Non-vitamin K oral anticoagulants in adults with congenital heart disease: *quod non?*

Peter Verhamme , Werner Budts , and Frans Van de Werf *

Division of Cardiovascular Diseases, University Hospitals Leuven and Department of Cardiovascular Sciences, KU Leuven–University of Leuven, Belgium

This editorial refers to ‘Current use and safety of novel oral anticoagulants in adults with congenital heart disease: results of a nationwide analysis including more than 44 000 patients’, by E. Freisinger et al., doi: 10.1093/eurheartj/ehaa844.

Non-vitamin K oral anticoagulants (NOACs) are more effective, cause less intracranial bleeding, and are more convenient than vitamin K antagonists (VKAs). The evidence is consistent and convincing at least for patients with non-valvular atrial fibrillation at risk for stroke and systemic embolism, and for patients who have suffered a deep vein thrombosis or pulmonary embolism and are at risk for recurrent events.^{1,2} However, the validity of these improved outcomes is questioned for adults with congenital heart disease (ACHD) in an analysis of a large German claims database published in this issue of the *European Heart Journal*.³ In this database that included >44 000 patients with ACHD, the proportion of anticoagulated patients who received NOACs steadily accrued up to 45% in 2018. Clinical outcomes of 6504 patients with a first prescription for an NOAC ($n = 1653$) or a VKA (4851) between 2010 and 2016 were analysed. Median follow-up was 90 months. Of concern, there was an excess mortality and there were more thrombo-embolic episodes, more major cardiovascular events, and more bleedings in ACHD patients treated with NOACs compared with VKAs. Even after adjustment, the excess mortality, major cardiovascular events, and bleedings (but not major or intracranial bleedings) persisted (*Figure 1*).

True or biased observations?

Although much larger and more trustworthy than previous registries that did not observe worse outcomes in ACHD patients treated with NOACs, this retrospective analysis is not a randomized

controlled study.⁴ Even when statistical analyses adjust for confounding factors with propensity score matching or in a multivariable model, no registry can fully exclude selection bias. The reasons why physicians opt for NOACs or VKAs in this challenging group of patients cannot be fully controlled for, even with sophisticated statistical analyses. Nonetheless, these striking and unexpected observations need consideration in clinical practice.

VKAs beat NOACs: precedents

Whereas atrial fibrillation and venous thrombo-embolism encompass the vast majority of indications for long-term anticoagulation, patients with mechanical heart valves also require life-long anticoagulation. A phase II study comparing dabigatran with VKAs in adults with a mechanical heart valve was halted because more thrombo-embolic events and more bleedings were observed with dabigatran.⁵

Also patients diagnosed with the antiphospholipid syndrome and tested positive for lupus anticoagulant, anticardiolipin antibodies, and beta-2 glycoprotein 1 antibodies experienced more recurrent thrombosis, mainly arterial thrombosis and stroke, when treated with NOACs compared with a VKA.⁶

Hence, the indication for anticoagulant therapy and its underlying pathophysiology may impact the efficacy and safety of NOACs and VKAs in a different way. Mechanistically, clot initiation in the left atrial appendage is triggered by stasis, whereas stasis, hypercoagulability, and vessel wall damage constitute Virchow's triad for venous thrombo-embolism. Here, thrombo-embolism is adequately prevented by targeting a single factor of the coagulation amplification. Pharmacologically, NOACs inhibit one activated coagulation factor, i.e. thrombin for dabigatran and factor Xa for rivaroxaban, edoxaban, and apixaban, whereas VKAs reduce levels of the zymogen

Figure 1 Differential outcomes with NOACs vs. VKAs. MACE, major adverse cardiovascular event; NOAC, non-vitamin K oral antagonist; RCT, randomized clinical trial; RR, relative risk; VKA, vitamin K antagonist. *The analysis of the high-dose NOACs is presented¹; **calculated from Cerdà et al.⁶

coagulation factors of the extrinsic pathway (FVII), the intrinsic pathway (FIX), and the common pathway (FX and FII).

ACHD: a heterogeneous patient group

Most patients in the ACHD registry had atrial fibrillation (66%) or venous thrombo-embolism (14%), and still VKAs appeared to be the better choice. The conundrum as to why ACHD patients seem to respond differently from adults with atrial fibrillation and venous thrombo-embolism studied in the landmark randomized clinical trials is unresolved and requires further study. Indeed, the CHA₂DS₂-VASc score, while commonly used in ACHD, has not been developed or validated for ACHD patients. The recent ESC guidelines on adult congenital heart disease highlight that patients with ACHD are at increased risk for thrombo-embolic events, but that the evidence for

preventive treatment is limited.⁷ In the study by Freisinger et al., patients with mechanical heart valves were rightly excluded from the analysis. However, some patients received anticoagulation because of the congenital heart defect itself. Indeed, patients with a Fontan circuit with low pulmonary blood flow are at risk of local thrombus formation. Similarly, cyanotic patients with the Eisenmenger syndrome may benefit from anticoagulation. Here, dedicated controlled studies are required to identify the optimal anticoagulant strategy.⁷

Should we switch adults with congenital heart disease back to VKAs?

The study of Freisinger et al. highlights that currently almost half of the anticoagulated ACHD patients are treated with NOACs. NOACs are more convenient because they do not require routine monitoring,

and because they less frequently cause intracranial and life-threatening bleeding. As observed in this large registry, NOACs may not be the optimal anticoagulants for all ACHD patients. In some patients with a congenital heart defect, contact activation may play a more important role in the hypercoagulability, explaining the excess of thromboembolic events in this patient group. It will thus be important to differentiate between ACHD patients with atrial fibrillation or venous thrombo-embolism, ACHD patients in whom the complexity of the congenital heart defect itself is the reason for anticoagulation, and ACHD patients with combined indications for anticoagulation. New controlled studies are needed for this growing patient group with ACHD. These future studies will need to take into account the complexity of the congenital heart defect, possible complications such as atrial fibrillation, and other patient characteristics relevant for the choice between no anticoagulation, NOACs, or VKAs. The design and financing of such controlled studies will be a challenge in the era of generic NOACs. Scientific societies and healthcare funding agencies will need to come up with an innovative study design to investigate the optimal anticoagulant strategy in the growing group of patients with ACHD. Meanwhile, physicians caring for ACHD patients will need to carefully evaluate the risk and benefits of anticoagulation, realizing that NOACs may not offer the same benefits as in patients with acquired cardiovascular diseases and, in fact, may be harmful. Awaiting the results of controlled studies, it is wise to use VKAs as the standard anticoagulant therapy in ACHD and consider NOACs for selected cases after consultation with a multidisciplinary team.

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