circulation and an increased bleeding risk in patients taking warfarin, more studies are needed to properly inform guidelines on this matter. To be sure, there are many questions that remain unanswered after this study, specifically the time in the therapeutic range for patients with Fontan circulation maintained on warfarin in this and other Fontan registries; the additional effects of the myriad anatomic, physiologic, and surgical configurations of Fontan circulations on their thrombotic risk; and additional surgical and medical factors that lead practitioners to choose warfarin or aspirin as the primary anticoagulant for these complex patients.

Another famous aphorism ascribed to van der Rohe is “God is in the details.” The details of ideal anticoagulation strategies for patients with Fontan circulation have yet to be fully realized. This study suggests that the long-term risk of thrombotic complications may be able to be managed with aspirin alone, which could greatly simplify outpatient management while sparing these patients the additional morbidity and inconvenience of long-term warfarin therapy. Whether there

is a subset of patients who require additional anticoagulation, either for a brief duration or for life, among this heterogeneous and challenging patient population requires further investigation. While studies continue that compare novel oral anticoagulants against warfarin in this challenging patient population, this and other studies should serve as important reminders that warfarin may not be the gold standard, and that less anticoagulation may, in fact, be more.

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Commentary: Aspirin versus warfarin in patients with a Fontan circulation—the clot thickens

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Thrombotic complications in single-ventricle patients with a Fontan circulation are common. They are likely secondary to a complex interaction of circulating coagulation factor

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CENTRAL MESSAGE

This study suggests an extraordinary incidence of brain injury in Fontan patients but is underpowered to demonstrate a difference between aspirin and warfarin in preventing thrombotic complications.

abnormalities, endothelial dysfunction, stasis of blood flow, the presence of prosthetic material and artificial valves, and residual right-to-left shunts. The absence of antithrombotic therapy is associated with an unacceptable incidence of thrombotic complications¹ and, therefore,

most patients are treated with either aspirin or warfarin. Numerous retrospective series and an early post-Fontan clinical trial have attempted to determine whether anticoagulation with warfarin is associated with improved outcomes compared with aspirin alone.¹⁻⁴ A recent meta-analysis of these studies found no significant difference in the incidence of thromboembolic events in those receiving aspirin compared with warfarin.¹ The incidence of thromboembolic events in these studies vary broadly due to the differing frequency and variety of tests used for thromboembolic screening,¹ and we remain underinformed in this crucial area of Fontan management.

In this issue of the *Journal*, Attard and colleagues⁵ describe a cross-sectional analysis of a subset of patients from the Australia and New Zealand Fontan Registry who were taking either aspirin or warfarin for a minimum duration of 5 years. Study participants underwent magnetic resonance imaging (MRI) of the brain to evaluate for evidence of silent arterial thromboembolic events. Participants also underwent assessment of bone density with a dual-energy X-ray absorptiometry scan and completed quality of life and bleeding history surveys. The study's brain imaging findings were staggering—of the 84 subjects (median age 20.7 years), 39% had evidence of ischemic infarction on MRI of the brain, 86% had white matter injury, and 96% had hemorrhagic changes. When evaluating the association between antithrombotic therapy, there was no difference in any of these brain imaging findings between the study participants on aspirin compared with those on warfarin. In addition, there was no difference in quality of life between those on aspirin versus warfarin. Warfarin use was found to be associated with more bleeding and lower bone mineral density.

The study provides striking data on the incidence of brain abnormalities in adolescent and adult patients with a Fontan circulation, but it fails to get us closer to knowing whether there is a difference between aspirin and warfarin. While the authors clearly state the study's many limitations, the conclusion remains overstated—that aspirin should be offered as primary long-term thromboprophylaxis after the Fontan. This recommendation is based on the lack of difference by treatment group on findings by brain imaging of only 84 patients and concerns that bone health is adversely affected by chronic warfarin therapy. For the recommendation to be robust, the current study would clearly have to have the power to support the null hypothesis for therapeutic benefit. In this regard, the data are lacking. While perhaps a surprising percentage, more than one-third of the study participants having evidence of stroke, the absolute number of events is tiny, the timing of when the stroke occurred could not be defined, and what antithrombotic medication each participant was taking at that time of the event is unknown. It is possible that these ischemic insults occurred earlier in life, intraoperatively, or in the perioperative period when

patients were on different medications. In addition, we do not have any data on the adequacy of anticoagulation (eg, time in therapeutic range) for those on warfarin (or the presence or absence of aspirin resistance for those on aspirin⁶). This is important, as a previous study early post-Fontan suggested that poorly controlled warfarin therapy is likely worse than aspirin.⁷ Finally, silent arterial thromboembolic complications were screened for by MRI of the brain; however, there was no complimentary evaluation for asymptomatic/silent venous or intracardiac thrombosis. In this regard, it is noteworthy that there was not a single reported deep-vein thrombosis in the study cohort. In the absence of a randomized controlled trial conducted on many thousands of patients over the course of several decades, analysis of large datasets such as the Australia and New Zealand Fontan Registry are our best chance of providing some answers, but more numbers, more comprehensive follow-up data, and better overall phenotyping and recording of outcomes are clearly required.

Although this study does not answer whether there is a difference between aspirin and warfarin, one should not lose sight its significant contributions. The brain imaging findings provide a baseline understanding of the incidence of brain imaging abnormalities in adolescent and adult patients. In addition, this study demonstrates that warfarin is an additional risk factor for low bone mineral density, a common problem in patients with a Fontan circulation.⁸ This suggests potentially more aggressive screening and treatment for osteopenia or osteoporosis for those receiving warfarin and may be an additional reason to switch patients to aspirin, or to direct oral anticoagulants, when reliable data of benefit, or noninferiority, for clinical outcomes for these treatments is available. This paper's legacy will be the further investigations spurred by the brain imaging and bone mineral density findings but not for settling the never-ending aspirin versus warfarin debate.

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