 1.07–6.07, respectively).

Other 3 comparisons were based on 1/2 small, poorly reported studies: VKA plus antiplatelet agent versus single antiplatelet therapy, dual antiplatelet therapy versus single antiplatelet drug, and VKA plus antiplatelet agent versus dual antiplatelet therapy. The evidence was nonconclusive (very low quality evidence).

Implications for Practice

Based on the gathered data, the review was unable to conclude on the benefits or harms of any of the following interventions: (1) nonvitamin K antagonist oral anticoagulants versus standard VKA anticoagulation; (2) antiplatelet plus VKA agents versus single or dual antiplatelet therapy; and (3) dual versus single antiplatelet therapy, for the secondary prevention of recurrent thrombosis in patients with APS. Likewise, there was insufficient evidence to draw any conclusion on the benefits of using high-intensity versus standard-intensity VKA although there was some evidence of harm (increased risk of minor and any bleeding) associated with high-intensity VKA. Five ongoing randomized controlled trials will likely provide additional data on the therapy of APS.

Received November 27, 2017; final revision received December 22, 2017; accepted December 23, 2017.

From the Department of Hygiene and Dietetics (M.M.B., W.S.), Systematic Reviews Unit - Polish Cochrane Branch (M.M.B., M.K., M.J.S.), 2nd Department of Internal Medicine, Department of Allergy and Immunology (M.C.-L.), and Institute of Cardiology (A.U.), Jagiellonian University Medical College, Krakow, Poland.

This paper is based on a Cochrane Review published in *The Cochrane Library* 2017, Issue 10 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and *The Cochrane Library* should be consulted for the most recent version of the review.

Correspondence to Malgorzata M. Bala, MD, PhD, Systematic Reviews Unit - Polish Cochrane Branch, Jagiellonian University Medical College, Kopernika 7, Krakow, 31–034, Poland. E-mail Malgorzata.1.bala@uj.edu.pl

(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.019900.)

Implications for Research

In conclusion, sufficiently powered studies with adequate treatment adherence are essential to assess the effects of the intervention on clinically relevant outcomes in patients with APS. It is of vital importance to evaluate the efficacy and safety of nonvitamin K antagonist oral anticoagulants agents other than rivaroxaban versus standard therapy with VKA for treating APS in randomized trials.

Sources of Funding

Internal sources include Jagiellonian University Medical College, Poland. All the review authors are either employed by Jagiellonian University Medical College (JUMC) or are students at JUMC and worked on the review within their research activities. External sources include Ministry of Science and Higher Education, Poland, Core funding for statutory R & D activities K/ZDS/006101.

Disclosures

Dr Bala receives honoraria as a freelancer from a company doing health technology assessments and systematic reviews for various clients; she is not aware of any direct conflict of interest. Dr Szot participates in clinical trials not related to the topic of this review. Dr Undas received lecture honoraria from Boehringer Ingelheim, Bayer Pharma AG, Sanofi-Aventis, Pfizer/Bristol-Meyers-Squibb within the previous 3 years and personal fees from the publisher Medycyna Praktyczna. The other authors report no conflicts.

KEY WORDS: anticoagulants ■ antiphospholipid syndrome ■ platelet aggregation inhibitors ■ secondary prevention ■ stroke

Stroke
Journal of the American Heart Association

Antiplatelet and Anticoagulant Agents for Secondary Prevention of Thromboembolic Events in People With Antiphospholipid Syndrome

Malgorzata M. Bala, Magdalena Celinska-Lowenhoff, Wojciech Szot, Agnieszka Padjas, Mateusz Kaczmarczyk, Mateusz J. Swierz and Anetta Undas

Stroke. published online February 6, 2018;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628