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Pass on the Investment Casino
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The Official Voice of Emergency Medicine

APRIL 2021 Volume 40 Number 4 FACEBOOK/ACEPFAN TWITTER/ACEPNOW ACEPNOW.COM

PLUS

EQUITY EQUATION

Moving from Race-Based to Race-Conscious Care

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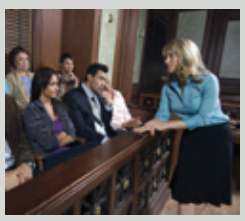

MEDICOLEGAL MIND

Physician on Trial: What to Expect

SEE PAGE 22

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For more clinical stories and practice trends, plus commentary and opinion pieces, go to:
www.acepnow.com

BECOMING THE PATIENT

SEVERAL EMERGENCY PHYSICIANS SHARE THEIR EXPERIENCES RECOVERING FROM COVID-19

The COVID-19 pandemic has stressed our health care system in many ways. It has strained hospital capacities, caused shortages of supplies and equipment, and required health care workers to take extra shifts and work without days off. Many physicians, nurses, and other health care workers have contracted COVID themselves, some requiring hospital stays and long recoveries. *ACEP Now* interviewed several emergency physicians who had COVID-19 to hear about their personal experiences and what they learned by being the patient. *Responses have been edited for length and clarity.*

CONTINUED *on page 16*

Dr. Ramon Johnson donating convalescent serum after recovering from COVID-19.

RAMON JOHNSON

NEMPAC Update

PAC Reviews Giving Criteria, Continues Legacy of Activism

by PETER J. JACOBY, MD, FACEP; GILLIAN SCHMITZ, MD, FACEP; WILLIAM PAUL JAQUIS, MD, MSHQS, FACEP; AND ARVIND VENKAT, MD, FACEP

As our National Emergency Medicine Political Action Committee (NEMPAC) Board examined our accomplishments in the 2020 election cycle and prepared for the 117th Congress, an act of violence took place at our nation's Capitol on Jan. 6, 2021. This event and votes that day to certify the election results generated thoughtful, and sometimes emotional, communications from ACEP members to our Board and ACEP leaders.

Many suggested the day's events should be integrated into NEMPAC's giving criteria going forward and some members of Congress should be held accountable. For the past several months, our Board has been thoroughly evaluating our current criteria and considering the viewpoints of ACEP members who have called, emailed, and responded to a member-wide NEMPAC survey.

CONTINUED *on page 20*

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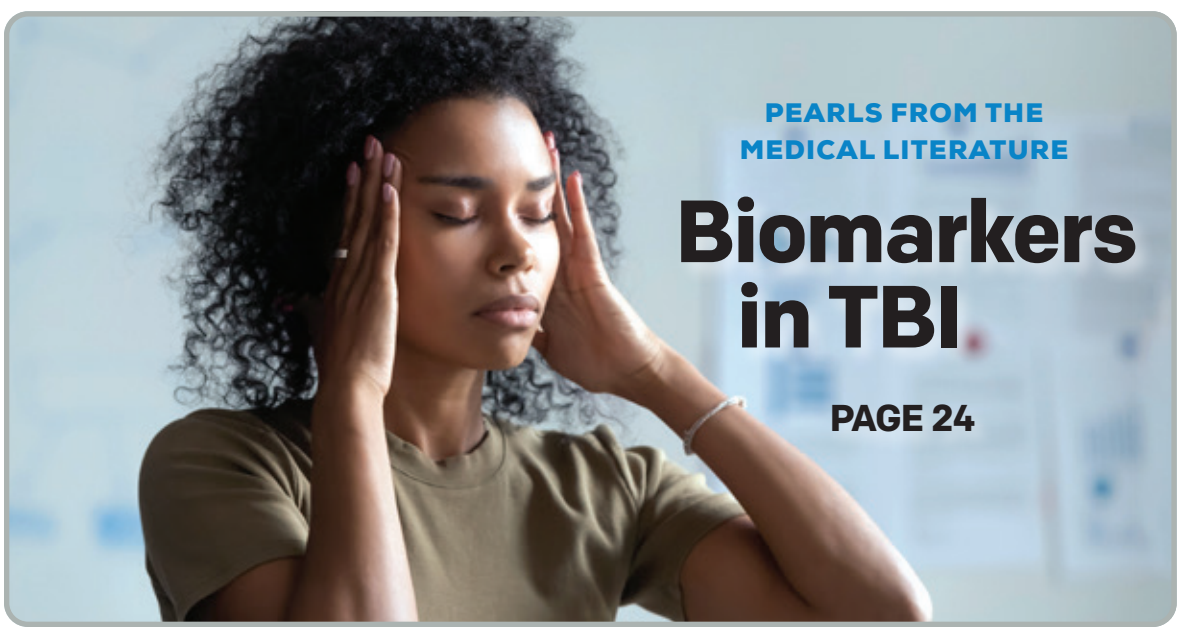

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NEWS FROM THE COLLEGE

UPDATES AND ALERTS FROM ACEP

New and Improved COVID-19 ED Management Tool

One of ACEP's most popular resources, the COVID-19 Severity Index Classification Tool, has been updated and expanded into the COVID-19 ED Management Tool. The new tool walks clinicians through the following steps in the management of COVID-19 patients: severity classification, risk prognostication/assessment, diagnostic testing/interpretation, disposition, and treatment. The tool now offers treatment recommendations curated from guidelines from the National Institutes of Health and Infectious Diseases Society of America and are consistently updated as the evidence on therapeutic options evolves. Smart phrases have been included so clinicians have guidance on the appropriate documentation to include in the electronic medical record based on the management approach that is best for each patient. Get the tool at www.acep.org/covid19-management-tool.

Join Your Peers in Washington, D.C., This July

The ACEP Leadership & Advocacy Conference (LAC) is returning to Washington, D.C., July 25–27. Emergency physicians have served on the front lines of the COVID-19 pandemic for more than a year, and their voices have never been more important or powerful. First-time attendees can participate in training sessions to learn tips for educating members of Congress on issues relevant to emergency physicians.

A large component of LAC is meeting with your members of Congress.

Note: ACEP anticipates congressional offices will be doing in-person meetings in July. If that changes, the event will be held virtually. Register at www.acep.org/lac.

Apply for ACEP Committees by May 1, 2021

The process to select members to serve on ACEP committees is under way, and all ACEP members are encouraged to apply. ACEP has more than 35 committees and task forces working on issues including ethics, EM practice, pediatric emergency medicine, disaster medicine, and more. Applications are due May 1, and more information is available at www.acep.org/committees.

Virtual Grand Rounds

April marks one year since ACEP started its monthly Virtual Grand Rounds (VGR), designed by ACEP's Academic Affairs and Education Committee to help emergency physicians and residency programs during social distancing. The program continues with new offerings through July. (Note that there is no VGR scheduled for June.)

- **April 28, 2021:** Communication: Difficult Conversations
- **May 19, 2021:** ENT Emergencies
- **July 28, 2021:** Health Care Policy

All ACEP members have free access to past VGR topics in the Online Learning Collaborative. Topics include COVID-19, Wellness, Airway, Ultrasound, Pediatrics, International, Neurology, Cardiology, Social Emergency Medicine, and Injury Prevention.

Spring Job Fair Coming in May

The latest virtual job fair hosted by ACEP and emCareers.org is coming up May 20, 2021. It's a great opportunity to "meet" virtually with employers and learn more about the diverse job settings and roles available in emergency medicine. Learn more at www.acep.org/careers.

PEERcert+ Train. Test. Thrive.

ACEP Launches New Exam Prep Tool

In late March, ACEP launched PEERcert+, a new tool designed specifically to help meet your certification needs. PEERcert+ offers new, updated, and thoroughly reviewed core content questions as well as board-style case series questions. The tool also includes Key Advance questions designated by the American Board of Emergency Medicine (ABEM) as "need-to-know" on recent changes in practice. Earn CME hours with each module, test yourself with ABEM exam-style questions, and create your own personalized study plan to help you prepare at your own pace. PEERcert+ includes image-based study aids and lets you address content gaps with customized quizzes. Learn more at www.acep.org/peercertplus.

Honoring Outstanding Medical Students

Congratulations to the winners of the 2021 ACEP/Emergency Medicine Residents' Association National Outstanding Medical Student Awards:

- Abraham Akbar, Baylor College of Medicine, Houston
- Jaskaran Bains, Weill Cornell Medical School, New York City
- Carolina Ornelas, University of California, San Francisco
- Samuel Rouleau, Mayo Clinic Alix School of Medicine, Rochester, Minnesota
- Joyce Wahba, University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City

ACEP Nowcast
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Check Out *ACEP Now* Podcasts

Did you know that *ACEP Now* has a monthly podcast? In ACEP Nowcast, Medical Editor in Chief Dr. Jeremy Faust highlights can't-miss articles from the latest issues of *ACEP Now*. Listen to the current installment and past podcasts at www.acepnow.com/podcast or subscribe through your favorite podcast service.

Eliquis® (apixaban) tablets 5mg 2.5mg

*BASED ON CLINICAL TRIAL DATA VS ENOXAPARIN/WARFARIN IN PATIENTS WITH DVT/PE.

Visit EliquisData.com

INDICATION

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

Please see additional Important Safety Information and accompanying Brief Summary of Full Prescribing Information, including **Boxed WARNINGS,** on the adjacent pages.

AMPLIFY study design[1,2]

A randomized, double-blind, phase III trial to determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent venous thromboembolism (VTE)* or VTE-related death in 5400 patients with objectively confirmed, symptomatic proximal deep vein thrombosis (DVT)/pulmonary embolism (PE). 2693 patients were randomized to ELIQUIS 10 mg orally twice daily for 7 days followed by 5 mg orally twice daily for 6 months, and 2707 patients were randomized to standard of care, which was initial enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2), followed by warfarin (target INR range: 2.0-3.0) orally for 6 months. The primary efficacy endpoint was recurrent VTE* or VTE-related death, and the primary safety endpoint was major bleeding.

≈90% of patients in the AMPLIFY trial had an unprovoked DVT/PE at baseline.[1]

- The 10% of patients with a provoked DVT/PE were required to have an additional ongoing risk factor in order to be randomized†

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
†Risk factors included previous episode of DVT/PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.
- **Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.

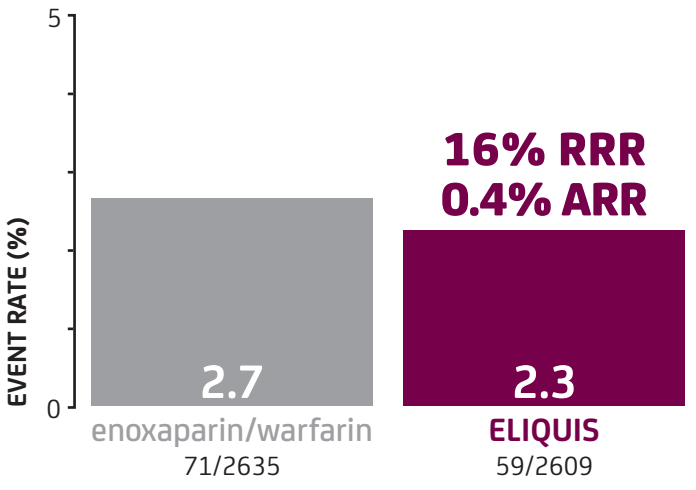
  Clarithromycin
  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.
- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.

FOR THE TREATMENT OF DVT/PE

ONLY ELIQUIS demonstrated BOTH comparable efficacy AND superiority in major bleeding events vs enoxaparin/warfarin[1]

COMPARABLE
in VTE*/VTE-related death

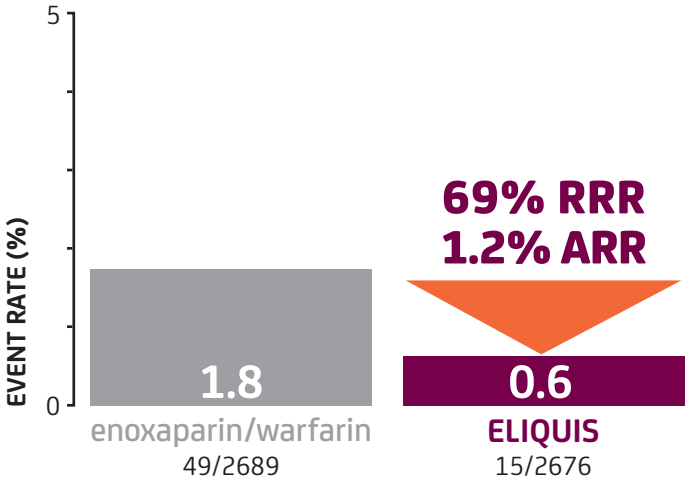
RR=0.84 (95% CI: 0.60–1.18); *P*<0.0001 for noninferiority



PRIMARY EFFICACY ENDPOINT

SUPERIOR
Major bleeding‡

RR=0.31 (95% CI: 0.17–0.55); *P*<0.0001



PRIMARY SAFETY ENDPOINT

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[1]

- Discontinuation rate due to bleeding events: 0.7% in ELIQUIS-treated patients vs 1.7% with enoxaparin/warfarin[1]
- In AMPLIFY, the most commonly observed adverse reactions in ELIQUIS-treated patients (incidence ≥1%) were epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, and gingival bleeding[1]

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following[2,3]:

A decrease in hemoglobin of ≥2 g/dL over 24 hours; transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; and fatal bleeding.

‡Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.
ARR=absolute risk reduction; CI=confidence interval; INR=international normalized ratio; RR=relative risk; RRR=relative risk reduction.

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (cont'd)

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY

- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
  - *Labor or delivery*: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

References: 1. Eliquis [package insert]. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. Supplement available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1302507/suppl_file/nejmoa1302507_appendix.pdf. Accessed April 14, 2020. **3.** Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708. Supplement available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1207541/suppl_file/nejmoa1207541_appendix.pdf. Accessed April 14, 2020.

Please see accompanying Brief Summary of Full Prescribing Information, including **Boxed WARNINGS,** on the adjacent pages.

Eliquis® (apixaban) tablets 5mg 2.5mg

Bristol Myers Squibb™ Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery— ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding *[see Warnings and Precautions]*. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of apixaban is available. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin) in individuals receiving ELIQUIS, and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS (apixaban) is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased Risk of Thrombotic Events After Premature Discontinuation *[see Warnings and Precautions]*
- Bleeding *[see Warnings and Precautions]*
- Spinal/Epidural Anesthesia or Puncture *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.
‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.
§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14 in the full Prescribing Information.
¶ GI bleed includes upper GI, lower GI, and rectal bleeding.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with ELIQUIS with diabetes bled more (3% per year) than did subjects without diabetes (1.9% per year).

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

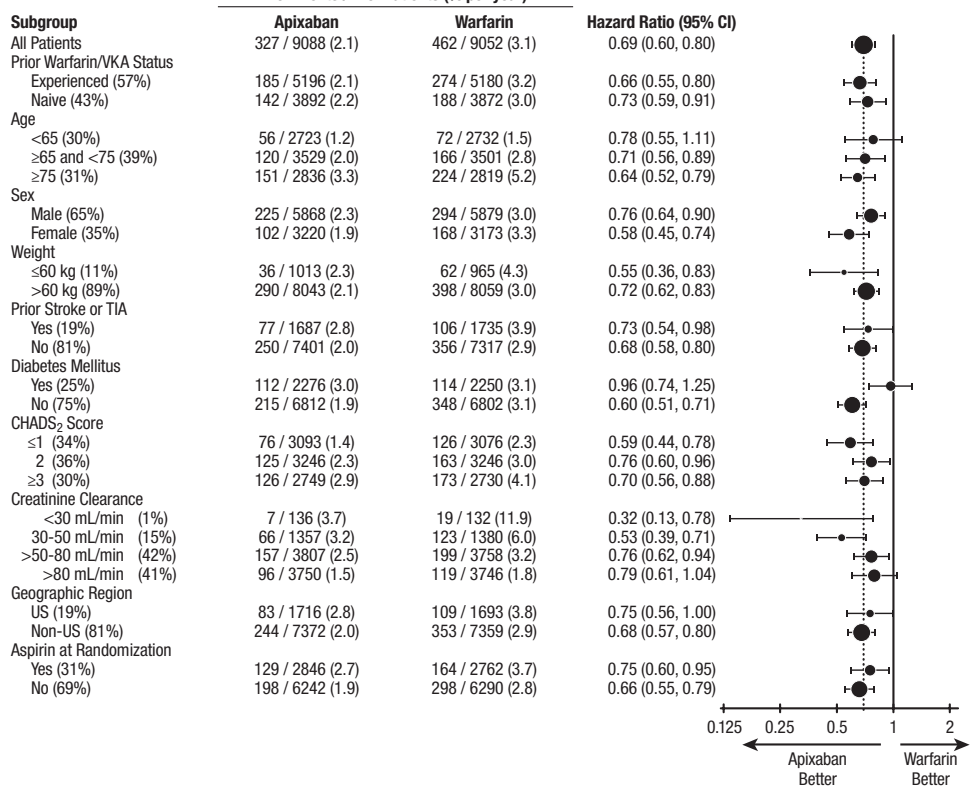
Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.
† Includes 13 subjects with major bleeding events that occurred before the first dose of ELIQUIS (administered 12 to 24 hours post-surgery).
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of ELIQUIS (administered 12 to 24 hours post-surgery).
§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
¶ CRNM = clinically relevant nonmajor.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma and catheter-site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in ELIQUIS-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in ELIQUIS-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of ELIQUIS in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with ELIQUIS compared to placebo. The rate of ISTH major bleeding was 2.8% per year with ELIQUIS versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with ELIQUIS versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery. In animal reproduction studies, no adverse developmental effects were seen when apixaban was administered to rats (orally), rabbits (intravenously) and mice (orally) during organogenesis at unbound apixaban exposure levels up to 4, 1 and 19 times, respectively, the human exposure based on area under plasma-concentration time curve (AUC) at the Maximum Recommended Human Dose (MRHD) of 5 mg twice daily.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk of thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reactions

Use of anticoagulants, including ELIQUIS, may increase the risk of bleeding in the fetus and neonate.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions]*.

Data

Animal Data

No developmental toxicities were observed when apixaban was administered during organogenesis to rats (orally), rabbits (intravenously) and mice (orally) at unbound apixaban exposure levels 4, 1, and 19 times, respectively, the human exposures at the MRHD. There was no evidence of fetal bleeding, although conceptus exposure was confirmed in rats and rabbits. Oral administration of apixaban to rat dams from gestation day 6 through lactation day 21 at maternal unbound apixaban exposures ranging from 1.4 to 5 times the human exposures at the MRHD was not associated with reduced maternal mortality or reduced conceptus/neonatal viability, although increased incidences of peri-vaginal bleeding were observed in dams at all doses. There was no evidence of neonatal bleeding.

Lactation

Risk Summary

There are no data on the presence of apixaban or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Apixaban and/or its metabolites were present in the milk of rats (see Data). Because human exposure through milk is unknown, breastfeeding is not recommended during treatment with ELIQUIS (apixaban).

Data

Animal Data

Maximal plasma concentrations were observed after 30 minutes following a single oral administration of a 5 mg dose to lactating rats. Maximal milk concentrations were observed 6 hours after dosing. The milk to plasma AUC (0-24) ratio is 30:1 indicating that apixaban can accumulate in milk. The concentrations of apixaban in animal milk does not necessarily predict the concentration of drug in human milk.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1) in full Prescribing Information]*:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1) in full Prescribing Information]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1) in full Prescribing Information]*. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2) in full Prescribing Information]*.

OVERDOSAGE

Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of ELIQUIS overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of apixaban is available.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in full Prescribing Information]*.

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SEND YOUR THOUGHTS AND COMMENTS TO ACEPNOW@ACEP.ORG

THE BREAK ROOM

On Sept. 25, 2020, *ACEP Now* published Ken Milne's article entitled "After Re-Analysis, No Trials Show Efficacy of tPA in Acute Ischemic Stroke," which focuses on reanalysis of NINDS (0–3 hours post-stroke onset) and ECASS III (3–4.5 hours post-stroke onset) data.

Excerpt

A [graphical] reanalysis of the NINDS data published in 2009 revealed that a baseline imbalance in stroke severity at presentation likely led to the difference in outcomes.[1] After controlling for these baseline differences, the claimed efficacy of tPA was no longer statistically significant.

Concern 1: Two responses to the reanalysis were published. Saver et al indicate this reanalysis of NINDS "depart[s] from best practices appropriate for the visual display of quantitative information."[2] They continue on to say, "Several methods exist that are appropriate to the graphical depiction of scales with ordinal functional values and skewed population distributions, including charting normalized gain and loss and charting clinically relevant ordinal categories. Graphical analysis of the NIHSS and delta NIHSS scores in the two NINDS-TPA trials, when conducted in this proper manner, delineate large magnitude treatment benefits of under 3 hour fibrinolytic therapy in acute stroke."

In a second response to this reanalysis, Dewey et al point out "such a conclusion cannot be justified by the findings from this post-hoc analysis of a secondary outcome from a randomized controlled trial with a positive primary outcome."[3] They also "question the relevance of the NIHSS as a measure of outcome at 90 days. At this late time point functional capacity is of much more direct relevance to patients and is routinely assessed with the modified Rankin and Barthel Scales."

As noted by these two different responses, the reanalysis was performed on a secondary outcome and did not account for the ordinal, noninterval nature of NIHSS' functional significance and the skewed population distribution, leading to misrepresentation of the results from the NINDS trial. The author also failed to discuss the graphical reanalysis of the two NINDS-tPA trials completed by Saver et al.[4]

Excerpt

Reanalysis of the ECASS III trial data with multiple approaches adjusting for baseline imbalances does not support any significant benefits and continues to support harms for the use of alteplase 3–4.5 hours after stroke onset.

Concern 2: Although Alper et al concluded their reanalysis of ECASS III data did not demonstrate significant benefits, they do note that a "limitation of reanalysis, or any method for adjusting for non-randomised factors influencing the effect estimates from a randomised trial, is such analyses cannot confidently produce new conclusions (neither a claim of efficacy nor a claim of absence of efficacy). ... In this case the reanalysis does not negate the original findings, but it greatly reduces the certainty for those findings."[5]

Although not obligatory, the author does not call attention to the flaws of conducting this reanalysis. As Activase in the 3–4.5-hour time frame is not FDA-approved, Genentech does not endorse the use of Activase use in this time frame. However, a reanalysis that examines the benefit or risk of a society-recommended treatment should be presented objectively to allow informed decision making on whether or not to offer such treatment to patients.

Excerpt

There are 13 RCTs of thrombolytics for AIS (see Table 1). Four were stopped early for harm (bleeding) or futility, and all 13 failed to show a statistical benefit after the reanalysis of NINDS-2 and ECASS-III.

Concern 3: Table 1 summarizes RCTs evaluating various thrombolytics for treatment of acute ischemic stroke. Because this table includes results from streptokinase and desmoteplase trials and from trials allowing time of alteplase treatment up to 6 hours from onset, inappropriate conclusions may be made about the safety and efficacy of alteplase for treatment of acute ischemic stroke.

Activase was FDA-approved for the treatment of acute ischemic stroke within 3 hours of symptom onset, based on the data from the two-part NINDS trial.[6] While symptomatic intracranial hemorrhage (sICH) was significantly higher in the Activase group (6.4 percent) versus placebo (0.6 percent), mortality was lower in the Activase arm (17.3 percent) compared to the placebo arm (20.5 percent).

FDA Clearance:

- Activase is not FDA-approved for use in treatment of acute ischemic stroke 3–4.5 hours from onset.
- Activase is FDA-approved for the treatment of acute ischemic stroke within 3 hours from onset of symptoms.
- Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at www.gene.com/download/pdf/activase_prescribing.pdf.

Emergency physicians rely on professional organizations such as ACEP to provide data-driven information to help inform clinical practice. Physicians are then responsible for evaluating the data and using their best judgment for incorporation into practice. This analysis requires presentation of unbiased material with each side impartially represented.

Emergency physicians rely on professional organizations such as ACEP to provide data driven information to help inform clinical practice.

Respectfully yours,
Rachel Garvin, MD, Senior Medical Director, Lytics, Genentech, Emergency Physician and Neuro Critical Care Specialist

Michael Liberman, MD, Senior Group Medical Director, Lytics US Medical Affairs, Genentech

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The Authors Respond

We are grateful for the letter by Garvin and Liberman, employees of Genentech. Our *ACEP Now* article was focused on the 2020 reanalysis of ECASS III by Alper et al, which added to the uncertainty about stroke thrombolysis. The 1995 NINDS trials were background information on the uncertainty.[1,2]

For a treatment to be scientifically sound, there must be replication of studies, minimization of bias, and healthy debate. These requirements have not been met for stroke thrombolysis. Discussions on controversies contribute to our understanding of deficiencies in existing data. The most glaring issue on this subject is the absence of replication studies suggesting benefit. The medical literature is replete with initially "positive" studies followed by larger, more reliable "negative" studies. This has contributed to the phenomenon of medical reversal whereby newer, superior results contradict current practice.[3] There are many examples where society guidelines promoting harmful treatments (eg, steroids for spinal cord injury) were later overturned.[4]

The concerns about the National Institutes of Health Stroke Scale (NIHSS) being a nonlinear scale are recognized. These concerns, although theoretically valid, do not appear to be relevant to NINDS, as the delta NIHSS was the same for all the treatment arms at every area of the scale—it changed equally with (early or later) tPA as with placebo for small strokes, for moderate ones, and for severe strokes. Changes in NIHSS measure discrete elements of neurological function rather than the more important overall functional status. Still, we might ask, "just how did tPA lead to better overall outcomes ... if it had no effect on any element of neurological function?"[5]

Alper et al also raised concerns around the dangers of selective analysis of trials. They refer to this as "selective analysis reporting bias" and state this could be involved in the stroke literature, specifically the reporting of ECASS III.[6] In reality, reanalyses are not often done. There is evidence that, when they are conducted, they frequently change the direction and magnitude of effect size and statistical significance.[7]

No claim was made in the *ACEP Now* article as to which analysis was correct. The bottom line stated that the reanalysis by Alper et al does not support a patient-oriented benefit of tPA given 3–4.5 hours after onset of stroke symptoms and confirms the known potential harm. This agrees with the conclusions of Alper et al's reanalysis, and we echo their call for the readers to reconsider the use of tPA in this time window.

Excerpt

Conclusions: *Reanalysis of the ECASS III trial data with multiple approaches adjusting for baseline imbalances does not support any significant benefits and continues to support harms for the use of alteplase 3–4.5 hours after stroke onset. Clinicians, patients, and policymakers should reconsider interpretations and decisions regarding management of acute ischaemic stroke that were based on ECASS III results.*

tPA is not FDA-approved in the 3–4.5-hour time frame. However, the 2015 ACEP policy does discuss the use of tPA in this time window. The recommendations were stated in the *ACEP Now* article background section and included a link to the full ACEP policy statement.[8] This highlighted the importance of shared decision making about the potential benefits and potential harms of tPA in this time frame.

The table in our article provides some details on 13 foundational randomized control trials (RCTs) evaluating thrombolysis for acute ischemic stroke. Each thrombolytic agent is clearly identified. There is no definitive data to suggest one thrombolytic agent is better than another.[9] To selectively highlight two "positive" tPA trials (both with questionable efficacy on reanalysis) and omit the other 11 RCTs (six tPA and five non-tPA) that did not report benefit for their primary outcome is a form of the "Texas sharpshooter fallacy" (ie, "counting" the positive trials but ignoring the negative ones).[10] Or putting it differently, all the evidence is positive, as long as we reject any evidence that fails to be positive.

It is important to note that there have been no "positive" replication studies. In addition, two tPA trials were stopped early due to harm or futility.[11,12] Importantly, it is recognized that harms are underreported in RCTs, systematic reviews,

and meta-analysis (SRMA).[13,14]

Garvin and Liberman are correct that symptomatic intracranial hemorrhage (sICH) was higher in the tPA group and mortality was lower compared to placebo. However, they failed to mention the statistical result. The harm (5.8 percent absolute increase in sICH) was statistically significant (P <0.001) while the benefit (absolute decrease in mortality 3.2 percent) was not (P=0.3). Shinton raised concerns regarding the NINDS methodology, stating "the evidence of benefit is precarious."[15] Overall, there is more confidence in the increase in harm (bleeding) than the potential decrease in mortality. In fact, two recent SRMA have reported a statistical increase in early mortality with tPA and a nonstatistical increase in late mortality.[16,17]

We note that Garvin and Liberman introduce the idea of being unbiased and impartial. The potential financial conflicts of interest (COI) around tPA have been documented and are a powerful form of bias.[18] It is also known that COI can introduce bias into RCTs and SRMAs and need to be managed during guideline drafting.[19–21] It is ironic that two Genentech employees suggest we are biased when there has been so much pro-tPA promotion in major journals. Indeed, in "Everyone's a Little Biased (Even Physicians)," Cain and Detsky point out that "everyone is likely capable of rationalizing beliefs and denying influences that bias them. The most important action physicians can take as a profession is to recognize this."[22]

We agree that physicians are responsible for evaluating the data and using their best judgment for incorporation into practice. We encourage physicians to read and critically appraise the primary literature, reflect upon their clinical experience, and engage with patients about their values and preferences. This is the foundation of evidence-based medicine.

For a treatment to be scientifically sound, there must be replication of studies, minimization of bias, and healthy debate. These requirements have not been met for stroke thrombolysis.

Respectfully,
Ken Milne, MSc, MD, CCFP(EM), FCFP, FRRMS, Schulich School of Medicine and Dentistry, Western University

Daniel M. Fatovich, MBBS, FACEM, PhD, professor of emergency medicine, University of Western Australia; head of the Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research

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Working Our Vaccine Clinic Was a Shot in the Arm

by ERIC ADKINS, MD, FACEP

The COVID-19 pandemic has affected physician mental health and has become an important focus in our response to it. To that end, one of the best things I've done for myself lately has been working at our vaccine clinic providing medical oversight.

The first time I had a shift in the clinic, we were vaccinating our hospital coworkers. I found myself happily chatting with colleagues I hadn't seen face to face in almost a year. It was so refreshingly *normal*. It felt like a family reunion in the best way, a welcome reminder that better times are coming for all of us who have been on the front lines of this crisis.

We quickly opened up the vaccine stations to the general public. We all know the patients we see in the emergency department do not want to be there if they don't have to. They're scared and worried and not in a good place physically or emotionally. It was a different experience to tend to those who had worked hard to secure a vaccination slot and were excited to be there. I felt my spirits lift as I spoke with people who had just received their shots and were waiting patiently to be dismissed.

Our vaccine station, located in The Ohio State University basketball arena (to allow for social distancing) is the most crowded place many of these people had been in a year. We are vaccinating up to 250 people per hour and up to 3,000 people a day. Some described feeling anxious and out-of-sorts. As we monitored them, we assured them these feelings were normal considering everything they had been through this year, and we got to share their relief at taking this step toward normalcy.

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER

The Ohio State University emergency physicians receive COVID-19 vaccinations at the clinic.

The arena was filled with a sense of hope, and it was contagious.

If you get an opportunity to work your local vaccination clinic, I say go for it. After having a front-row seat to so much despair, it feels incredible to spend a few hours surrounded by hope and gratitude.

DR. ADKINS is an associate professor of emergency medicine and pulmonary/critical care medicine, vice chair of clinical operations, and associate chief clinical information officer at The Ohio State University.

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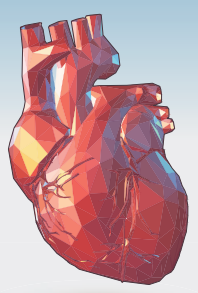

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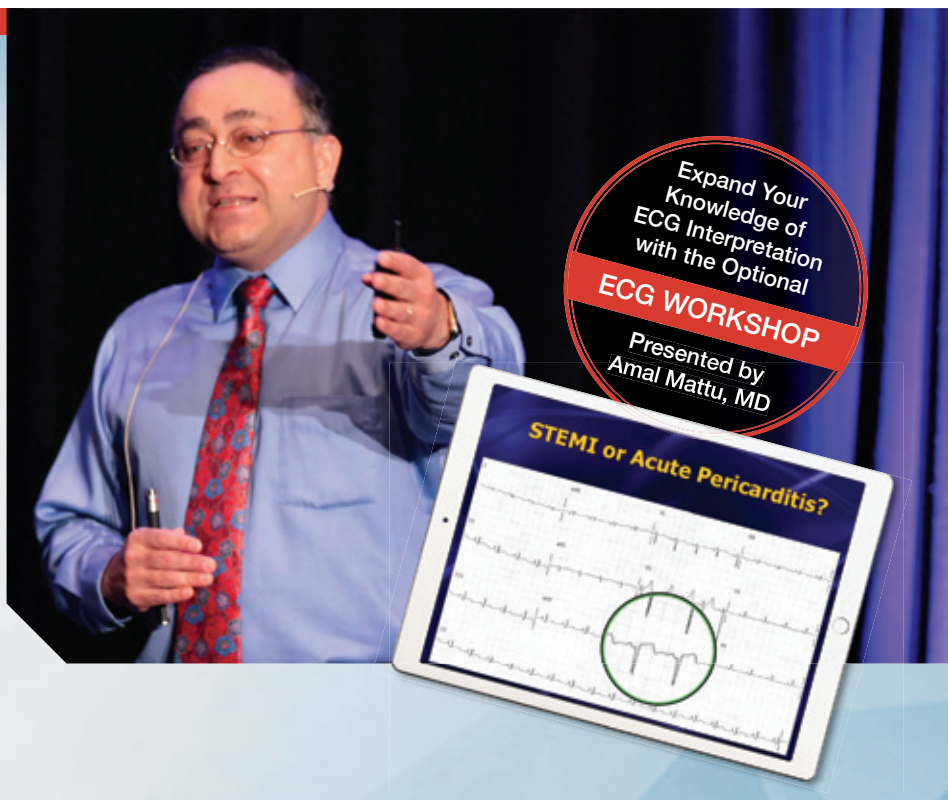

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THE EQUITY EQUATION

DR. BAKER is chair of emergency medicine at Chestnut Hill Hospital at Tower Health in Philadelphia.

Moving from Race-Based to Race-Conscious Care

Acknowledging, examining, and dismantling structural racism is critical to shifting our approach to care

by JENICE BAKER, MD, FACEP

The year 2020 highlighted our flaws. Unprepared, we faced a pandemic that has now killed more than 540,000 people in the United States. Because of quarantines, a captive audience witnessed horrible acts of police brutality displayed on television and portable screens all across the nation. Systemic racism was highlighted from our legal system to our medical institutions. Outrage led to protests, and protests led to conversations.

So in 2021, after all of our talking, what do we do now? Health care disparities in medicine have long been recognized and discussed. We know that minorities are at increased risk of death from almost every disease process. The major cognitive shift that 2020 helped many see is that much of these racial disparities are social and not biological. How do we change from race-based medicine to race-conscious medicine?

A recent article in *Lancet* about race-based care highlighted the fact that race is often blindly used as a biological proxy in how we characterize, diagnose, and administer care to all of our patients.[1] However, it would be naive to think that race does not impact the care administered to patients every day. Some are aware of race but claim to be "color-blind"—to imply that race does not affect one's decisions if the individual does not acknowledge race. Color blindness leads to systemic racism blindness. If you cannot see race, how can you see the structures and policies created to discriminate because of race?

One way to incorporate the social effects of race on medicine is to be race-conscious (see Figure 1). This means acknowledging race not as a biological risk factor but as a social risk factor that promotes policies and procedures that discriminate against minorities.

But how exactly can we do that? Education—or rather the re-education—of students, residents, and attendings on this subject is critical. Understanding the history of race in medicine that translated into race as a proxy for disease can highlight medicine's implicit biases. This acknowledgment could cause a paradigm shift in medical education that teaches race as a proxy for medical discrimination that leads to racial health disparities. Doing this offers us something positive and substantive to do: It helps us better identify where our focus belongs in our work to improve outcomes.

Along with this shift in education, new policies and procedures are necessary to overcome existing structural barriers to care in realms of research and clinical practice. A few peer-reviewed journals are actively taking this important step. *The New England Journal of Medicine* published an article in 2020 called "Hidden in Plain Sight—Reconsidering the Use of Race Correction in Clinical Algorithms."[2] As the authors wrote, "To be clear, we do not believe that physicians should ignore race. Doing so would blind us to the ways in which race and racism structure our society. However, when clinicians insert race into their tools, they risk interpreting racial disparities as immutable facts rather than as injustices that require intervention. Researchers and clinicians must distinguish between the use of race in descriptive statistics, where it plays a vital role in epidemiologic analyses, and in prescriptive clinical guidelines, where it can exacerbate inequities."

The journal *Circulation* published "Call to Action: Structural Racism as a Fundamental Driver of Health Disparities: A Presidential Advisory from the American Heart Association" in November 2020.[3] As the authors wrote, "The American Heart Association must look internally to correct its own shortcomings and advance antiracist policies and practices regarding science, public and professional education, and advocacy. With this advisory, the American Heart Association declares its unequivocal support of antiracist principles."

These peer-reviewed journals' acknowledgement of structural racism gives support to begin dismantling racist policies and practices that contribute to health disparities.

Structural racism is a thread in the fabric of medical care in the United States. Moving from race-based to race-conscious care is using the same thread but creating new practice patterns that truly reflect and affect everyone equitably.

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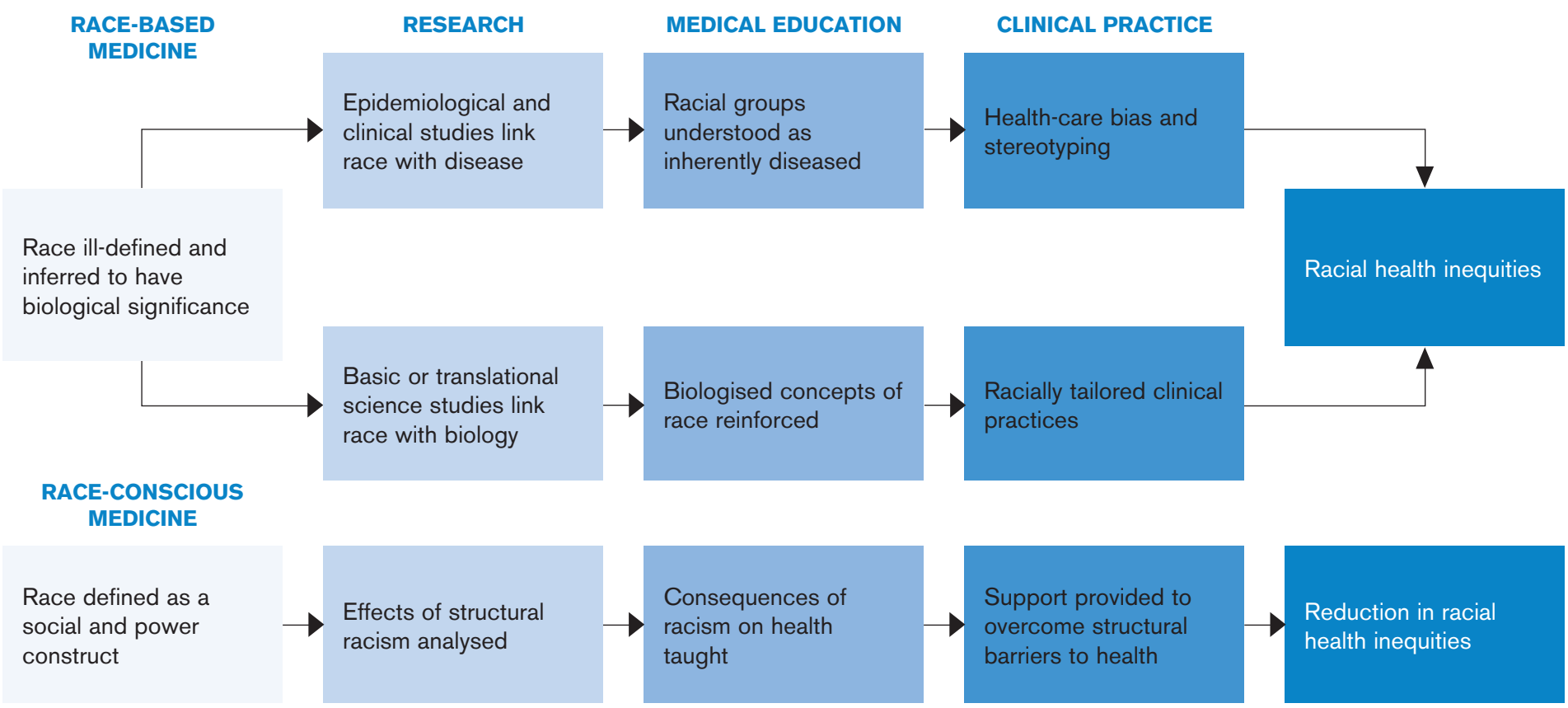
FIGURE 1: How Race-Based Medicine Leads to Racial Health Inequities



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ACEP4U: Navigate Career Changes and Opportunities

ACEP HAS RESOURCES TO HELP YOU AT EVERY STAGE OF YOUR CAREER

by JORDAN GRANTHAM

More than a year into this pandemic, it's clear that the emergency medicine job market has been significantly affected. Not only that, but many emergency physicians are using this opportunity to make changes, whether it's switching to a new job setting or branching out into telehealth. ACEP is committed to helping you navigate these twists and turns by growing our career resources to serve members with various needs. Keep reading for an overview of career-advancement content available to ACEP members.

New Career Center

ACEP has recently gathered our job-related resources into a one-stop shop to make it easier to find what you need, when you need it.

- The **emCareers.org job board** offers the largest bank of validated emergency physician openings. It allows sorting by specialty, location, employment type, experience, benefits, and more.
- Take a look at current job listings around the country in our new **interactive map**.
- Members of the ACEP Board of Directors have offered to provide **free CV reviews**.
- **Career profiles** allow you to learn more about different EM jobs, from rural to academic, to better understand what settings might suit you.
- The **job-hunting resources** take a deeper dive into the many considerations of the EM employment market.
  - » **Salary Reports:** View recent compensation reports to see the salary trends in your region.
  - » **Employment Contract Considerations:** Utilize the expanded contract tools to make sure your agreement suits your needs. Check out the new checklist that details key considerations for EM employment contracts.
  - » **Liability Assistance:** Want to better understand your liability risks? The legal tools, including the option for consultations, are there to help. You'll also find a directory of available legal services.
  - » Check out **upcoming events**, including any career-related webinars and job fairs.
  - » Learn more about **ACEP's Wellness and Assistance Program** (www.acep.org/support), a multifaceted program primarily focused on physician wellness. We know employment, legal, and financial concerns can be primary sources of stress, so there is an option to add legal and financial support from Mines & Associates for only $15 per year. That $15 annual fee includes services related to legal concerns (both business and personal/family), financial matters, IRS, real estate and estate planning, immigration and naturalization, and civil/consumer issues.

Visit www.acep.org/careers to find an interactive map showing job listings around the country.

Upcoming Job Fair

If you're in the market for a new job, make plans to participate in a virtual job fair hosted by ACEP, EMRA, and emCareers.org, 5–8 p.m. ET on May 20, 2021. It's free for all members.

Wondering what a virtual job fair looks like? It's an online event connecting emergency medicine professionals with private practice employers, group practices, hospitals, health systems, and other recruiters around the country. Job seekers can browse employer profiles and general emergency medicine and subspecialty positions, then privately interact with employers via live chat or live video chat on a mobile device or desktop. Learn more about the upcoming job fair at www.acep.org/spring-job-fair.

Workforce Update

ACEP shares your concerns about the EM workforce landscape and is working to lead the specialty into the future. The final EM workforce report from the multiorganizational task force, including ACEP, the American Board of Emergency Medicine, the American College of Osteopathic Emergency Physicians, the American Osteopathic Board of Emergency Medicine, the Council of Emergency Medicine Residency Directors, the Emergency Medicine Residents' Association, and the Society for Academic Emergency Medicine, will be published this spring. Private and public summits were scheduled for early April to discuss the findings of the task force and strategies for a path forward. Look for more information about the workforce report in the May 2021 issue of *ACEP Now*.

MS. GRANTHAM is ACEP communications manager.

KEEP SAFE WHILE BOARDING

A recent study underscores the value of implementing a multilevel protocol for psychiatric patients boarding in the ED

by BERNARD P. CHANG, MD, PHD, FACEP

Mental health complaints comprise a significant and growing portion of ED visits nationwide. A recent governmental report found that ED visits related to psychiatric complaints increased more than 15 percent from 2007 to 2011.[1] Many of these psychiatric complaints, such as suicidal ideation or severe depressive/anxiety episodes, may necessitate inpatient psychiatric hospitalization for further specialized care and treatment. In fact, patients with psychiatric chief complaints are two times more likely to require inpatient admission and also experience significant lengths of stay.

Like many patients, those with psychiatric complaints may encounter prolonged stays in the emergency department while awaiting inpatient beds. One study found that patients with psychiatric complaints had mean lengths of stay in the emergency department of 16.5 hours (more than 21.5 hours for those who requiring transfer to another institution for inpatient care).[2,3] This is an issue of concern, as psychiatric patients face several unique challenges in the ED setting that may expose them to elevated risk for adverse outcomes during their acute care. For example, patients with severe depression or other mood disorders may be at an increased risk for self-injury or harm in the emergency department while they await further psychiatric care.

What can the practicing emergency physician, who is already tasked with managing multiple critically ill patients simultaneously, do to help support these patients and ensure smooth transitions of care?

Establishing a Protocol

Interdisciplinary approaches among emergency physicians and mental health specialists may help improve safety outcomes and enhance the ED experience for psychiatric patients. Recently, a multispecialty team composed of emergency physicians, psychiatrists, security, hospital administration, and nurses, crafted a comprehensive safety program aimed at reducing the incidence of adverse events, such as those involving attempted self-harm.[4] The protocol was an iterative process involving a diverse group of stakeholders from clinicians to security staff and hospital legal counsel. Prior to implementation of the program, the interdisciplinary group reviewed all reported historical incidents of self-harm in their emergency departments. A series of potential interventions were identified including bathroom safety, number and training of patient observers, management of personal belongings and clothing search/removal, and the need for enhanced protocols for high-risk patients.

Based on these initial qualitative approaches, a comprehensive, multilevel care approach designed to balance patient safety with a recognition of and focus on patient experience was implemented. Details such as the use of shatterproof fixtures and the removal of wastebasket liners (to minimize ligature risks) lowered the potential for self-injury, while additional training for patient observers helped strike a balance between patient visualization in the bathroom while being minimally intrusive. Some of the highest-risk patients (identified by factors such as repeated episodes of self-harm) required enhanced protocols, including 1:1 observation, additional search of the patient and/or belongings, and expedited psychiatric consultation. Following implementation of the protocol, the authors reported a reduction in episodes of attempted self-harm, with half the number of cases reported when compared to the year prior (1.33 per 1,000 at-risk patients versus 2.95 per 1,000 at-risk patients).

Multidisciplinary Approach

Although this project was a quality/operations program in a high-volume emergency department with a large number of psychiatric patients, given the relative rarity of self-harm in the ED setting, the study may not have been sufficiently powered (ie, large enough to detect a statistical change) for us to reach definitive conclusions about the efficacy of the specific intervention that was evaluated. Also, many emergency departments may not have access to 24-hour in-house psychiatric consultation or an on-site liaison. Therefore, some of the proposed interventions might not be feasible in all practice settings.

However, the study does represent an important contribution to our understanding of management strategies for the boarding psychiatric patient, and some of its broad takeaways might be applicable to a wide breadth of practice settings. First, similar to the approach to scene safety in field assessment for EMS workers, emergency physicians should consider and mitigate any potential opportunities for self-harm or harm to others for patients with acute psychiatric illness. Second, early coordination and conversation with mental health specialists are important, particularly when the search for placement for psychiatric patients requiring inpatient psychiatric hospitalization may be a prolonged process. Lastly, as with all of our patients, it is vital to treat and address those who suffer from acute psychiatric illness with compassion and respect.

Although patient satisfaction data were not collected in this study, future work involving all key stakeholders, including the patients themselves, may shed light on which aspects of the acute care experience most minimize adverse behavioral effects and improve outcomes in the emergent setting. Behavioral and psychiatric emergencies continue to represent some of the most challenging clinical cases. A multidisciplinary approach focused on patient safety and harm reduction represents a promising and innovative approach that can lead to improved patient care and positive health outcomes, ensuring the safety of this vulnerable group of patients.

> As with all of our patients, it is vital to treat and address those who suffer from acute psychiatric illness with compassion and respect.

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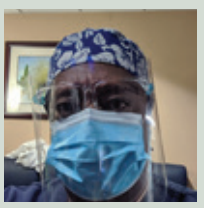

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BECOMING THE PATIENT

CONTINUED FROM PAGE 1

Do you know how you got COVID-19?

GB: My hospital initially had a good number of COVID cases as the pandemic hit. I also saw a very ill elderly woman who fit the bill for COVID in mid-March. Might have been a false negative.

PD: Not sure how I caught it, but I was caring for multiple patients with COVID-19 in the days before I became ill. I had been having chills for two days but didn't check my temperature until the end of the second day. My son, daughter, and wife all got sick within two to three days of each other.

TF: Most likely from an intubation I performed that was rushed and didn't have all the PPE needed. We didn't have HEPA filters on our machines set up on every mechanical ventilation until mid-April.

JG: I do not know where I contracted it. I suspect via community spread. Our ED COVID-19 counts were still relatively mild at the time and all my recent patient encounters had been while wearing full PPE. I was supposed to work a night shift on October 30. My wife jokingly called me "Mr. Sniffles" because I had some mild nasal congestion. I heavily debated still going to work given the mild symptoms. Ultimately, I decided to activate sick call, which turned out to be the right decision!

LL: We had a work outbreak.

JP: Not really. I'd been seeing lots of COVID patients and don't remember a specific moment or situation where I could've got it.

KS: Not a clue. I worked treating more COVID patients than any other patients for nine months. I took two weeks off, not being around anyone, and then got COVID.

What did it feel like?

GB: My symptoms never included respiratory trouble. My biggest issues were fatigue and a need for significant sleep, fever, malaise, and loss of taste. Cognitive processing was tough, too.

PD: The worst part was the overwhelming fatigue. Even though I didn't lose my sense of taste or smell, the mere act of trying to eat was too strenuous. I barely ate anything for a week. Taking a shower required a two-hour nap afterwards. After about seven to 10 days, I started coughing and had difficulty breathing. My wife, who's a physician, too, said I had rales throughout, so I probably had pneumonia, though I never had a chest X-ray. My pulse ox dropped to 90 percent. I told myself that if I dropped to 88 percent I would have to go to the hospital. Fortunately, I didn't require hospitalization. I also felt remorse that my colleagues were fighting so hard for their patients and I was not able to be there to help them. By the time I got back to work, the major surge was behind us.

TF: I had severe headache (like it was going to explode), fever, SOB, and body aches for the first three to four days and another week of exhaustion and loss of taste and smell.

JG: My symptoms were fortunately quite mild: some congestion, muscle aches, and eventually loss of taste and smell. I was terrified that my symptoms would progress. The worst part was the stress of worrying about my family. I was terrified I would infect them. I had immediately isolated myself in the basement. My wife would leave food at the top of the stairs, which I would retrieve while wearing a mask and gloves. I only emerged from the basement in the dead of night to put away my dishes, wiping everything I touched with bleach. Thankfully, my wife consistently tested negative, and my daughter never developed any symptoms. It was tough on all of us, and lonely. We still tried to have family dinners. I'd sit at the bottom of the stairs with the basement door open. It was the only time during the day we really got to see one another.

RJ: The first week, I had tremendous fatigue (sleeping 12 hours a day) and no appetite (I lost 10 pounds). It was the second week that I realized I had the virus when I "broke" quarantine and went to lunch on my birthday. The glass of wine I had tasted terrible!

JP: The first two to three days were the worst with fever, unbelievable headache, and pain all over. The anosmia part was terrible, being isolated and having one of your senses abolished gives you the sense of depersonalization. I got a CT scan and had mild pneumonia, no desaturation, but mild dyspnea.

KS: I initially had horrible fatigue, body aches, loss of taste, and terrible thirst. On Christmas Eve, my boss picked me up at home and took me to the ED. I had bilateral COVID pneumonia, was severely dehydrated, had a glucose 600 in DKA, and was septic. I was admitted to the ICU for five days, med/surg for four days, and rehab for three days as I was hypoxic. I continued to recover for three weeks and then became severely hypoxic—sats in the low 70s with any exertion (long COVID symptoms).

I went back to the ED with a CT scan showing persistence of the bilateral pneumonia. I was placed on prednisone 40 mg for five days and then 20 mg for five days. The lowered dose saw the severe hypoxia return. I was placed on supplemental oxygen, which allowed me to do ADL for short periods. I was placed on inhaled steroids since the oral steroids blew up my sugars, about 400–450. In about four days on PulmoCort [budesonide] inhaled steroids, I was off the supplemental oxygen. Within a week I was able to ride a bicycle a short distance (I was a mountain bike racer before COVID) with a lot of coughing and deep breathing. I feel this exercise has really helped clear out my lungs so I could continue to progress.

How long was your recovery?

GB: I had symptoms one week or so. After the seventh or eighth day, I started to improve. Perhaps part of this was recognizing that I had made it past the point of developing the late developing respiratory issues. By post-symptomatic day 10, I was back working. I had a glossitis that is just now improving. Since the infection, I need about an hour more sleep a day. Maybe that's seasonal or related to being 52. I had no residual effects on my lungs. I've returned to my half marathons.

PD: I started to feel better after about two weeks and was able to return to work three and a half weeks after I was diagnosed. I don't think I have any residual symptoms.

JG: They had me on a standard 10-day isolation. Physically, I felt fine by the end of those 10 days and returned to work. At home, we kept the isolation going for another full week, just to be safe. At this point, I don't seem to have any lingering symptoms other than perhaps a mildly diminished sense of smell.

RJ: I felt back to normal several days later (about 10 days total), but it took several weeks for my sense of taste to return. Fortunately, I never developed any cough or breathing issues and have had no lasting symptoms.

LL: I was really ill for one week, but the fatigue lasted for several weeks after I was "recovered."

JP: Fourteen days, going on 30 with pulmonary rehabilitation. I still have dyspnea on exertion, and I've been having insomnia and trouble remembering words. Neurologists tell me that's normal post-COVID.

KS: Initial symptoms Dec. 11. I really felt I had improved by Feb. 11. So, two months duration with initial COVID and long COVID. Only now mild fatigue and mild SOB, but part of that could just be deconditioning.

JW: A week or so. I was never very sick, so never really worried that I would get ill. My son got it from me and had more severe symptoms, so I was a bit worried about him. Due to my mild symptoms, I worked two shifts in the ED before I started really feeling sick. This was very early when there was a lot of fear in the media and public. [The media found out that I worked while

J. DAVID GATZ

Dr. J. David Gatz and his family having dinner while he was in COVID isolation.

having symptoms] and they made it sound like I dragged myself into work just to spew viral particles on patients. The mayor called me out, and criminal charges were entertained for a brief period. There were death threats against me in social media. Fortunately, no one knew my name.

What did you learn by being in the patient role?

GB: This coronaviral infection crosses the pathological spectrum; it certainly involves multiple organ systems, including the CNS. The pathology is widespread and variable. I didn't need any medical care but the psychological impact for a few days was interesting. Waiting for a cough to develop that could lead to a significant decline, hospitalization, etc. provides insight into anxiety of the unknown and the impact of the psychology of a disease process. Particularly interesting: Is it better to know the pathology and process of a disease or not?

PD: I was very worried about the course the illness was going to take with me. Reading the various blogs and message boards didn't help. I finally had to stop following them. It was just too depressing and scary. I have never been really sick, and the sense of fear and helplessness was difficult to deal with. That is something that I understood was normal and was experienced by my patients and their families, but this illness brought it into sharper focus for me.

TF: Since I became ill early in the pandemic, there were many unknowns. I felt the fear and mental health consequences, like many. There was a day that I thought I was going to die because my HR would jump to 180s just from a walk from the bedroom to the bathroom.

JG: It's scary, and tough not just on the patient. My isolation left my wife singlehandedly taking care of herself, our daughter, and me. I was furious with my inability to assist.

RJ: The most difficult part of the entire experience was being in quarantine for two weeks in my bedroom. My wife brought me meals. Fortunately, and surprisingly, she never got any symptoms. I also hated being home while my colleagues were doing everything they could to take care of patients in my community who were starting to get ill.

LL: It is very difficult to be in a situation where you don't feel like doing anything. I am a contracted worker, so my income was affected like so many other people. Going back to work when you don't feel 100 percent was also difficult. I felt like I needed to be at work to take care of people but honestly did not feel up to the strenuous 12-hour shifts. However, I needed to go back for a lot of reasons, including the fact that other people were ill and it made a lot of holes in the schedule.

JP: That everyone lives this experience differently, and circumstances (age, family, general activity) play a very important role in isolation. Also, uncertainty is a big enemy—you don't know if you're going to be OK or not.

KS: There is a significant difference between nursing and being a physician—they are completely different outlooks on patient care. Rehab centers are not prepared to treat the pulmonary complications of long COVID (approximately 30 percent of severe COVID cases). In a significant number of severe COVID cases, DKA can develop, especially in pediatric patients.

What do you want people to know about this disease?

GB: Viral infection with SARS-COV-2 is a spectrum of clinical illness. We are capable of rapidly addressing these sort of crises as seen by current vaccine developments and improvement in clinical care practices. Also, public health is the single most important aspect of our species' medical care. The outbreak and the mass of illness we saw were all fairly accurately predicted based on knowledge, work, and investigation. Vaccines and the simple act of separating fresh water from contaminated water are two things that do more than the work of all physicians combined for humanity. More emphasis and appreciation of primary preventative, community, and national health care policy must emerge from this. I am cynical regarding any improvement for our country. Politicizing and ignoring this outbreak might be seen as crossing the line to the immoral. The vast number of physicians who have openly advocated and aligned with those politicizing this are an embarrassment to our profession and bring forth a better understanding of why the U.S. has some of the worst outcomes in health care among industrialized nations. In my state, we were almost certainly penalized for our voting history and having states compete for resources is a political ideological failure. But the fracturing extremes of this nation make it such that I do not know if we will do better.

PD: COVID-19 is *not* just the flu. People I know became very ill and some died. This is something we have never experienced before in our lifetimes. So many ventilators and critically ill patients. I hope that people take the illness seriously, follow guidelines that are scientifically developed and GET VACCINATED! However, do not let fear consume you. Be sensible and we will get through this.

JG: Don't ignore symptoms, even mild ones. My only initial symptom was nasal congestion. I had debated still going to work and might have infected numerous colleagues. We're used to pushing through mild symptoms and abhor activating our colleagues for sick call. The reality is we must take all such symptoms seriously and be ready to activate sick call. Early isolation can work. I was pleasantly surprised that my wife and daughter were never infected. Infecting our families is a fear many of us share. With early isolation, it is possible to get COVID and not infect your family!

RJ: It is pretty clear that everyone's susceptibility is different. I did everything to protect myself both at work and when outside my home and yet still somehow managed to get infected. While each person can try to reduce the risk of contracting the virus, nothing puts the risk at zero. Anyone with risk factors should be even more cautious.

LL: It is not a made-up … disease. During the epidemic I lost my father to COVID-19. It has affected our family a lot.

JP: That is very relevant in one's life, even life-changing. Family and the support you receive is basic in recovery and managing all of the other symptoms.

KS: Have faith you will get better! Get the vaccine so you don't have to go through COVID the hard way. Take precautions, like wearing a mask and maintaining physical distancing. I started PulmaCort early in the disease process. If you test positive and have SOB, you might consider that too. In severe cases, accept you will have "long COVID." It is coming. Check your sugars on a daily basis if you get COVID.

A Gift of Breath

Cushions help larger COVID-19 patients with proning

by KAREN APPOLD

As COVID-19 cases continued to escalate in the United States in April 2020, Richard M. Levitan, MD, FACEP, an emergency physician at Littleton Regional Healthcare, a 25-bed hospital in Littleton, New Hampshire, wanted to do something to help.

Work was actually slower for him at that time because people were avoiding emergency departments and there weren't any COVID-19 cases in the rural, mountainous area. So, he decided to volunteer at Bellevue Hospital in New York City, where he did his residency in emergency medicine.

When he arrived, the number of beds in Bellevue's ICU had been expanded fivefold, and several hundred patients were in the emergency department with COVID-19 pneumonia. Unbeknownst to him, his time at the hospital would have a far greater impact on his own outlook than he could ever have imagined.

Dr. Levitan and other New York City physicians quickly became concerned about an insufficient supply of ventilators. But as they began to care for a high number of COVID-19 patients, many clinicians became convinced that the best way to care for these patients was to avoid intubation if possible. They also began to believe that turning patients onto their stomachs (ie, prone positioning) significantly improved oxygenation and avoided intubation. Proning helps aerate the posterior and lower parts of the lungs, areas that are often the most affected by COVID-19. These practices pioneered by New York City clinicians would go on to become the standard of care nationally over the next few months.

Proning can be difficult for many patients, however. In particular, heavier patients complained of back pain and were extremely uncomfortable proning on emergency department stretchers. Knowing the substantial benefits of proning, Dr. Levitan sought a way to make it possible for patients to prone more comfortably. He surmised that a cushion supporting a patient's torso and hips could make the position more comfortable.

Implementing a Vision

Armed with his idea, Dr. Levitan asked a California company that makes pregnancy massage mattresses to overnight some samples. An obese husband and wife with severe COVID-19 at Bellevue Hospital were the first to try them out. "They were quite comfortable on the cushions," he said. "Their oxygenation went up significantly, they didn't have to work so hard to breathe, and they fell asleep. They averted intubation."

Dr. Levitan shared this success story with his two brothers, who were eager to help him get cushions to other hospitals. It was important that free samples would be available so hospitals could avoid the administrative burden of ordering them during a pandemic. They ultimately decided that the best way to accomplish this would be to create a charitable organization.

Dr. Levitan's twin brother, Robert Levitan, a technology entrepreneur, worked to get charitable approval from the state of New York, and "Prone2Help" was born. A creative services company, Sid Lee, donated its time and talents to create a website (Prone2Help.org) and logo for the nonprofit organization.

Two mattress manufacturers, Earthlite in California and Oakworks Medical in Pennsylvania, worked with Dr. Levitan to design the cushions. "They had been shut down due to COVID and reopened as essential businesses," Dr. Levitan said. "They were grateful for the opportunity to make a product to help out with the pandemic and gave the charity reduced pricing." Any hospital administrator, physician, or nurse can go to Prone2Help.org and request a cushion for free, along with free shipping.

Robert, who serves as Prone2Help's executive director, also worked with FedEx to get a significant shipping discount for the nonprofit. The cushions ship directly from the manufacturer to a hospital, sometimes in just one day.

Dan Levitan, Dr. Levitan's older brother who works in venture capital, focused his efforts on fundraising for the nonprofit. To date, Prone2Help has donated 1,200 proning cushions to 512 hospitals across the United States.

"The initiative that doctors and nurses took to order the cushions has been incredible," Robert said. "Their level of dedication is inspiring."

One hundred percent of donations to Prone2Help go toward paying for cushions and shipping them. Everyone associated with the organization is an unpaid volunteer.


EARTHLITE

Earthlite proning cushion.

RICHARD LEVITAN

The Prone2Help founders, from left: Dr. Richard Levitan, Dan Levitan, and Robert Levitan.

The Importance of Proning

Prone positioning has been a standard of care among intubated patients with acute respiratory distress syndrome for 20 years. However, the coronavirus pandemic was the first time in history that a large number of patients were awake when proned but not intubated, Dr. Levitan noted.

When COVID-19 first hit the United States, many clinicians believed that all patients should be intubated early on. Part of this was due to concern of spreading the virus if patients weren't on ventilators. But it was also believed, based on the severity of patients' X-rays and their low oxygenation, that intubation would be inevitable in all of these patients, Dr. Levitan said.

As discovered in New York, however, many patients who were treated with noninvasive oxygenation (including high-flow nasal cannula) managed to recover without intubation.

If intubation could be avoided, it occurred to Dr. Levitan and other clinicians that this would be a tremendous win for patients, hospitals, and the entire health care system. The resources needed for intubated patients are substantially greater than for patients who can be managed with high-flow nasal cannula or other noninvasive ventilation options.

In addition, intubated patients require tre-

Oakworks proning cushion.

mendous amounts of sedation, and many develop thrombosis, renal failure, or neurological injury.

The benefits of awake proning were demonstrated in a study published by Dr. Levitan and colleagues.[1] The study showed among patients with advanced COVID-19 lung injury, two-thirds of patients avoided intubation during hospitalization.

Lead study author Nicholas D. Caputo, MD, an emergency physician at NYC Health + Hospitals/Lincoln in the Bronx, said, "The Prone2Help cushions have provided patients with a level of comfort they need in order to prone for an extended period of time. Some patients who couldn't prone at all were able to do so with these cushions."

Anand Swaminathan, MD, MPH, FACEP, assistant professor of emergency medicine at St. Joseph's Regional Medical Center in Paterson, New Jersey, had similar sentiments. "The cushions have been extremely helpful in facilitating proning," he said. "This has been particularly true for patients with higher body mass indexes. We continue to use the cushions today to great effect."

Pulse Oximetry's Benefits

Awake proning requires frequent monitoring with pulse oximetry and ongoing assessments of work of breathing. Some proned patients' oxygenation improves, but their effort to breathe doesn't improve enough to avert intubation, Dr. Levitan noted.

He believes that severe illness and mortality due to COVID-19 can be greatly diminished by detecting lung injury early on with pulse oximetry. In fact, he maintains that all patients diagnosed with COVID-19 should have pulse oximetry monitoring for two weeks after diagnosis. (Visit ACEPNow.com to read an article on pulse oximetry by Dr. Levitan.) If patients are identified when they still have only mild hypoxia and are treated with nasal cannula and proning as well as dexamethasone, they can often avoid critical illness, Dr. Levitan believes.

Dr. Levitan has been working to make pulse oximetry monitoring a standard of care that all public health agencies implement for patients diagnosed with COVID-19. Currently, Vermont is the only state that does this universally for all COVID-19 patients. Impressively, it has had fewer cases per capita and deaths per capita than any other state. Many of the nation's leading health care systems, including Mayo Clinic, have also taken this approach. Recently, New York City distributed 250,000 pulse oximeters to hospitals, enabling all COVID-19 patients to be monitored.

The Ultimate Goal

Robert hopes that all hospitals will make the cushions part of their equipment list. Even when the pandemic subsides, they can be used for heavy or pregnant patients with respiratory issues to help avoid ventilators.

"When we started, our goal was to get the product out there and help educate people about the benefits of proning and how the cushions can help," said Dr. Levitan, who has practiced emergency medicine for more than 30 years. "Our ultimate goal is to make everyone aware and put our organization out of business."

Robert agrees: "We look forward to the day when Prone2Help is no longer needed."

Reference

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KAREN APPOLD is a seasoned writer and editor with more than 20 years of editorial experience based in Lehigh Valley, Pennsylvania.

What's your COVID CAUSE?

Do you or a colleague have a COVID-related project we should feature in "My COVID Cause"? Send your suggestion to **acepnow@acep.org**.

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U.S. House Majority Leader Steny Hoyer (D-MD) makes closing remarks during the debate on H. Res. 24, the U.S. House Impeachment resolution in the U.S. Capitol in Washington, D.C., on Jan. 13, 2021.

NEMPAC UPDATE

| CONTINUED FROM PAGE 1

We pride ourselves on being a PAC that listens, and we are committed to keeping an open, transparent dialogue with our donors going forward. Only ACEP members can support NEMPAC, so it is incumbent upon us to be responsible stewards of your contributions.

We want you to know your voices are valued and we are taking action. We have made some changes to our criteria for the 2022 election cycle after reviewing the feedback of ACEP members and reflections of our PAC Board.

Evaluation criteria for the 2022 elections will continue to follow past NEMPAC practices of focusing on a candidate's support of ACEP's key legislative and regulatory initiatives, co-sponsorship of ACEP legislation, committee assignment, leadership position, relationship to state chapter and/or local ACEP members, and difficulty of the reelection race.

We have also now made it clear in our guidelines that candidates and incumbents who receive NEMPAC support are expected to exhibit behavior and actions consistent with the mission, vision, and values of ACEP and uphold the principles of our nation's democratic process and orderly governance.

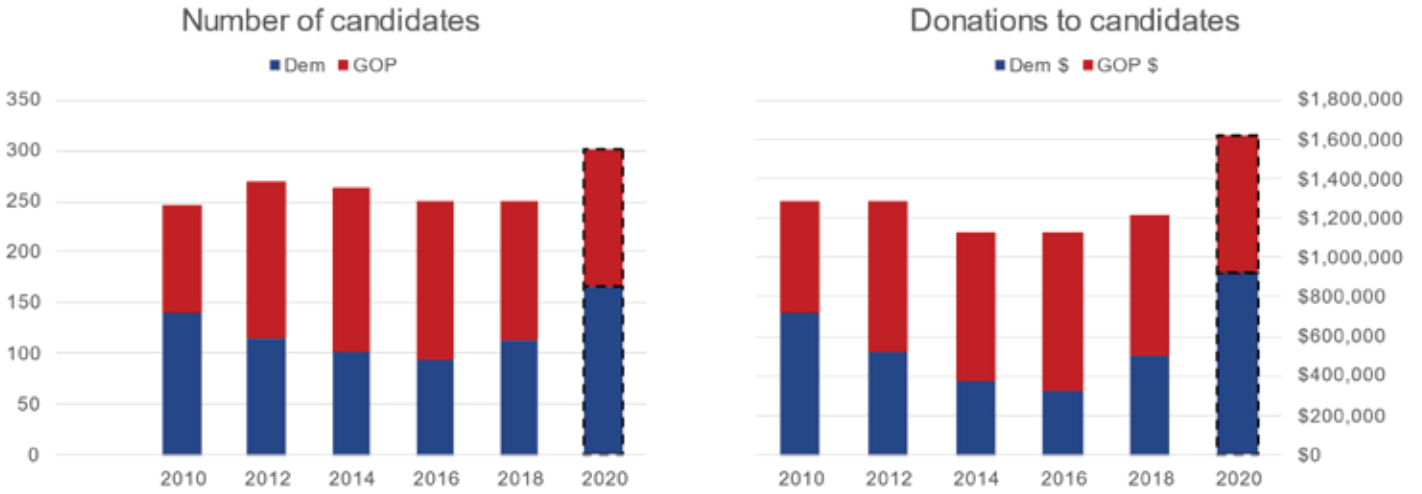
We believe NEMPAC-supported candidates should affirm science, evidence, and fact in their words and actions. We also intend to assess the integrity and character of the candidates on an ongoing basis and may consider ceasing contributions to a candidate or committee if credible, specific, and serious allegations about the candidate's behavior arise. NEMPAC will also continue our commitment to inclusiveness and respect for diversity.

Please know that a decision to financially support a candidate for office is not an endorsement of every vote the candidate has or will cast in Congress. NEMPAC supports candidates based on their ability to influence emergency medicine–related issues affecting your practice environment and access to care for patients.

Figure 1

NEMPAC reaches 250+ lawmakers each cycle

***NEMPAC only supports federal congressional candidates and committees**



More than 40 years ago, a group of ACEP members started NEMPAC, and today, we continue to carry forth their mission to work in the best interest of emergency medicine.

Political action has become an integral part of the business culture found in nearly every sector of the economy. Grassroots activism and financial strength through a PAC can be a profession's best tools to broaden relationships with influential members of Congress.

NEMPAC is a mobilizing force that we use to protect and advance ACEP's mission of promoting the highest-quality emergency care and serving as the leading advocate for emergency physicians, your patients, and the public. It is the only national PAC solely dedicated to representing our shared, bipartisan interests in Washington, D.C.

The importance and relevance of our PAC continues to grow. Over the past year, NEMPAC played a crucial role in helping ACEP find success on issues like Medicare reimbursement cuts, surprise medical billing, and obtaining needed resources during the pandemic. Now, with issues on the table such as addressing emergency physician mental health, preventing additional Medicare cuts, alleviating workplace violence, and providing access to treatment for emergency department patients suffering from mental health and substance abuse disorders, we need a voice more than ever.

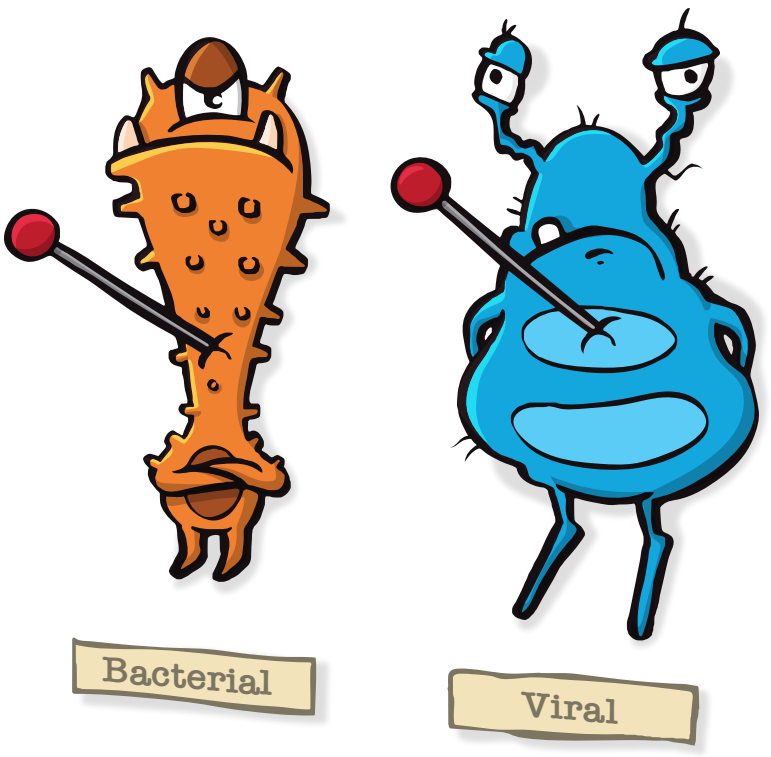
NEMPAC has never been partisan—we always have been strategic about whom we decide to support based on their support of us. During the 2020 election cycle, NEMPAC contributed nearly $1.7 million to federal candidates, party committees, and independent expenditures on both sides of the aisle. Of that, we allocated 55 percent to Democrats and 45 percent to Republicans. In the prior election cycle when Republicans held the House and Senate, our giving was reversed at 55 percent to Republicans and 45 percent to Democrats (see Figure 1). To further the breakdown, in 2020, 42 percent of all support went to diverse candidates, 24.2 percent of all support went to female candidates, and 23 physician candidates were supported.

We are proud of these accomplishments and thank the generous donors who made this possible, even amid being on the front lines during an ongoing global pandemic.

We understand that ACEP members are a diverse group, but all rise every day to take care of patients and their community with a unique, selfless dedication. While you take care of others, we want you to know you can rely on NEMPAC to protect your livelihood in the political arena. We have always made every effort to do what is best for emergency medicine, and we are not planning on changing that now.

If you have questions, comments, or concerns, we greatly welcome feedback. More information about our giving strategy can be found on the NEMPAC website.

THE AUTHORS are on the Executive Committee of the NEMPAC Board of Trustees.



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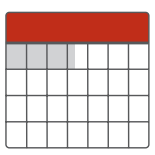
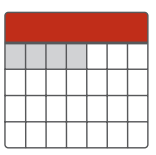
Time to diagnosis–adult patients[1]



3.3-day reduction

Time to diagnosis–pediatric patients[2]



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Physician on Trial: What to Expect

Court trial procedures and protocols follow a predictable course, but for the defendant, the emotional toll is hard to predict

by GITA PENSA, MD

Part 1 of 2

In my last column, we discussed case settlement offers and the complex calculations that both parties make when deciding whether to go to trial. If a settlement amount is not established, a trial date will be set, and both parties prepare for a fight to the verdict (though settlement may still be negotiated during the trial itself). In this column, we'll talk about what to expect at trial and review the general sequence of events.

Know that the road to trial—as well as the trial process itself—may take many years. In some states, there is a financial incentive for plaintiff's attorneys to drag out high-value cases because pre-judgment interest accrues on any judgment in their favor, with accrual usually going back to the date of the alleged injury. In Rhode Island, for example, the annual rate is 12 percent. In Illinois, HB 3360 (under the governor's consideration now) would award 9 percent per annum pre-judgment interest. As a result, a multimillion-dollar award for an injury that occurred many years ago could yield a significant amount of pre-judgment interest for the plaintiff.

One source of stress is sitting through the trial itself. Defendant physicians are usually expected to attend the trial in person. (This assumes that in-person trials are required—COVID-19 has put many jury trials on hold nationwide.) Even when attendance isn't requisite, from the jury's perspective, a defendant's absence paints the picture of an uncaring or egotistical physician who couldn't be bothered to break away, barring any significant extenuating circumstances. Trials often last for more than a week; complex cases may last more than a month. Time away from work is distressing for many physicians whose income is dictated by patient volume or hours worked. Aggravation compounds when trial dates are changed at the will of the court, upending carefully laid plans for at-work coverage, childcare, vacation time, and even travel arrangements if the trial is occurring at a prior practice location. The inconvenience and lack of control can be a great source of distress for the physician.

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Jury Selection

Once the trial finally begins, your attorney is your guide. The first order of courtroom business is jury selection. As attorneys and insurers know all too well, factors such as the jury pool ZIP code can alter both the value of a case and the likelihood of a verdict for either the defendant or the plaintiff. Although these factors are known and predictable, selection or rejection of individuals who may be perceived as likely to lean more toward one side than the other is critical.

Potential jurors are called up for jury duty and assembled in court on the day trial is set to start. Depending on the court and pretrial agreements, six to 12 jurors are typically needed, plus two alternates. Individuals are called up to the jury box by the court clerk, then the judge gives instructions regarding the kind of case it is and what types of beliefs or relationships might make for bias on the potential juror's part.

Then begins the process of *voir dire* ("to speak the truth"), during which the attorneys and judge question potential jurors to uncover any potential bias toward one side. Each attorney can ask the judge to dismiss a juror "for cause," meaning there's a strong reason the person might be biased. For example, the juror might personally know the defendant or plaintiff or may be a nurse or doctor themselves. The judge rules on each of these requests. When a potential juror is dismissed, another is called up from the pool. Each attorney also has an agreed-upon number of "peremptory challenges," which permit them to remove a juror without explanation as long as the reason doesn't involve race or sex. Attorneys use these challenges strategically, each hoping to assemble a jury as sympathetic to their side as possible. The *voir dire* process can take hours or even days.

Case Presentations

After all of the jurors are selected and sworn in by the clerk and the judge has recited the jury instructions, opening statements begin. The plaintiff's attorney usually goes first. Although this statement is meant to be more road map than argument, defendants often find listening to it very uncomfortable. It will, however, be followed by your attorney's opening statement, which will hopefully put you a bit more at ease.

After opening statements, the first witness is called by the plaintiff, whose side is typically presented first. Called one at a time, each witness is sworn in for testimony. Generally, they are either "fact witnesses," whose testimony provides factual details of what took place, or "expert witnesses," who render their professional opinions (in medicine, economics, or other relevant area) designed to teach the jury about the matter at hand. Even as defendant, you may be called as a fact witness by the plaintiff, even though most physicians can't help but bring their expertise into their testimony. (We will discuss more about your testimony in Part 2 of this article.)

During the plaintiff's presentation, each called witness is first questioned by the plaintiff's attorney ("direct examination"), after which the defense attorney has time to question ("cross-examine") them. This questioning is generally limited to topics brought up during the plaintiff's questioning. The plaintiff then has the right to re-question ("redirect") the witness, after which the defense can re-question ("re-cross") if desired. During these examinations, the plaintiff's attorney may ask the jury to review "exhibits," or physical evidence, such as medical charts, photographs, diagrams, etc. Exhibits must be approved by a judge prior to being seen by the jury.

Once the plaintiff has finished calling all witnesses, they "rest" their case. Now it's the defense's turn. Given how emotionally difficult it might have been for you as the defendant to listen to the plaintiff's attorney or experts portray you as an uncaring and incompetent physician, you may feel a bit better as your interpretation of the events as presented by the defense become clearer to the jury. The defense's case proceeds in a similar manner to the plaintiff's, until the defense also rests. Following the defense's presentation, the plaintiff may call witnesses to respond to the defense's case in a "rebuttal."

Recess and Deliberations

After both sides rest their cases, there is usually a recess during which the judge and attorneys convene to discuss jury instructions, which may vary from case to case. Then everyone reassembles in the courtroom for the "charge to the jury," wherein the judge instructs them on how to proceed with deliberations. The jury is responsible for deciding what the facts are, and the court is responsible for

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THE END OF THE RAINBOW

DR. DAHLE blogs at www.whitecoatinvestor.com and is a best-selling author and podcaster. He is not a licensed financial adviser, accountant, or attorney and recommends you consult with your own advisers prior to acting on any information you read here.

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Pass on the Investment Casino

Contrary to popular belief, investing in the stock market is not a crapshoot—if you follow a few key guidelines

by JAMES M. DAHLE, MD, FACEP

Q. I want to eventually retire with a healthy nest egg for me and my family. My accountant says I should invest in the stock market, but that sounds risky. Isn't Wall Street just a giant casino?

A. Given all of the market gyrations and shenanigans that have occurred on Wall Street and Main Street in the last few months, it's easy to mistake the stock market for a rocky riverboat casino. Without a doubt, investors can use the market this way, and many do. However, investing—when done properly—differs greatly from gambling.

One reason Wall Street has been looking more like an oversize craps table is the development of app-based brokerages such as Robinhood, which have been widely criticized for "gamifying" the investment process. Using these apps, investors are regaled with on-screen congratulations for making trades and are rewarded for winning trades with displays of balloons and confetti. Of greater consequence is the ease with which the brokerage has enabled investors to engage in high-risk trades such as options and cryptocurrency, practices that were implicated in the suicide of one young investor who believed he had lost $750,000 on a risky bet.

Social media has also fed a frenzy of trading in the market, perhaps most famously with members of the Wall Street Bets on Reddit pitting themselves against the hedge funds and shorting "stonks"* such as GameStop and AMC Theatres.

Fortunately, there's an important difference between investing in the stock market and placing a blind bet at the gaming table, and that's the expected return. In a casino, on average, the house wins. A correctly played blackjack game yields the gambler a 49.75 percent chance of beating the house. In craps, the odds fall to 49.6 percent. The chances of defeating a slot machine can be as low as 41.5 percent. On the whole, casino gamblers lose money because the long-term expected return is negative.

In the stock market, however, the average investor makes money, at least over the long term because the expected return is positive. The reason? There is input to the system beyond just a stack of chips, in the form of millions of talented and ambitious people whose hard work fuels the companies whose stocks are traded on the exchanges. As a result, these companies are able to develop new products and services that add value to the world. This value translates to higher revenue, and as time goes on, the value of market investments also increases.

Jack Bogle, founder of The Vanguard Group in Malvern, Pennsylvania, famously said, "The stock market is a giant distraction from the business of investing." Put simply, in the long run, investors make money by owning profitable companies. It isn't the trading from one company to another that pays off. In fact, on average, trading yields zero return before trading costs and a negative return after those costs. (Do those odds sound familiar?)

In both gambling and investing, one saying does hold true: "The croupier always gets his cut." Whether you're doing the investment work yourself or paying someone else via an actively managed mutual fund, managed stock account, or hedge fund, investment costs—which might include commissions, spreads, management fees, and capital gains taxes (if done in a taxable account)—reduce the value of your investment. You can minimize the "cut" by making as few trips through the casino as possible. Trading, even just to rebalance your portfolio, is akin to an extra trip. Ideally, you would take only one round trip, meaning you would buy as you save and invest throughout your career, then sell to pay your living expenses in retirement. With a low-cost, broadly diversified liquid investment like an index fund or exchange-traded fund—available from companies like Vanguard, Fidelity, Charles Schwab, or iShares—the cost of holding an investment is very small. Essentially, you can ignore it.

Many people today seize on this idea that "investing is gambling," and instead of putting their hard-earned money into rational investments that will provide for them when they can no longer work, they spend it on pricey designer watches and luxury vehicles. "Beats losing it in Vegas or on Wall Street," they claim. However, they could have invested those funds and avoided the "market casino" altogether by minimizing higher-risk investments such as options and day trades and putting some of that Tesla money into nonstock investments over which they would have significant control, such as bonds, certificates of deposit, real estate, and small business investments.

The bottom line is that good investing is boring investing. It isn't meant to be entertainment. With casinos closed and vacations canceled due to the coronavirus pandemic, it's understandable that many people have turned their attention to the trading of stocks and other assets. However, just because the markets can be used as a casino does not change the fact that investing and gambling are completely different activities. If you invest wisely, save regularly, diversify broadly, and keep investment costs low, you'll be able to reach reasonable financial goals. For most of us, that means having the time to focus on our patients, family, and own wellness without the burden of financial worries. You may find yourself in a better position to help others and even occasionally indulge in a luxury or two. You don't have to gamble to do that.

**"Stonks" is a term for highly volatile stocks recently coined by day traders.*

EM LITERATURE OF NOTE

PEARLS FROM THE MEDICAL LITERATURE

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Biomarkers in TBI

Should we use this new blood test to rule out traumatic intracranial hemorrhage?

by RYAN PATRICK RADECKI, MD, MS

Earlier this year, news circulated through typical press release channels regarding U.S. Food and Drug Administration (FDA) approval of a rapid, handheld traumatic brain injury (TBI) blood test. These press releases conveyed the advancement as "revolutionary" and "a game changer."

Does the substance match the hype?

The test in question is the Banyan Biomarkers' Brain Trauma Indicator (BTI) running on the Abbott i-STAT Alinity platform. This BTI panel measures two biomarkers of cerebral injury: ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP). GFAP is a cytoskeletal protein belonging to the class of intermediate filaments specific for astrocytes. UCH-L1 is a 24-kDa protein component of the ubiquitinylation pathway with specific expression in cerebral neuron cell bodies. GFAP peaks approximately 20 hours after injury and declines over 72 hours, while UCH-L1 peaks eight hours after injury and declines rapidly within 48 hours. These tests, when combined, produce area-under-the-curve estimates for predicting traumatic intracranial injury ranging between 0.72 and 0.93 within the first 12 hours from injury.[1] The BTI implements this combination at predetermined cutoff values with the intention of predicting traumatic intracranial injuries on CT scan, and it is this specific use that the FDA approved.[2]

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The Data

The key trial reviewed by the FDA was ALERT-TBI, a multicenter trial sponsored on multiple levels by Banyan Biomarkers.[3] In this prospective trial, which recruited between 2012 and 2014 and published in 2018, the study team enrolled 1,977 adults with nonpenetrating traumatic brain injury (TBI) and a Glasgow Coma Scale (GCS) score of 9–15. The average age of those enrolled was 49 years, and the bulk of these (93 percent) had a documented GCS of 15 on presentation. There were 42 percent with loss of consciousness, 33 percent with posttraumatic amnesia, and 21 percent intoxicated with drugs or alcohol. Of the 1,959 included in their final analysis, 125 had a traumatic injury identified on neuroimaging, with eight requiring neurosurgical intervention.

The topline results touted by the authors and spokespeople for the manufacturer are sensitivity and its cousin, negative predictive value. Of the 125 patients with traumatic injury identified on neuroimaging, three were missed by the BTI panel.

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This provided a sensitivity of 97.6 percent, with the lower limit of the 95 percent confidence interval down to 93.1 percent. With 671 patients showing a negative BTI result, the negative predictive value was therefore 99.6 percent, with the lower confidence interval bound at 98.7 percent. The authors' publication concluded with the suggestion that these results support the "role of this biomarker test for ruling out the need for a head CT scan among patients with TBI presenting at emergency departments in whom a head CT is felt to be clinically indicated."

Unfortunately, this conclusion is best described as aspirational. There is no disputing these biomarkers rise and fall in relation to TBI, but the key missing feature for generalizing these data into practice is the inclusion criteria for the study. Patients became eligible for inclusion if CT of the head was planned for their emergency department evaluation, but the eligibility criteria did not provide definitions regarding appropriateness of that CT. Simply stated, it is a straw-man comparator to imply value for imaging reduction when the imaging being performed was of uncertain necessity.

Simple clinical decision instruments, such as the Canadian CT Head Rule, are readily available and cost nothing, in contrast to the BTI.[4] Despite the introduction of this rule nearly 20 years ago, in community practice, it is estimated that unnecessary imaging occurs in one-third of ED visits for minor head injury.[5] So perhaps before we clamor for a blood test, we ought to simply realize the preexisting low-hanging fruit for imaging reduction already available to us.

The other unfortunate aspect of these results is that the panel functions as a one-way exclusion instrument only. In ALERT-TBI, the BTI demonstrated a specificity estimate of 36.4 percent, leading to a positive predictive value of merely 9.5 percent. These test characteristics are hardly dissimilar to our richly flawed experience with D-dimer over the past few decades. As we've found time and time again, inappropriately selecting patients for evaluation with D-dimer causes a downstream increase in advanced imaging rather than a decrease. A negative BTI result may potentially prove helpful, but a positive result does not. Two-thirds of those enrolled in ALERT-TBI showed positive BTI results, as do almost a fifth of normal healthy controls in the general population. If the BTI assay were to be as widely deployed as its proponents might wish, the overall result would be *more* imaging, not less. This is indication creep.

Lastly, there remain false negatives with the BTI, with the upper bound of the 95 percent confidence interval reaching up to 7 percent of traumatic injuries. Because of this, in part, the FDA has required compliant labeling to explicitly state, "A negative result is generally associated with the absence of acute intracranial lesions. An appropriate neuroimaging method is required for diagnosis of acute intracranial lesions." None of the missed cases ultimately required neurosurgical intervention, but this sample simply isn't large enough to produce reliable estimates of the overall safety of this product.

Conclusion

This BTI biomarker is likely to be aggressively marketed, as evidenced by boldly worded press releases such as, "Finally, A Blood Test for Traumatic Brain Injury."[6] Likewise, similarly favorable materials describing "the remarkable significance of such markers in assessing and managing neurotrauma" are added to the scientific literature through open-access review articles authored by Banyan's founder.[7]

The molecular diagnostics market is measured in the tens of billions of dollars annually, and while there is every possibility such innovations will ultimately prove to add value, we ought to require a high bar of quality implementation data. Without demonstrating their value and safety in prospective, real-world use, these observational test characteristics are not nearly enough to justify considering the use of biomarkers in traumatic brain injury.

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deciding what the law is.

After the jury is charged, the attorneys make their concluding arguments, and the jury departs the courtroom to deliberate. (In some states, concluding arguments occur before the jury is charged.) At this point, there's nothing for the defendant to do but wait.

Jury deliberation may take hours or days. Your attorney will instruct you if you need to remain in court while deliberations take place. Once the jurors have reached a verdict, all parties reassemble to hear their decision. If a jury absolutely cannot come to a conclusion, there is the possibility of a "hung jury," which results in a mistrial. There are numerous other reasons a judge may declare a mistrial, such as the death of a juror, the discovery of juror misconduct, or a fundamental error by an attorney or witness that may prejudice the jury in a way that can't be easily remedied. In this event, the case may go to trial again in the future with a new jury, or the involved parties may decide not to proceed further.

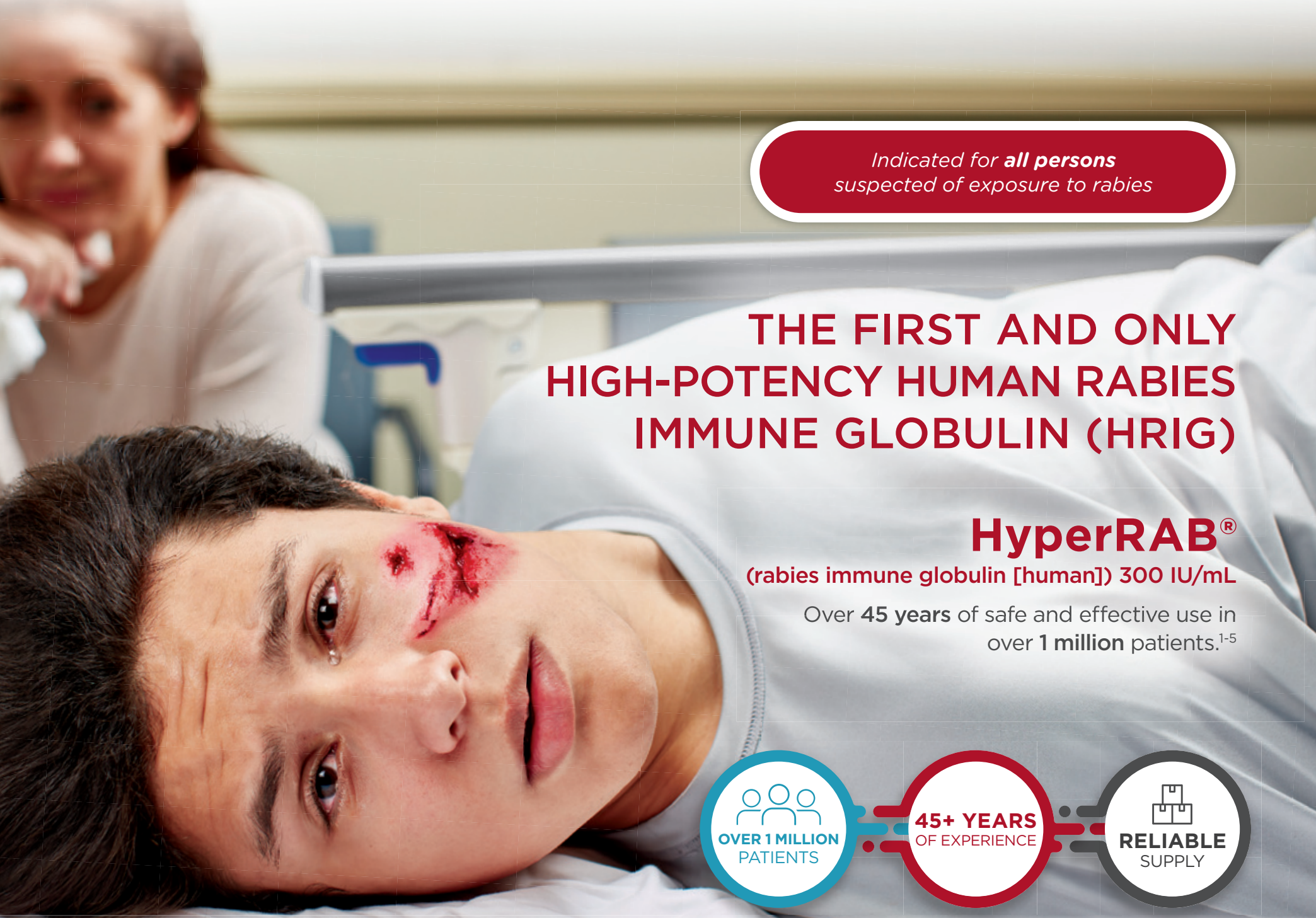
The Verdict and Aftermath

Receiving the verdict in a court trial is an emotional moment for most defendants. Even when there is a defense verdict (you "win") and the relief is welcome, it will likely take a long time to put the ordeal behind you. If the verdict is for the plaintiff, the disappointment can be overwhelming. Recall from previous columns that most cases that go to trial are defensible, meaning they're cases that you and your insurer feel might be won. A verdict for the opposite side can be crushing, and a large award to the plaintiff can exacerbate that.

Any damages to be paid to the plaintiff may be determined in a separate conference, and in some states, the judge may alter this amount when entering their judgment on the decision (their order that the decision be filed in the public record). If there are co-defendants, the jury will typically assign responsibility for each one, though the rules on how this happens may vary by state.

Motions for a new trial may be entered after the verdict if it is felt that the judge made errors that unduly influenced the outcome. A notice of appeal may be filed if one side feels there is a legal basis, which will begin the appeals process.

In my next column, we'll discuss how to prepare yourself practically and psychologically to deliver effective trial testimony and put your best foot forward.



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