

THE AUTHORS REPLY: We agree with Girard and Le Gal that the definitions of VTE-related death across contemporary trials of thromboprophylaxis may not be sufficiently specific to include as part of the definition of fatal pulmonary embolism. This may have especially been the case in the MARINER trial, in which a broader definition of unexplained sudden death without objective verification was used and probably included deaths that were not due to thrombotic causes. However, we disagree with the view that the incidence of VTE-related death that was seen in our trial is clinically unrealistic, given the higher incidence of fatal pulmonary embolism among acutely ill medical patients than among nonmedical (surgical) patients.¹ Although efforts to standardize the definition of fatal pulmonary embolism are welcome, these may be difficult given the very low rates (<1.0%) of autopsies in contemporary clinical trials of thromboprophylaxis. A more feasible and methodologically sound approach would be to include all-cause mortality as

the mortality end point in trials of anticoagulant treatment, which would capture all thrombosis-mediated causes of death, such as pulmonary embolism, ischemic stroke, and myocardial infarction.

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Since publication of their article, the authors report no further potential conflict of interest.

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Aspirin-Exacerbated Respiratory Disease

TO THE EDITOR: In Figure 1 of the review article by White and Stevenson (Sept. 13 issue),¹ there was an unfortunate, but important, misrepresentation of the prostaglandin E₂ (PGE₂) synthesis pathway. The figure incorrectly shows PGE₂ as a downstream product of the sequential metabolism of prostaglandin I₂ (PGI₂), prostaglandin F₂ (PGF₂), and prostaglandin D₂ (PGD₂). Instead, PGE₂, PGD₂, prostaglandin F_{2α}, and PGI₂ are each independently synthesized from prostaglandin

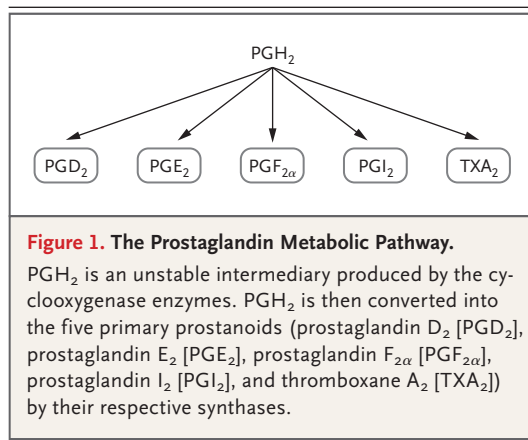
H₂ (PGH₂) through different enzymes (Fig. 1).² The synthesis of PGE₂ from PGH₂ is catalyzed by four distinct PGE synthase enzymes: microsomal PGE synthase-1 (mPGES-1), cytosolic PGE synthase (cPGES), microsomal PGE synthase-2 (mPGES-2), and glutathione-S-transferase μ (GSTμ).³

The figure correctly shows that the generation of the cysteinyl leukotrienes is sequential from the immediate upstream product (leukotriene E₄ [LTE₄] from leukotriene D₄ [LTD₄] and LTD₄ from leukotriene C₄ [LTC₄]), so the arrows are accurate in this part of the figure. However, there should be individual arrows from PGH₂ to PGD₂, PGE₂, PGF_{2α}, and PGI₂ — similar to the arrow from PGH₂ to thromboxane A₂ (TXA₂) (Fig. 1). This is important because the figure in the article by White and Stevenson implies that inhibition of PGI synthase, PGF synthase, or the prostaglandin D synthases (hematopoietic PGD synthase or lipocalin PGD synthase) will block production of PGE₂.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: As a practicing pulmonologist who sees many patients with aspirin-exacerbated respiratory disease (AERD), I would raise two points about the article by White and Stevenson. First, it seems questionable that tests to detect sensitivity to acetylsalicylic acid (aspirin) are in fact necessary to confirm the diagnosis of AERD in most patients as the authors implied. Many patients have such a classic presentation of “Samer’s triad” (nasal polyps, asthma, and sensitivity to aspirin) that formal testing appears to be both unnecessary and unduly burdensome.¹ Second, it would have been helpful to include a discussion of the role of newer biologic agents such as omalizumab (Xolair) (a monoclonal antibody against IgE) or mepolizumab (Nucala) (an anti-interleukin-5 monoclonal antibody) in the management of this disease.^{2,3} In particular, my colleagues and I have noted substantial success with the use of omalizumab, specifically in patients with persistently active asthma or with poor compliance that was thought to preclude safe, effective, or lasting desensitization.

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No potential conflict of interest relevant to this letter was reported.

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3. Tuttle KL, Buchheit KM, Laidlaw TM, Cahill KN. A retrospective analysis of mepolizumab in subjects with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2018;6:1045-7.

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THE AUTHORS REPLY: We appreciate the proper depiction of the prostaglandin metabolic

pathway in the figure provided by Rusznak and Peebles.

In reply to Kuhn: although some patients have a classic presentation and history of AERD, we disagree that it is unnecessary to clarify the diagnosis of AERD through an aspirin challenge in most patients. An oral aspirin challenge or desensitization should be considered in all patients with rhinosinusitis and asthma who report any history of respiratory symptoms after ingesting nonsteroidal antiinflammatory drugs (NSAIDs), since 15 to 20% of patients with asthma who have pansinusitis and who report a history of respiratory symptoms after ingesting NSAIDs will have a negative aspirin challenge.¹ Also, approximately one eighth of patients with rhinosinusitis and asthma who have not recognized respiratory symptoms after ingestion of NSAIDs or might not take NSAIDs at all actually have AERD.² Finally, in most clinics, the aspirin challenge and aspirin desensitization occur simultaneously. In patients with suspected AERD, desensitization is planned, and thus the initial part of the challenge confirms the diagnosis and the rest of the process successfully desensitizes the patient. Treatment with aspirin after desensitization is now recognized as the standard of care for patients with AERD; therefore, aspirin desensitization is usually planned. However, in cases in which the history is unclear, the patient does not wish to receive daily aspirin, or the use of aspirin is contradicted, a challenge should still be considered to make a proper diagnosis and determination of the phenotype. The aspirin challenge plus desensitization is now streamlined to be completed in 1 or 2 days. Kuhn also mentions the exciting topic of new biologic agents for patients with asthma. Although it is likely that in the future these agents will play a therapeutic role in the treatment of patients with AERD, studies of biologic therapy for AERD are scant. Currently, the role of biologic agents in AERD is limited to the Food and Drug Administration–approved indications for poorly controlled asthma.

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Since publication of their article, Dr. White reports receiving lecture fees from Regeneron. No further potential conflict of interest relevant to this letter was reported.

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Sequencing of Circulating Cell-free DNA during Pregnancy

TO THE EDITOR: The review article by Bianchi and Chiu (Aug. 2 issue)¹ offers an international scope and provides an accurate presentation of data showing the value of cell-free DNA (cfDNA) screening for common aneuploidies in all risk populations. The authors also acknowledge that insurance creates access challenges for many pregnant women.

As experts in obstetrics and genetic counseling, we can attest to the high performance and clinical usefulness of cfDNA screening. We also witness insurance coverage gaps that cause considerable disparity in access to quality prenatal care.

Although some commercial insurers cover cfDNA screening regardless of risk status, two major insurers continue to restrict coverage to high-risk pregnancies. A total of 11 state Medicaid programs and the District of Columbia do not cover cfDNA screening in high-risk pregnancies, despite universal support from professional guidelines. Currently, only 3 public insurers cover cfDNA screening in the general obstetrical population (Rhudy M, Coalition for Access to Prenatal Screening; personal communication). We hope that the authors' optimistic prognosis regarding public insurance coverage of cfDNA screening in the general obstetrical population will soon become reality.

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Ms. Hoskovec and Dr. Swigert report serving as clinical advisory board members for the Coalition for Access to Prenatal Screening; and Dr. Swigert, serving as a clinical advisory board member for Integrated Genetics. No other potential conflict of interest relevant to this letter was reported.

1. Bianchi DW, Chiu RWK. Sequencing of circulating cell-free DNA during pregnancy. *N Engl J Med* 2018;379:464-73.

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