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Is a Dabigatran Reversal Agent Effective?

By Michael H. Crawford, MD, Editor

SYNOPSIS: A pragmatic clinical study of idarucizumab for counteracting the effects of the oral anticoagulant dabigatran showed rapid and complete reversal of its effects in patients with major bleeding or urgent surgery, without any adverse safety concerns.

SOURCE: Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med* 2017;377:431-441.

One advantage of dabigatran therapy for stroke prevention in atrial fibrillation (AF) patients is the existence of an antidote, but how well does it work? Investigators performed a multicenter, international, prospective, open-label study of idarucizumab 5 mg IV in 503 patients on dabigatran needing anticoagulant reversal, the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study.

The authors studied two groups of patients. Group A had life-threatening bleeding (n = 301). Group B required surgery and couldn't wait eight hours for hemostasis to return after stopping dabigatran (n = 202). The primary endpoint was the maximum percent reversal of anticoagulation four hours after completion of the infusion of idarucizumab as measured by either the thrombin time or the ecarin clotting time. Serial blood samples for pharmacologic studies were performed over the first 24 hours after the infusion of idarucizumab. A second dose of idarucizumab was permitted for recurrent or continued bleeding or objective evidence of residual anticoagulant effect.

Clinical outcomes were secondary endpoints. Adverse effects were attributed to idarucizumab if they occurred within five days. More than 95% of the patients were receiving dabigatran for stroke prevention in AF. The mean age was 78 years. The median percent reversed at four hours was 100%. Dabigatran concentrations fell from around 100 mg/mL to near zero within minutes of the infusion of idarucizumab and remained < 20 mg/mL for 24 hours. A second dose of idarucizumab was administered to only eight patients. In group A, 46% experienced gastrointestinal bleeding, and 33% experienced intracranial bleeding. The median time to cessation of bleeding was 2.5 hours after idarucizumab was administered. In group B, the planned surgery commenced at a median time of 1.6 hours. Perisurgical hemostasis was normal in 93%. At 90 days, about 7% of patients experienced a thrombotic event and 19% experienced mortality.

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There were no serious safety issues with idarucizumab administration. The authors concluded that idarucizumab was shown to rapidly reverse the anticoagulation caused by dabigatran without any serious safety issues.

■ COMMENTARY

Although idarucizumab worked well in animals and normal volunteers to reverse the effects of dabigatran, it is always useful to see how such agents work in real-world patients. Thus, this uncontrolled, pragmatically designed, open-label study is of interest. Clearly, idarucizumab rapidly drops dabigatran blood levels to near zero for at least 12 hours. Between 12 and 24 hours, some anticoagulant effect (dabigatran levels < 20 mg/mL) returned in about 20% of patients. The authors attributed this to the redistribution of dabigatran from extravascular spaces into the vasculature. This was associated with bleeding in only 10 patients. A second dose of dabigatran was administered to seven of these patients. Overall, only one dose of 5 mg of idarucizumab was given to 98% of patients. Anti-idarucizumab antibodies were detected in about 6% of patients, but at low titers. Three patients demonstrated possible hypersensitivity events: one with a rash who also started tramadol; one with vomiting and loss of consciousness who had intracerebral hemorrhage; and one with possible anaphylaxis who was started on amoxicillin. Other potential adverse events were observed in about one-quarter of patients, but all could be ascribed to worsening of the index event or the underlying condition of the patients.

In group B, the surgeons reported 95% of patients appeared to exhibit normal or mildly impaired hemostasis at a median start time of 1.6 hours after idarucizumab was administered. Considering these data and the safety of idarucizumab, surgery probably could start as soon as the idarucizumab is administered. In group A, the efficacy of idarucizumab is more difficult to determine. These were sick patients with a high mortality rate (7% at five days, 13% at 30 days). Also, there were many factors affecting hemostasis. Often, blood transfusions occurred and other products were administered. In addition, many received antiplatelet agents at a mean of four days, and most restarted anticoagulants at a mean of 13 days. Investigators started such agents within 72 hours in 23% of group A patients. Further, the authors noted that mortality reported in patients undergoing surgery or experiencing a major spontaneous bleeding event on warfarin is about 30%, which is higher than the 19% observed in this study. Finally, thrombotic events are to be expected if one rapidly reverses anticoagulation, but the 7% observed in this study is lower than that reported with warfarin. No procoagulant effect of idarucizumab has been observed in animals or normal human volunteers. Since there is no effective alternative to idarucizumab for reversing the effects of dabigatran, there was no comparison group, and the investigators believed that it was unethical to create a control group given the strength of the pre-clinical data. The FDA has approved idarucizumab at the doses used in this study. This makes dabigatran an attractive oral anticoagulant for patients who demonstrate indications for oral anticoagulation but are at high risk of bleeding. ■

Natriuretic Peptide-guided Therapy Does Not Improve Systolic Heart Failure Outcomes

By Van Selby, MD

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Dr. Selby reports no financial relationships relevant to this field of study.

SYNOPSIS: Among high-risk patients with heart failure and reduced ejection fraction, a strategy of titrating medical therapy to a target natriuretic peptide level was not associated with improvements in hospitalization or survival.

SOURCE: Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA* 2017;318:713-720.

Cardiac biomarkers, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), correlate with disease severity and predict adverse outcomes in heart failure with reduced ejection fraction (HFrEF). Several small trials have evaluated the use of serial measurement of biomarkers to guide titration of medical therapy for HFrEF, with mixed results.

The authors of the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study randomized patients with HFrEF to either an NT-proBNP-guided strategy or usual care. All patients were considered "high risk," defined as baseline NT-proBNP level > 2,000 pg/mL and a history of HF hospitalization or the equivalent. The median left ventricular ejection fraction was 25%. Patients in the NT-proBNP-guided group had HF therapies, titrated with the goal of achieving a level < 1,000 pg/mL. Patients randomized to usual care received HF care in accordance with guidelines, focusing on titration of neurohormonal therapies with proven efficacy in HF. The primary endpoint was a composite of time to first HF hospitalization or cardiovascular mortality.

The trial ended early because of futility after 894 of the planned 1,100 patients had been enrolled. Patients randomized to NT-proBNP-guided therapy logged more clinic visits and more adjustments to HF therapies during the study period. Over a median follow-up of 15 months, the primary outcome occurred in 37% of patients in both the NT-proBNP-guided therapy and usual care groups (hazard ratio, 0.98; $P = 0.88$). Similarly, there were no observed differences in any of the secondary endpoints, including all-cause mortality or total HF hospitalizations. There was no significant difference in the percentage of patients achieving the target NT-proBNP level of 1,000 pg/mL (46% in the guided-therapy group compared to 40% in the usual care group; $P = 0.21$). Adverse event rates were similar between the two groups. The authors concluded that among high-risk patients with HFrEF, a strategy of NT-proBNP-guided therapy is not more effective than usual care for improving outcomes.

■ COMMENTARY

Multiple large, randomized trials have shown that medical therapy substantially improves morbidity and mortality in HFrEF. These trials generally involve strict protocols with clearly specified target doses. Although these target doses subsequently are recommended in practice guidelines, clinicians and patients in the real world often fail to reach them. One aim of natriuretic peptide-guided therapy for HFrEF is to provide an objective metric to assess the adequacy of treatment, thereby encouraging clinicians to titrate medical therapy to higher doses. A recent meta-analysis of 11 trials showed a significant reduction in all-cause mortality with natriuretic peptide-guided therapy, although the individual trial results varied substantially. GUIDE-IT, the largest trial of its kind to date, failed to demonstrate any meaningful advantage to a biomarker-guided management.

There are several possible explanations for the negative result. GUIDE-IT specifically enrolled "high-risk" HFrEF, with more advanced disease than patients enrolled in previous trials of biomarker-guided therapy. With more advanced disease, there may have been higher rates of hypotension, renal failure, and other contraindications to the up-titration of medical therapy. Therefore, providers may have been unable to reach target doses, even when the NT-proBNP level suggested further increases were warranted.

Another important explanation for the negative result is the level of usual care provided to the control group. Clinicians received clear guidelines for use of neurohormonal therapy, and were encouraged to up-titrate to evidence-based doses whenever possible. Thus, patients in the usual care arm of GUIDE-IT likely received more aggressive (and therefore effective) medical therapy compared to control groups

in previous studies of biomarker-guided therapy. Patients also logged more frequent clinic visits and medication adjustments than what is seen typically in "usual" clinical care of HFrEF. Because of this more intensive therapy, patients in the control arm of GUIDE-IT saw decreases in NT-proBNP levels, comparable to what was observed in the NT-proBNP-guided arm. By comparison, control groups in prior studies have shown much smaller decreases in biomarker levels. The most recent HF guideline update from the American Heart Association/American College of Cardiology states the evidence base is too discrepant to inform specific guideline recommendations related to the use of serial natriuretic peptide measurement to guide therapy for HFrEF (Class IIb). The strength of this recommendation clearly will not increase based on the results of GUIDE-IT, and at this time the routine use of a biomarker-based approach to medication titration is not advisable. What GUIDE-IT ultimately demonstrates is the absolute importance of target doses when titrating medical therapy of HF. Reaching the doses used in pivotal clinical trials appears to be more important than any specific clinical target or marker of adequate therapy. ■

Angiotensin II Raises Blood Pressure in Patients with Vasodilatory Shock

By Samuel Nadler, MD, PhD

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Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: Infusion of recombinant angiotensin II improved blood pressure control in patients with vasodilatory shock already receiving conventional vasopressors.

SOURCE: Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017;377:419-430.

Shock is a common and life-threatening condition often seen in the ICU. Sepsis commonly causes vasodilatory shock and continues to produce a significant mortality, despite improvements in care. The treatment of shock includes fluid resuscitation and vasopressor agents such as norepinephrine, epinephrine, or vasopressin. Some patients require multiple vasopressor agents and still are unable to meet resuscitation goals.

The authors of the ATHOS-3 trial examined a new class of vasopressor agent, angiotensin II (ATII), as add-on therapy to conventional vasopressors. This study of 344 patients ≥ 18 years of age randomized patients with confirmed vasodilatory shock despite fluid resuscitation to receive an infusion of ATII or placebo in addition to conventional vasopressor agents. Vasodilatory shock was defined by cardiac index > 2.3 L/min/m^2, central venous O_2 saturation > 70% with central venous pressure > 8 mmHg with a mean arterial pressure (MAP) 55-70 mmHg despite vasopressor therapy. During the first three hours of the study, the conventional vasopressor agents were held constant while ATII or placebo could be titrated with a goal MAP > 75 mmHg. Between three and 48 hours, all vasopressor infusions could be titrated with goal MAP 65-75 mmHg. The primary endpoint was MAP > 75 mmHg or an increase in MAP of > 10 mmHg without an increase in baseline vasopressors. During the first three hours of the study, more patients in the ATII arm achieved MAP > 75 mmHg than in the placebo arm (69.9% vs. 23.4%; $P < 0.001$). During the 48-hour trial period, patients in the ATII group required less conventional vasopressors than placebo and demonstrated greater improvements in cardiovascular SOFA scores (-1.75 vs. -1.28; $P = 0.01$), although overall SOFA was unchanged at 48 hours. Patients with hypoalbuminemia were more likely not to respond to ATII therapy. Adverse effects leading to discontinuation of study medications occurred in 14.1% of patients receiving ATII and 21.5% of patients on placebo. All-cause mortality at seven and 28 days was not statistically different between the two groups.

■ COMMENTARY

ATII is a novel vasopressor agent that works via the renin-angiotensin-aldosterone system. It increases blood pressure via vasoconstriction mediation by G-coupled proteins as well as the stimulation of both antidiuretic hormone and aldosterone secretion. As in previous trials, the ATHOS-3 trial demonstrated that infusion of recombinant ATII increases blood pressure compared with placebo. However, several features of this study deserve attention. First, during the first three hours of the study, only ATII could be titrated, and other vasopressors were continued at their pre-study doses. Thus, the conclusion that ATII improved MAP does not imply that these goals could

not have been achieved with conventional vasopressors alone. Second, the primary endpoint was MAP > 75 mmHg or an increase in MAP by at least 10 mmHg. Current guidelines recommend goal MAP > 65 mmHg, and it is unclear what benefit, if any, would be achieved by increasing the MAP beyond 65 mmHg.[1] In fact, most patients enrolled in the study started with MAP > 65 mmHg (68.1% and 68.4% in the ATII and placebo groups, respectively). Thus, most patients in this trial did not exhibit an indication for additional vasopressors under current guidelines. Ultimately, the goal of shock treatment is to improve organ perfusion and preserve function. MAP is a surrogate but as with phenylephrine, vasopressors may increase MAP yet decrease perfusion. Indeed, there was no change in total SOFA scores between the two groups. Although underpowered to detect a change in mortality, no statistically significant change was observed.

The ATHOS-3 trial represents an important proof of concept trial regarding ATII as a new vasopressor in the armamentarium to treat vasodilatory shock. Clearly, ATII increases blood pressure in patients. The appropriate indications for ATII still must be established. One might consider the synergistic use of ATII to enable reducing dosing of adrenergic agonists and reduce adverse effects. However, while there were fewer episodes of supraventricular tachycardia in the ATII arm, there were more episodes of ventricular tachycardia and tachycardia overall. The notion of synergism of vasopressin with adrenergic agents is increasingly coming under question. Future well-powered and well-designed trials of ATII are required before further adoption of this agent for the treatment of vasodilatory shock. ■

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Caring for Providers: Mindfulness for Healthcare Practitioners

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: A review of studies regarding brief mindfulness interventions for healthcare providers found an association with improved measures of provider well-being and no evidence of behavioral changes.

SOURCE: Gilmartin H, Goyal A, Hamati MC, et al. Brief mindfulness practices for healthcare providers — A systematic literature review. *Am J Med* 2017; July 4. pii: S0002-9343(17)30633-2. doi: 10.1016/j.amjmed.2017.05.041. [Epub ahead of print].

The popularity of mindfulness can be a double-edged sword. Some may be wrongfully tempted to dismiss the term as part of a new trend with "Mindful Eating," "The Mindful Teen," and "Mindful Work" publications offering seemingly unlimited possibilities of finding solutions to life problems through this technique. Yet, the concept of mindfulness dates back to the late 1800s, when the term emerged as an adaptation of a Buddhist concept, *Sati*, one of the factors considered to be on the pathway to enlightenment.[1] This Buddhist construct appears unrelated to the Hindi use of *Sati*.[2]

About 100 years later, the Buddhist concept was secularized by molecular biologist and meditator Jon Kabat-Zinn, who defined mindfulness as "the awareness that arises through paying attention on purpose in the present moment, and nonjudgmentally."[3]

Medical evidence for use of mindfulness techniques, such as meditation, guided imagery, yoga, and desensitization-relaxation exercises, coexist with a more casual use in lay literature. Quality studies looking at use of these interventions to decrease stress and improve decision-making are growing.[4] Given the high-tension and high-stakes outcomes inherent in medical practices, it is no surprise that attention has been paid to the use of mindfulness techniques among medical providers.

Preliminary studies show some promise for use of mindfulness interventions in healthcare practitioners, but the time required for training medical providers in these techniques is identified as a limitation to implementation.[5] Brief interventions were developed as an attempt to surmount this obstacle. Gilmartin et al conducted a review of 14 relevant studies to determine if these brief mindfulness interventions showed significant association with improvement

in provider well-being and/or behavior. For the study purposes, brief interventions were defined as those with training periods lasting less than four hours. Within this time frame, any technique that fit a general definition of mindfulness was included. Delivery systems ranged from in-person to recordings to virtual.

Measurements of well-being included self-reports of stress and anxiety levels, depression, symptoms of burnout, and quality of life. Behavior changes were more objective and included changes in academic performance, tests of attention, or incidence of diagnostic errors.

Fourteen studies met inclusion criteria, with just more than half of the studies published since 2015. More than 800 healthcare providers participated within hospital or inpatient settings. Studies were drawn from four countries — United States (nine studies), Canada (two studies), Thailand (two studies), and Australia (one study). Almost 80% of the participants were female. Half of the studies were conducted with nurses or nursing students, while the other half used physicians, medical students, or residents.

All fourteen studies used multiple measures of provider well-being. Although several of the studies identified significant change in only a subgroup of measures of well-being, only two studies found no significant improvement in any measure of provider well-being. On the contrary, only two studies included an assessment of changes in provider behavior following intervention, and neither found a significant association between a brief mindfulness intervention and change in provider behavior. (*See Table 1.*)

■ COMMENTARY

This effort to better understand the effect of brief mindfulness interventions on healthcare providers is a welcome approach to a poorly studied area of healthcare: how to best take care of the caregivers. It is tough to argue against the concept that better-functioning providers leads to better medical care, but the scientific connection is essential to explore, delineate, and document.

While looking at the combined results analyzed in this review, it is important to be cautious assigning causality. The heterogeneity of the included studies (in design, population, methodology, and outcomes) makes understanding and generalizing these results particularly challenging. This leads to the hope that the future will bring more robust and rigorously conducted investigations to best understand interventions that offer healthcare providers the maximum benefits.

Do healthcare providers need care? Results of multiple recent studies regarding the rise of burnout in this profession, as well as the association of an engaged and empathic provider to improved care outcomes, suggest the importance of addressing symptoms of stress, anxiety, and burnout in providers.[19,20] It is interesting that this review was not able to identify any provider behaviors that were changed in association with the interventions, but important to note that only two studies attempted measurements in this area. Large-scale studies looking at specific targeted provider behaviors are needed before drawing conclusions

Table 1: Selected Outcomes of Measures of Provider Well-being

Measure	Consolidated Results	Type(s) of Intervention
Stress: measured with Perceived Stress Scale or Nursing Stress Scale	5/6 studies reported reduced stress levels with *P* values < 0.05[6,7,8,9,10]	Stress Management and Resiliency Training (SMART); 5-minute guided practice; brief home practice
Anxiety: measured with a variety of specific scales	4/5 studies reported reduced anxiety levels with *P* values < 0.05[7,8,9,10]	SMART; brief home practice
Burnout Symptoms: measured with Maslach Burnout Inventory	1/4 studies reported reduced burnout symptoms with *P* value < 0.05[6,11,12,13]	Guided daily practice; weekly practice; home practice
Mindfulness: measured with Mindfulness Attention Awareness Scale or Cognitive and Affective Mindfulness Scale	3/6 studies reported improved mindfulness with *P* values < 0.01[14,6,15,16,9,13]	5-minute guided daily practice; 5- to 20-minute online modules
Tasks of Attention: measured with self-checklists; memory scale	1 study only: results not significant[17]	20 minute guided daily practice
Medication administration errors measured by observation	1 study only: significance of results not reported (embedded in a multifaceted intervention)[18]	Mindful breathing prior to medication administration or med prep

regarding brief mindfulness interventions and these type of outcomes.

Prior to this publication, studies of the effect of mindfulness interventions for healthcare providers concluded that the techniques hold promise for the field, but that the time required to train, practice, and implement represented a significant barrier to use in hospital work.[5,21] This review study helps bring some clarification to this area, suggesting that brief mindfulness training is associated with a reduction in healthcare providers' perception of stress and anxiety. The results do not lean strongly toward any one type of training — it may be that the type of mindfulness training is not as important as accessibility to providers.

It is worth noting that although many studies measured lower rates of stress and anxiety, few studies showed an association of these brief measures with reduction in burnout symptoms. This is consistent with other studies in the area of provider burnout that have suggested the need for organizational interventions along with individual interventions to affect this syndrome.[22]

Criteria for inclusion in this review were limited to studies only involving inpatient settings; the results showed no evidence or implication that these brief measures have a place in outpatient settings. Healthcare providers work in many environments — even within the broad categories of inpatient and outpatient work specifics of job description — and patient population, administrative strategies, and mission create unique, site-specific demands and challenges. It is not clear how to generalize results of studies (such as the ones included in this review) to all settings and to all healthcare providers, but it is important to clarify this point through future work. Even though data are lacking, there is little evidence of downsides to the use of brief techniques and time commitment, the only identified barriers to the use of the more comprehensive mindfulness interventions.

In the practice of medicine, we tend to rely on evidence-based studies to make recommendations to our patients. Make no mistake — we should expect no less for ourselves. Despite some limitations to the studies, the results point to clear potential benefits of incorporating a degree of mindfulness into the professional life of healthcare providers. Providers can be confident that trying a time-limited or more extensive mindfulness technique to help modulate stress and/or anxiety has merit and emerging evidence of effectiveness. ■

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CME QUESTIONS

1. In the uncontrolled open-labeled study by Pollack and colleagues, what was the median percentage of patients whose dabigatran anticoagulation was reversed with idarucizumab at 4 hours?

a. 25%

b. 50%

c. 75%

d. 100%

2. In the GUIDE-IT trial published by Felker, et al., high-risk patients with heart failure with reduced ejection fraction (HFrEF) were treated based either on usual guidelines or to an NT-proBNP-guided strategy. Which group of patients had better outcomes?

a. The usual care (control) group had significantly better outcomes.

b. The NT-proBNP-guided strategy group had significantly better outcomes.

c. There was no difference between the two groups.

d. The usual care group had a shorter time to repeat hospitalization but a lower mortality.

3. In the randomized, placebo controlled trial reported by Khanna and co-investigators, in patients on vasopressors with vasodilatory shock, the use of angiotensin II (ATII) increased blood pressure compared to placebo. What other outcomes were observed?

a. No difference in survival or organ dysfunction.

b. Increased risk of acute kidney injury

c. Decreased risk of acute kidney injury

d. Increased survival

[IN FUTURE ISSUES]

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