Off-Label Use of Direct Oral Anticoagulants in Intracerebral Hemorrhage Patients With Prosthetic Valves

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The Case

A 75-year-old man with a prosthetic mechanical valve presents with a cortical intracerebral hemorrhage and international normalized ratio of 2.7. Magnetic resonance imaging shows 3 to 4 microbleeds (mixed lobar and deep).

The Question

Should the patient be resumed on warfarin or should off-label use of direct oral anticoagulants be considered?

The Controversy

Off-label use of direct oral anticoagulants in intracerebral hemorrhage patients with prosthetic valves.

Yes, Off-Label Use of Direct Oral Anticoagulants Should Be Considered in Intracerebral Hemorrhage Patients With Prosthetic Valves

Seemant Chaturvedi

In this patient, the conventional treatment approach would be to place him back on a vitamin K antagonist (VKA) once the hemorrhage has stabilized and then recommend close monitoring of the international normalized ratio (INR) in the future. However, at times, an unconventional treatment strategy may be best for the patient.

In this patient scenario, there are several facts to consider. First, the patient has already bled once in the brain with an INR within the therapeutic range. Second, he has evidence of microbleeds on magnetic resonance imaging, some of which are cortical. This raises concern for potential cerebral amyloid angiopathy. Third, it is known that patients with cerebral amyloid angiopathy have an elevated risk for oral anticoagulant (OAC)–related brain hemorrhage.

Given this constellation of facts, it would be wise to discuss with the patient and family the full range of potential treatment options. On the basis of trials in patients with atrial fibrillation, it is established that direct oral anticoagulant (DOAC) medications have a substantially lower risk of intracerebral hemorrhage (ICH) compared with warfarin. The marked reduction in ICH makes DOACs particularly attractive for patients at increased ICH risk. This category includes elderly patients, patients in whom therapeutic anticoagulation is difficult to keep in the proper INR range and patients with prior ICH.

Some clinicians may be hesitant to use DOACs in this patient because of the mechanical heart valve and lack of atrial fibrillation. However, patients with moderate-to-severe valvular disease have been treated with DOACs with very good results. In a combined analysis of 4 pivotal trials evaluating DOACs in patients with atrial fibrillation, there were >10 000 patients enrolled with moderate-to-severe mitral regurgitation.[1] In addition, 873 patients had prior heart valve surgery. Among patients with valvular heart disease in these 4 trials, there was no heterogeneity for prevention of embolic stroke and there was a 53% reduction in ICH. With apixaban, the reduction in hemorrhagic stroke was 60% in patients with valvular heart disease.[2]

I concede that the main trial that evaluated dabigatran in patients with artificial valves (RE-ALIGN study [Randomized Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran in Patients After Heart Valve Replacement]) did not show efficacy of dabigatran.[3] However, I believe the study design was flawed. Patients were enrolled too soon after the cardiac surgery, and this created excess bleeding risks. Some patients were even treated within 3 to 7 days of major cardiac surgery. It would be valuable to conduct new studies of patients treated with DOACs several months after they receive a prosthetic heart valve. If such a trial included patients at increased risk for ICH, it very well could demonstrate a lower risk of overall stroke (and ICH) with DOAC treatment. With regard to DOACs and mechanical valves, a previous editorialist commented that "there is a palpable downside … to premature abandonment of research into the use of such drugs in patients with mechanical heart valves.[4]"

The opinions expressed in this article are not necessarily those of the American Heart Association.

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In the event that this patient had a second ICH, emerging data show that outcomes of DOAC- and VKA-related ICH are similar. In a recent series of 500 patients from 13 stroke registries, including 97 with DOAC-related ICH, hematoma expansion, 90-day mortality, and functional outcome were similar for patients with NOAC- and VKA-related ICH.[5] Ninety-day mortality was still substantial at 31% in the VKA group and 33% in the DOAC group. With the development of specific reversal agents, it is possible that outcomes of DOAC-related ICH could be better than VKA-related ICH in the future.

As clinicians, we should pursue treatment approaches that reduce the risk of serious adverse medication effects. If we have an option (DOACs) that is associated with a 50% to 60% reduction in the risk of an event with 30% to 35% mortality, isn't it the wise choice to think outside the box and offer off-label DOAC treatment? If we stubbornly stick with conventional treatment approaches, it will be difficult to make progress in reducing the rate of iatrogenic ICH and our patients will be worse off.

No, Off-Label Use of DOACs Should Not Be Considered in ICH Patients With Prosthetic Valves

Stefan Hohnloser and Hans-Christoph Diener

Prosthetic heart valve surgery is performed in several hundred thousand patients with severe valvular heart disease each year.[6] Mechanical and bioprosthetic heart valves are the predominant valve types with mechanical valves having a superior durability, albeit at the expense of a much higher and persistent risk of thrombosis. The need for lifelong anticoagulant therapy in patients with mechanical heart valves is not debated because observational studies have demonstrated that the use of antiplatelet therapy is associated with prohibitive high rates of thromboembolic events.[7] As recommended by current European and North American guidelines,[7,8] long-term anticoagulation of mechanical prostheses utilizes VKAs with the INR adapted to the characteristics of the prosthesis and the patient.[7] VKA therapy, however, is associated with several limitations such as the difficulty to achieve a time in therapeutic range >65% to 70%, restrictions on diets, numerous interactions with other medications, and need for lifelong coagulation monitoring. This has resulted in an extensive and successful search of new oral anticoagulants with direct thrombin or factor Xa inhibitors representing the new therapeutic standard for instance in stroke prevention in atrial fibrillation. Hence, the question arises whether the non–vitamin K oral antagonists (DOACs) can substitute VKAs similarly in patients with mechanical heart valves.

Unfortunately, the answer is clearly no. US guidelines have assigned a class III (harm) indication to the DOACs in patients with prosthetic heart valves.[8] This recommendation is based on several case reports demonstrating thrombosis on mechanical valves despite therapeutic dosing with DOACs. Of note, one dedicated randomized trial examined the question whether dabigatran would represent a suitable alternative to VKA in this clinical scenario. In this phase II study, patients were assigned to warfarin or dabigatran therapy, the later dosed in a way to achieve a trough plasma level of at least 50 ng/mL.[3] This trial was prematurely stopped by the data safety monitoring board because of an excess not only in thromboembolic but also in bleeding events. Specifically, there were 9 ischemic or unspecified strokes in the dabigatran group but none in the warfarin group. Whereas the causes for this lack of protection by dabigatran have not been fully elucidated, it seems likely that warfarin is more effective than dabigatran at suppressing coagulation activity because it inhibits the activation of both tissue factor–induced coagulation (by inhibiting the synthesis of coagulation factor VII) and contact pathway–induced coagulation (inhibition of factor IX).[4] There are other preclinical studies with different DOACs looking at their ability to provide effective and safe anticoagulation in the presence of mechanical heart valves, but no studies in humans have been conducted as yet.

The present case is further complicated by the presence of cerebral microbleeds. These hemosiderin deposits caused by minor bleeding from microangiopathy[9] may be located either in deep regions of the brain or more lobar, with a higher bleeding risk associated with the latter. Most commonly, cerebral microbleeds are associated with cerebral amyloid angiopathy and poorly controlled hypertension.[9] Studies in patients with atrial fibrillation have found a potential association between the number of cerebral microbleeds and the risk of intracerebral bleeding with >5 microbleeds indicating a high risk.[10] Unfortunately, there are no specific studies dealing with patients fitted with mechanical heart valves and cerebral microbleeds. On the other hand, even in patients with atrial fibrillation, evidence of optimal stroke preventive treatment in the presence of cerebral microbleeds is sparse. As yet, there are no controlled studies comparing DOACs with VKAs in this patient population. Several clinical trials in patients with atrial fibrillation are currently underway.[9] Until more evidence stemming from controlled clinical studies becomes available, expert consensus recommends stroke prevention by oral anticoagulation in the majority of patients with a diagnosis of cerebral microbleeds. Because of the significantly lower incidence of intracerebral bleedings associated with the use of DOACs (compared with warfarin), preference should be given to one of these agents.[9] In elderly subjects, the lower NOAC doses may be considered.

In our patient, however, the underlying prothrombotic condition is not atrial fibrillation but the presence of a prosthetic heart valve. For the reasons outlined, we firmly believe that off-label use of DOACs in ICH patients with prosthetic heart valves is prohibitive and should not be considered as a therapeutic option, even in the presence of cerebral microbleeds. Unfortunately, this patient will remain at high risk of recurrent intracerebral bleeding which may occur even at therapeutic INR levels.

Rebuttal By Dr Chaturvedi

My opponents argue that because there is no high-level clinical trial data demonstrating the safety and efficacy of DOACs in patients with a mechanical valve, we should continue to use warfarin. He includes the RE-ALIGN randomized trial in his argument.

However, if one examines the RE-ALIGN study closely, one will notice that a group called Population B was

included in the trial. Population B represents patients in whom the valve was implanted at least 3 months before study enrollment. In this small group of 53 patients, there were no stroke events, systemic emboli, or deaths in either the dabigatran or warfarin group. Therefore, this supports my contention that in patients at elevated bleeding risk who have had the valve placed several months ago, further study is warranted.

Finally, my opponent does not address the issue of what type of stroke poses a higher risk of death for the patient? Is it an embolic stroke or an OAC-related ICH? Considering that the patient has recently had an ICH with an INR in the therapeutic range, the risk of another OAC-related ICH is considerable. And this would engender a higher risk of fatality compared with an ischemic stroke. Therefore, off-label DOAC use is worth a discussion with the patient and family.

Rebuttal By Drs Hohnloser and Diener

We certainly agree with Dr Chaturvedi that this is an exceptionally difficult to treat patient. We also agree with all of his arguments about the reduction of bleeding risk, particularly bleeding into the brain, which has been demonstrated for DOACs over VKA. However, his statements about the efficacy and safety of DOAC therapy in patients with atrial fibrillation and moderate-to-severe valvular disease deserve clarification. In the meta-analysis of Renda et al[1] and in the study of Avezum et al,[2] patients with mechanical heart valves (MHV) were excluded from all of the DOAC trials. Current guidelines list mechanical heart valves as a clear contraindication for the use of DOACs for stroke prevention. Similarly, the discussion of the RE-ALIGN study needs some comments. Whereas Dr Chaturvedi focuses on the bleeding complications observed in that trial, he does not discuss the lack in efficacy which was observed with dabigatran. In fact, 9 of 168 (5%) patients on dabigatran had a stroke compared with 0/84 warfarin-treated patients.[4] All major bleeding events consisted of pericardial bleeds. As pointed out earlier, warfarin is more effective than dabigatran at suppressing coagulation activity because it inhibits the activation of both tissue factor–induced coagulation (by inhibiting the synthesis of coagulation factor VII) and contact pathway–induced coagulation (inhibition of factor IX). Furthermore, this lack of efficacy was observed despite high doses of dabigatran and careful monitoring of dabigatran plasma level, which is not done in routine clinical practice. In summary, therefore, despite the undisputable advantages of DOACs over VKA in patients with nonvalvular atrial fibrillation, DOACs are no valid alternative for this patient.

Comments by Drs Molina and Selim

The safety and efficacy of using anticoagulation for MHV requires a delicate balance of the risk of thromboembolic events and bleeding. Resuming warfarin in an MHV patient with suspected cerebral amyloid angiopathy who just had an ICH with an INR within the therapeutic range looks like spining the revolver cylinder again in a Russian roulette. Could off-label use of DOACS stop this macabre and lethal game of chance? Given its excellent safety profile in stroke prevention for patients with AF, using DOACs seems to be an attractive and even intuitive alternative to warfarin in patients with MHV. However, in the RE-ALIGN trial, dabigatran was compared with warfarin in 2 strata of patients with MHV: those with newly implanted valves and those with valves implanted >3 months before randomization. The study was stopped early because of more ischemic strokes and bleeding with dabigatran. Furthermore, in patients with newly implanted valves, there was a trend for more pericardial bleeding with dabigatran than with warfarin, a finding that precluded dabigatran dose escalation. RE-ALIGN results led to a black box warning advising against the use of dabigatran in patients with MHV. In patients with MHV, dabigatran, rather than stopping the Russian roulette, would be the finger that fires the gun.

Several differences between patients with AF and those with MHV preclude extrapolations of the safety and efficacy profile of DOACs. First, compared with patients with AF, the higher doses of anticoagulants and greater intensity of anticoagulation needed to prevent ischemic stroke in patients with MHV confer this patient population an extremely high bleeding risk. Second, compared with native valves, mechanical valves induce a greater generation of thrombin concentrations that overwhelms the effect of dabigatran,[11] this may explain the increased risk of ischemic strokes seen in RE-ALIGN trial. In the RE-ALIGN protocol, dabigatran dose escalation to 300 mg BID was allowed in an attempt to maintain trough plasma concentrations at 50 ng/mL. Recent studies demonstrate that a trough plasma levels of dabigatran at 260 ng/mL would be needed to attenuate thrombin generation by mechanical valves components, which translates into a dose of 620 mg twice daily to achieve this target trough plasma levels,[11] a dose more than double the maximum dose administered in the RE-ALIGN study and 4× the dose approved for patients with AF. This high dabigatran dose needed to effectively prevent embolic events in patients with MHV is unfeasible, skyrocketing bleeding risk in this population. Whether oral FXa inhibitors would be superior to dabigatran in patients with MHV is uncertain. Third, although patients with microbleeds on magnetic resonance imaging and suspected cerebral amyloid angiopathy have an increased risk for warfarin-related ICH, there is no currently available evidence from randomized controlled trials that DOACs have a better safety profile compared with warfarin in this patient population.

In our illustrative case, the patient had an ICH with an INR in the proper therapeutic range (INR, 2.7). A third option for our patient would be playing the Russian roulette game with a half-charged revolver. Low anticoagulation intensity (INR between 2.0 and 2.5) has been shown to be more beneficial for the patients with MHV using the lowest thrombogenic risk bileaflet valves. However, for other types of MHV, this level of OAC would be insufficient.

In summary, despite their clear advantages over warfarin for stroke prevention in patients with AF, DOACs are still far to be a valid and evidence-based alternative for patients with MHV. In our patient, sticking to warfarin in a Russian roulette game remains a better option than jumping off the DOAC plane without a parachute.

Disclosures

Dr Hohnloser received honoraria for contribution to advisory boards or membership of speaker's bureau from Bayer Healthcare, BMS, Boehringer Ingelheim, Boston Scientific, Cardiome, Forest RI, Gilead, J&J, Medtronic, Otsuka, Pfizer, Portola, Sanofi Aventis, Servier, and St. Jude Medical. Dr Diener received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, St. Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, National Institutes of Health, Bertelsmann Foundation, and Heinz-Nixdorf Foundation. Dr Diener has no ownership interest and does not own stocks of any pharmaceutical company. The other authors report no conflicts.

References

1. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-Vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol*. 2017;69:1363–1371. doi: 10.1016/j.jacc.2016.12.038.
2. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *Circulation*. 2015;132:624–632. doi: 10.1161/CIRCULATIONAHA.114.014807.
3. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–1214. doi: 10.1056/NEJMoa1300615.
4. Hylek EM. Dabigatran and mechanical heart valves–not as easy as we hoped. *N Engl J Med*. 2013;369:1264–1266. doi: 10.1056/NEJMe1310399.
5. Wilson D, Seiffge DJ, Traenka C, Basir G, Purrucker JC, Rizos T, et al; CROMIS-2 Collaborators. Outcome of intracerebral hemorrhage associated with different oral anticoagulants. *Neurology*. 2017;88:1693–1700. doi: 10.1212/WNL.0000000000003886.
6. Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet*. 2009;374:565–576. doi: 10.1016/S0140-6736(09)60780-7.
7. Iung B, Rodés-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. *Eur Heart J*. 2014;35:2942–2949. doi: 10.1093/eurheartj/ehu365.
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:e57–e185. doi: 10.1016/j.jacc.2014.02.536.
9. Selim M, Diener HC. Atrial fibrillation and microbleeds. *Stroke*. 2017;48:2660–2664. doi: 10.1161/STROKEAHA.117.017085.
10. Karayiannis C, Soufan C, Chandra RV, Phan TG, Wong K, Singhal S, et al. Prevalence of brain MRI markers of hemorrhagic risk in patients with stroke and atrial fibrillation. *Front Neurol*. 2016;7:151. doi: 10.3389/fneur.2016.00151.
11. Jaffer IH, Stafford AR, Fredenburgh JC, Whitlock RP, Chan NC, Weitz JI. Dabigatran is less effective than warfarin at attenuating mechanical heart valve-induced thrombin generation. *J Am Heart Assoc*. 2015;4:e002322. doi: 10.1161/JAHA.115.002322.

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