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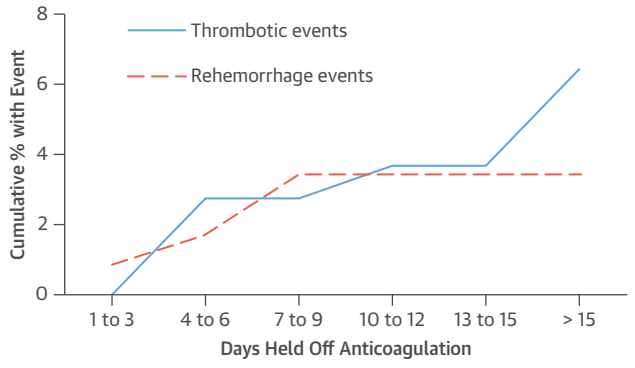
Letters

Risks of Thrombosis and Rehemorrhage During Early Management of Intracranial Hemorrhage in Patients With Mechanical Heart Valves

Intracranial hemorrhage in patients with mechanical heart valves carries a risk of thrombosis and of rehemorrhage. Because interruption of anticoagulation with a mechanical heart valve may lead to thrombotic events, cardiologist recommendations generally lean toward minimizing the time off anticoagulation, although valve guidelines do not specifically address the duration of anticoagulation interruption (1,2). At the same time, when anticoagulation is resumed in these patients, there is a risk of recurrent hemorrhage, and longer periods of anticoagulation interruption should, in theory, reduce the risk of rehemorrhage. Because this scenario is rare, the extent of these 2 competing risks is poorly understood. Data regarding these risks come from small single-center retrospective case series, with the largest series to date consisting of 52 patients with intracranial hemorrhage on anticoagulation for mechanical valves (3).

FIGURE 1 Cumulative Distribution of Thrombotic and Hemorrhage Events



The x-axis plots 3-day bins of time off anticoagulation; the y-axis displays cumulative percentage with thrombotic events during anticoagulation interruption **(solid line)** and with intracranial rehemorrhage after resumption of anticoagulation **(dashed line)**.

To help clarify the risks of thrombosis and rehemorrhage during the early management of intracranial hemorrhage in patients with mechanical heart valves, we performed a multicenter retrospective chart review over a 16-year period (1996 to 2011) in an integrated health care delivery system (Kaiser Permanente Northern California: 18 hospital centers, >3 million patients). Patients were identified by clinical database query with confirmation of all cases by manual chart review. Patients with mechanical valves with or without concomitant atrial fibrillation were included, but patients with bioprosthetic valves were not included.

We identified 141 mechanical heart valve patients who had a total of 153 intracranial hemorrhage events. Forty-four patients died from their initial intracranial hemorrhage; the remaining 109 hemorrhage events had both interruption and resumption of anticoagulation without hemorrhage expansion during anticoagulation interruption. All 109 received warfarin reversal agents and completed warfarin reversal. Operative neurosurgical intervention for the hemorrhage event was performed in 32 of 109 (29.4%). Ninety-eight mechanical heart valves (63.8%) were 1 device type (St. Jude Medical, St. Paul, Minnesota). Thirty-nine (27.7%) mechanical valves were in the mitral position, 78 (55.3%) were in the aortic position, 21 (14.9%) were in both mitral and aortic positions, and 3 (2.1%) were in another position.

Thrombotic events occurred in 7 of 109 patients during anticoagulation interruption (6.4%; 95% CI: 2.6% to 12.8%), including 5 ischemic strokes, 1 episode of valve thrombosis, and 1 fatal cardiac arrest of unknown etiology. Thrombotic events occurred in 5 of 52 patients (9.6%) with mechanical valves in the mitral position (with or without another mechanical valve), compared to 2 thrombotic events in 57 patients without a mitral mechanical valve (3.5%), but this difference was not significant ($p = 0.26$). The type of warfarin reversal agent used was not predictive of the risk of thrombotic events.

Rehemorrhage within 2 weeks of anticoagulation resumption occurred in 4 of 109 patients (3.7%; 95% CI: 1.0% to 9.3%). All rehemorrhage events occurred

in patients with subdural hematomas (4 of 48 patients; 8.3%) and consisted of significant increase in subdural hemorrhage with clinical deterioration; no rehemorrhages occurred in other types of intracranial hemorrhage (0 of 61 patients; 0%) ($p = 0.04$). No rehemorrhages occurred in the 32 patients who had neurosurgical intervention for their initial hemorrhage, compared to 4 recurrent hemorrhages in the 77 patients without neurosurgical intervention, but this difference was not significant ($p = 0.32$).

All rehemorrhage events occurred during anticoagulation resumption after ≤7 days of anticoagulation interruption, while less than one-half of the thrombotic events occurred during an anticoagulation interruption of ≤7 days (**Figure 1**).

Both thrombotic and rehemorrhage events are relatively uncommon when anticoagulation is interrupted in mechanical heart valve patients with intracranial hemorrhage. While clinical decisions regarding anticoagulation interruption must be tailored to an individual patient's clinical situation, a general strategy of interrupting anticoagulation for 7 to 10 days may minimize the risk of both thrombotic and rehemorrhage events. Mechanical heart valve patients with subdural hematoma may be a group with a higher risk of recurrent hemorrhage.

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Pathology of Intercalated Discs in Friedreich Cardiomyopathy

Friedreich ataxia (FA) is best known for its neurological phenotype, but the most common cause of death is heart disease (1). The pathogenesis of FA cardiomyopathy includes failure to clear iron from myocytes, chronic inflammation, fiber necrosis, and scarring (2). On cross section, heart fibers are significantly enlarged and excessively lobulated (2). In the longitudinal dimension, the pathogenesis also involves modifications of intercalated discs (ICDs), the plasma membrane specializations that connect heart fibers end-to-end. Many proteins participate in the assembly of fascia adherens junctions, desmosomes, and gap junctions (GJs) within or near ICDs (3).

Paraffin-embedded heart sections of 15 FA patients with confirmed homozygous guanine-adenine-adenine trinucleotide repeat expansions (13 autopsies, 1 biopsy specimen, 1 explant) and 12 controls (all autopsies) were stained with antibodies to N-cadherin (**Figures 1A and 1B**), α-actinin, vinculin, and desmoplakin to visualize fascia adherens junctions and desmosomes and ZO-1 and connexin 43 to reveal GJs. N-cadherin reaction product was used to measure distances between ICDs (**Figure 1B**, inset) in sections of the left ventricular wall, right ventricular wall, and ventricular septum (VS). Strips of fixed VS were processed for ultrastructural visualization of ICDs (**Figures 1C and 1D**).

In FA, all ICDs revealed by immunohistochemistry (**Figure 1A**), toluidine blue staining (**Figure 1C**, inset), or electron microscopy (**Figure 1C**) were disorganized, discontinuous, fragmented, and hyperconvoluted. N-cadherin reaction product showed an overall paucity of ICDs (**Figure 1A**). Connexin 43 reaction product revealed disorganization of ICDs as well as lateralization to plasma membranes (not illustrated). Inter-ICD distances were significantly and uniformly greater across all heart sections in FA (76 ± 11 μm) than in controls (54 ± 10 μm; $p < 0.001$, main effect of FA in analysis of variance), but did not correlate with age of onset or death, disease duration, or guanine-adenine-adenine trinucleotide repeat expansion. Distances between Z discs remained normal (**Figures 1C and 1D**).

The underlying mutation in FA causes frataxin deficiency, which may adversely affect ICDs and GJs before the onset of heart disease and perhaps prenatally. The critical step in the faulty assembly and