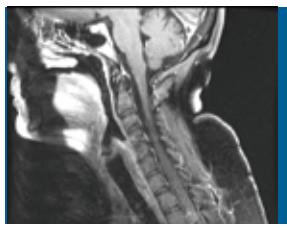

CASE REPORT

Mysterious Back Pain

SEE PAGE 19

ELECTION RECAP

EPs Headed to Congress

SEE PAGE 17

IMAGES IN EM

Diversity Should Be a Priority

SEE PAGE 21

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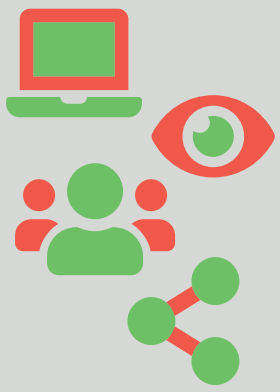

RECAP

ACEP20 By the Numbers

SEE PAGE 12

COUNCIL RESOLUTIONS

Council Addresses PPE, Terminology, and More

SEE PAGE 16

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

PEARLS FROM THE MEDICAL LITERATURE

2020 YEAR *in* REVIEW

UPDATES ON CARDIOLOGY, INTRA-ABDOMINAL INFECTIONS, ADVANCED IMAGING, AND CEREBROVASCULAR DISEASE

by RYAN PATRICK RADECKI, MD, MS

While COVID-19 occupied much of our bandwidth in 2020, new medical literature on other important topics still descended upon us faster than it could be consumed. We've already covered some of this in previous *ACEP Now* updates touching on critical care, tranexamic acid, and spontaneous pneumothorax. But those barely scratched the surface of the year in research.

Here's a quick tour of more of the most talked-about articles from the past year.

CONTINUED *on page 19*

Leadership During Adversity

Dr. Mark Rosenberg outlines his goals for the year and the challenges of being ACEP President during COVID

At ACEP20, Mark S. Rosenberg, DO, MBA, FACEP, began his term as President of ACEP. He spoke with *ACEP Now* Medical Editor in Chief Jeremy Faust, MD, MS, MA, FACEP, in late November over Zoom. Some of the questions were provided by the Editorial Advisory Board of *ACEP Now*. This interview has been edited for clarity and continuity.

JF: Congrats on being at the helm.

MR: Well, thank you. It's only been a month.

JF: Let's start with a really hard-hitting question: How's the job going so far?

MR: It has always been my dream and goal to lead the College, and sometimes I wake up and I pinch myself wondering, is this real? Am I really president of ACEP? And then I realize that I am, and it is a wonderful feeling. I'm doing this as a full-time commitment, so I'm not tied to clinical work. I'm now chairman emeritus, and so it gives me a lot more time to really understand the problems, concerns, and issues that our members have. And I'm learning a lot.

One thing that I'm doing this year is I'm going to each and every state chapter with the power of Zoom and trying to better understand what their needs are and how ACEP can better support them.

JF: What's on your desk today related to our COVID response?

MR: One of the best parts about having a new administration is President-Elect Biden and [Vice President-Elect] Harris put together a task force. We were lucky

CONTINUED *on page 10*

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NEWS FROM THE COLLEGE

UPDATES AND ALERTS FROM ACEP

Utilize Updated COVID Resources

ACEP continues to update its COVID resources regularly to reflect the latest information. Visit the COVID-19 Center at www.acep.org/covid-19 for access to all COVID content, including the following most popular tools from the past few months:

- The **COVID-19 Field Guide** is a living document. Recent updates include return-to-work criteria, ventilation guidance, late sequelae and long-term effects of COVID-19, and treatment (including a new section on antibodies).
- **COVID-19 Severity Index Tool**, created by ACEP and EvidenceCare, is a seven-step triage process for emergency physicians to better classify COVID-19 patients and inform next steps. This pathway integrates into many electronic health record systems, can be downloaded for offline use, and is updated often with the latest developments.
- **Elemeno Express for COVID,** a free benefit for ACEP members, is an internet-based point-of-care platform that puts ACEP-approved COVID content and best practices at your fingertips and helps connect your ED team. Find it at www.elemenohealth.com/express-acep.
- **COVID-19 Clinical Alert** is our resource library where ACEP's clinical team has gathered and organized the most helpful COVID-19 resources from across the internet into topics including clinical assessment and management, personnel, EMS, system/community, and more.
- **The COVID-19 Forum** on ACEP's EngagED platform houses peer-to-peer discussions from around the globe. Get connected and share lessons learned.
- **COVID-19 Literature Library** is a curated selection of relevant international publications organized by topic: clinical assessment, disease, testing, etc.
- **COVID-19 Physician Wellness Hub** helps ACEP members find the right support, whether it's peer-to-peer support or free professional counseling. It includes wellness advocacy and mental health resources organized by source of stress.

ACEP Board Approves New and Revised Policy Statements

During its October meeting held in conjunction with ACEP20 Unconventional, the ACEP Board of Directors approved the following new, revised, or reaffirmed policy statements:

- Overcoming Barriers to Promotion of Women and Underrepresented in Medicine Faculty in Academic Emergency Medicine (new)
- Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the ED with Community-Acquired Pneumonia (new, replacing 2009 clinical policy with the same name)
- Deferral of Care for ED Patients (revised, replaced Deferral of Care After Medical Screening of ED Patients)
- ED Patient Advocate Role & Training (revised)
- Emergency Physician Compensation Transparency (new)
- Social Work and Case Management in the ED (revised, replaced Patient Support Services)
- Third-Party Payers and Emergency Medical Care (revised)
- Worldwide Nuclear Disarmament (reaffirmed)
- Handoffs: Transitions of Care for Children in the ED (reaffirmed)
- Immunization of Adults & Children in the ED (revised)
- Patient- and Family-Centered Care & the Role of Emergency Physicians Providing Care to a Child in the ED Policy Statement and Joint Technical Report with the American Academy of Pediatrics (reaffirmed)
- Adult Psychiatric Emergencies (new)
- Prevention of Harm from Internet and Social Media Challenges (new)
- Collective Bargaining, Work Stoppages, and Slowdowns (revised)

The ACEP Council also addressed a variety of topics during its October meeting. See page 16 for a summary.

Reimbursement and Coding Conferences Go Virtual

ACEP's Reimbursement and Coding courses are the most authoritative and informative conferences available regarding emergency physician reimbursement and coding. Make plans to join the virtual conferences Jan. 12–14, 2021. Learn more at www.acep.org/RC.

Join the ED Directors Academy (EDDA)

In its new virtual format, EDDA Phase I features 10 modules that need to be completed during a three-month window. The current window ends in February, so you still have time to plug into this unique conference designed to lay the groundwork for your success throughout the Academy with a series of courses on topics you need to know as ED director. Learn more at www.acep.org/edda.

Now Accepting Nominations for ACEP Board, Council

The ACEP Nominating Committee is accepting individual and component body recommendations for Board of Directors, Council Speaker, and Council Vice Speaker candidates. Nominations are due March 22, and qualifications and application details are available at www.acep.org/board-nominations. Elections for the Board of Directors and Council officers will be held Oct. 24, 2021, during the ACEP Council meeting.

Access ACEP20 Content

ACEP20 attendees can access select meeting content at http://acep20.acep.org. This content will remain on the ACEP20 platform for 90 days post-conference before moving to the ACEP Online Learning Collaborative for the rest of your three-year access period. Those unable to attend can still get the education they missed and earn up to 276 CME hours for three years with the virtual component of ACEP20. Learn more at www.acep.org/acep20/virtual.

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.

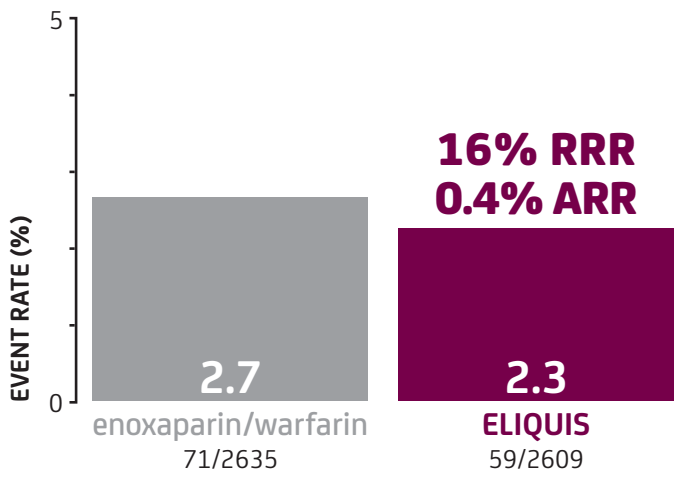
FOR THE TREATMENT OF DVT/PE

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

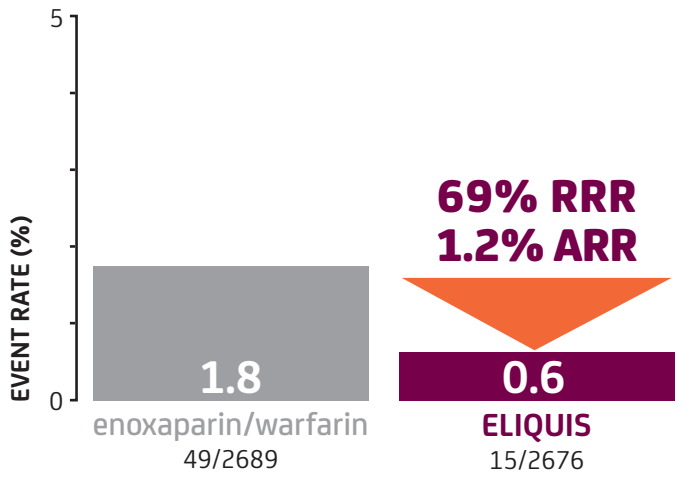


PRIMARY EFFICACY ENDPOINT

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.

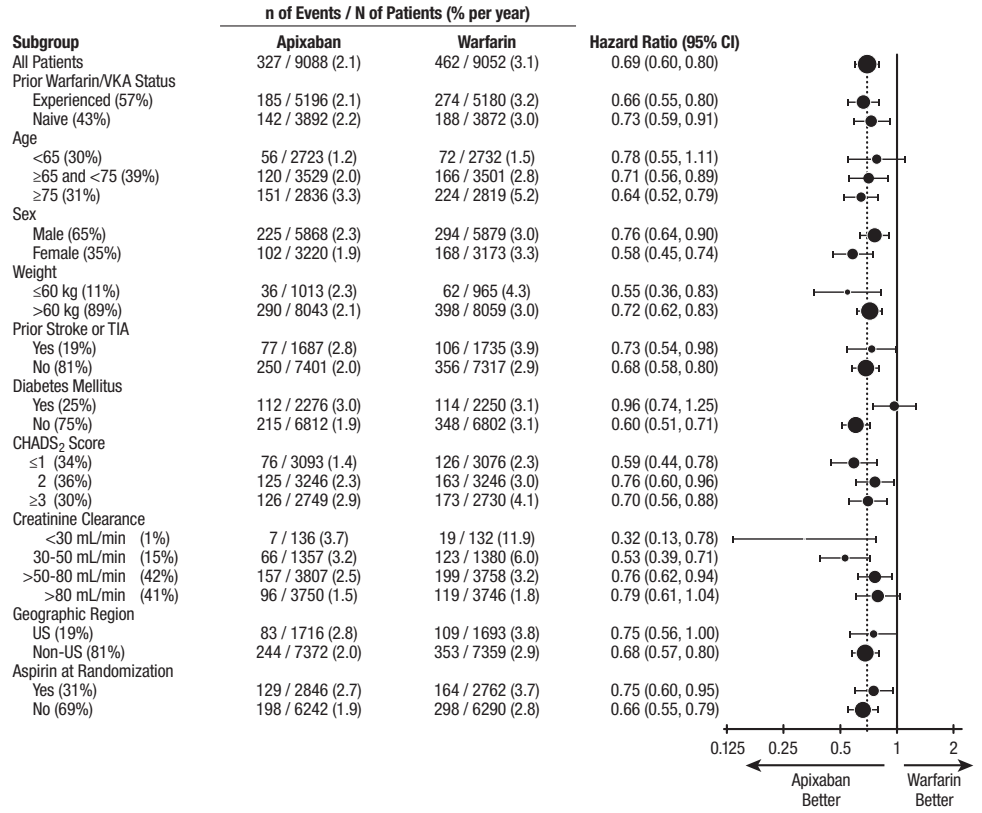
Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

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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WE DID IT ALL

by JEREMY SAMUEL FAUST, MD, MS, MA, FACEP

As Medical Editor in Chief of *ACEP Now*, feedback is never in short supply. When you love something we printed, I hear often about it. When you don't? Well, I *always* hear about that. Many of our most popular articles come from your ideas, whether suggested via email or in person. (This is one reason I really miss in-person conferences!) But one thing can't be denied: people vote with their clicks. The top 10 most read *ACEP Now* articles this year reflect your needs and interests, and they fall into three categories: COVID-19, equity, and "everything else."

The four COVID-19 articles trace our collective journey through this crisis. An early article gave background on SARS-CoV-2 itself, and described the initial patients who were considered "persons under investigation." Highly informative, the article now reads like a historical document; just 10 months later, just about *everyone* we encounter with symptoms (and even many without symptoms) are now considered at risk. We also contextualized COVID-19 versus previous years' pneumonia and flu rates, providing an important window into the magnitude of the pandemic. We then covered pros and cons of various types of coronavirus testing. And while we have subsequently covered all manner of COVID-19 treatments, unsurprisingly, our most popular article on the topic described the safety of ibuprofen for children. (Pediatric pieces always get a lot of attention.)

CONTINUED *on page 11*

TOP 10 ARTICLES OF 2020

COVID-19 for the Emergency Physicians: What You Need to Know *by Christopher Greene, MD, MPH; and David C. Pigott, MD, RDMS, FACEP*

Treatment Strategies for Precipitated Opioid Withdrawal after Naloxone Rescue *by Rachel Haroz, MD; Gerard G. Carroll, MD; and Reuben J. Strayer, MD*

Data Snapshots: U.S. Influenza and Pneumonia Deaths 2013–2020 *by Sam Ashoo, MD, FACEP*

The Safety of Ibuprofen in Children with COVID-19 *by Landon Jones, MD; and Richard M. Cantor, MD, FAAP, FACEP*

Tips for Managing Weber B Ankle Fractures *by Joseph Noack, MD; and Spencer Tomberg, MD*

IV vs. PO: Which Antibiotics Are Better for Common ED Infections? *by Anton Helman, MD, CCFP(EM), FCFP*

Simple Strategies for Combating Microaggressions in the Workplace *by Uché Blackstock, MD*

COVID-19 Testing: What's Available, and Each Test's Pros and Cons *by Ryan Patrick Radecki, MD, MS*

'It's Not a Female Resident Problem' *by Anita Chary, MD, PhD; Emily Cleveland, MD, MPH; Farah Dadabhoy, MD, MSc; Melanie Molina, MD; Margaret Samuels-Kalow, MD, MPhil, MSHP; and Adaira Landry, MD, Med*

After Re-Analysis, No Trials Show Efficacy of tPA in Acute Ischemic Stroke *by Ken Milne, MD*

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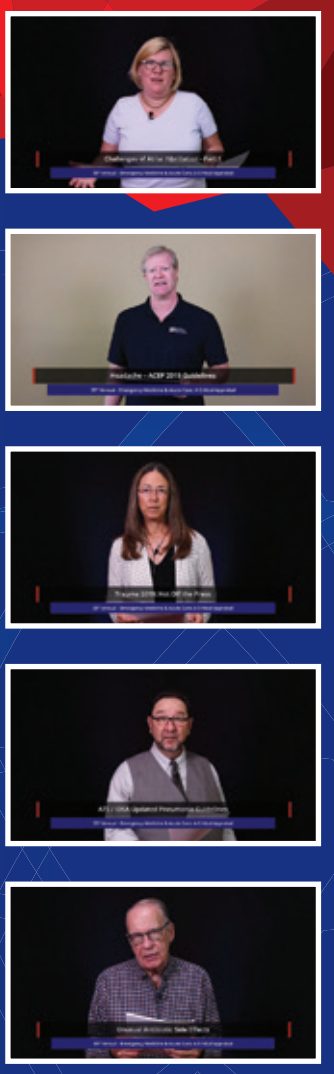
*Topics listed with an asterisk (*) are 90-minute faculty panel discussions; all other topics are 30 minutes.



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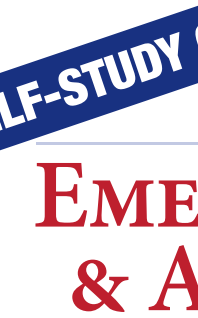

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- Can't Catch Me: Narrow Complex Tachycardias
- Welcome to the Machine: Device Emergencies
- For the Faint of Heart: Cardiogenic Syncope
- Ripping It to Pieces: Acute Aortic Dissection
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enough to have a member, Rob Rodriguez, be on the task force and we've had several conference calls with Rob to see how ACEP can be supportive of his task force initiatives.

Then we have some of our advocacy issues. We want to make sure that we get legislation passed that helps support emergency physicians—for PPE [personal protective equipment], for funding, and also for our wellness, such as the Lorna Breen Provider Protection Act. So many of our members are suffering. We really need to make sure that we can protect, treat, and do harm reduction on all emergency physicians to make sure that they remain healthy and we can have the strongest workforce possible.

Jeremy, what I found that's so amazing is what ACEP has been doing over the years. A lot of our initiatives seem to be coming together as a fabric to help us move forward. Whether we're dealing with health equity or a pandemic response or staffing, all of these pieces seem to be coming to a head right now. It's so exciting because, at the end of the day, the support of ACEP, the support of the entire team, means we will have better solutions in a year than we're walking into right now.

JF: We definitely have embraced our role in testing. For example, tents and adjacent facilities, if not in the emergency department, are certainly run by the emergency department in many cases. Do you foresee that vaccine distribution might work similarly? On one hand, you could say, "Well, the emergency department is isn't the ideal place to have people lining up for vaccines." On the other, again, meet them where they are.

MR: Well, a large portion of the population comes to emergency departments for primary access to health care, and we have to ask ourselves: What is our role in vaccine distribution or administration of monoclonal antibodies and different treatments? I don't want to be so bold to say what our role is because I don't know, but that's where the question comes in. Where can we be part of the solution here? We already are part of the nation's solution when it comes to managing trauma, managing overdoses, managing all these different aspects that plague society. What's our role when it comes to COVID-19?

JF: Looking beyond COVID-19 into the future of ACEP, big picture. With the changing landscape—increasing access to online training, EM subspecialty groups, virtual meetings—what exactly is the value proposition of ACEP itself in the year 2020 and after?

MR: We can't stick to what was status quo. There are evolving needs and roles of emergency physicians, and we can break it down into new graduates versus mid-career versus late career. We could break it down into practice environment, whether we're dealing in rural emergency medicine or academics. ACEP has a different role in each of these areas. This is not just an evolution. This is a complete change in how we managed things in the past and our current needs. We have to be more nimble than ever before because we don't know what's going to happen with the vaccine. We don't know what's going to happen with COVID long term. We don't even know the evolution of emergency medicine when it comes to some future aspects of telemedicine, telemedicine policy, legislation, and payment. I believe that ACEP's role and ACEP's value proposition is bigger than it ever has been.

Every member has different needs, and ACEP can supply those needs to each member. I have always believed, "it's ACEP for life," because if you join us at residency or as a new attending, there are certain aspects of what ACEP can offer you—helping you build a nest egg, helping with your first contract and what it should and shouldn't say, best practices when signing your first job contract. Mid-career, you really start to talk about different life challenges, and wellness and health becomes a bigger issue. What is our role in promoting physician wellbeing, physician support, and physician safety in their practice? As you get into later in your career, the evolution continues because now you're looking toward retirement. How do you stay safe? How do you keep working? So, it's one continuum that we're talking about.

MARK ROSENBERG

Dr. Mark Rosenberg (bottom) and Dr. Jeremy Faust (top) during their Zoom interview.

JF: How are we embracing new technology to reflect the changing world we live in?

MR: One of the things that we have done is try to make our current type of educational meetings fit into a Zoom platform because that's all we understood. What we're learning is if Zoom is part of our culture going forward, our meetings don't have to be the same as they were in person. We tried doing a lot of different things at ACEP20. Some of those worked out really well, but we need to transition from an in-person meeting environment to one that incorporates virtual technology and still make it meaningful. Should a lecture be 20 or 30 minutes instead of 45 minutes or an hour? How long should a Zoom meeting take? Should it be asynchronous? We have an opportunity to find what works best for our members, but one thing for sure is we can't expect it to be the same as completely in-person meetings.

JF: What should ACEP's role be in shaping health care financing reform, and how do we balance concerns for our patients' financial wellbeing with fair reimbursement for our services? How do we get around that inherent conflict?

MR: We've always heard that the emergency department has high costs. But a lot of that comes from the facility charge, not the physician charges. We need to come up with strategies that allow emergency physicians in their practice to earn a decent living, or we're not going to have people working in emergency medicine.

If it was all about balanced billing, that would be one thing, but this really comes down to an insurance question and how health care should be managed and financed. We cannot continue to be paid at a decades-old price structure for the work that we're doing now. There needs to be a whole evolution in payment strategies. We're there 24-7-365 for all our patients. We have the unfunded federal mandate of EMTALA. So, to let the insurance companies be the go-between and restrict how much we get paid is an unfair system.

The emergency department offers a service, and we offer the full capability of the hospital with consultation services and everything else that's available and a pure hand off to the next level of care. Nobody else can do that, and that's where our value is. We are a rapid assessment, diagnosis, and treatment area that can get things done for patients regardless of an emergency, an urgent, unscheduled urgent, or unscheduled acute care situation. We're there, and we have a lot of opportunity to evolve in our future.

JF: What are a few things that you think that ACEP will do over the next two or three years to transform itself and the specialty?

MR: I am in a diverse environment in Patterson, New Jersey. In Patterson, the life expectancy is 73 years, and six miles away, it's 86 years in a more lucrative neighborhood. Why the health disparity, and what's the role of emergency medicine when it comes to providing health equity? That's one major area where I believe the emergency departments can help bring resources to their communities because most emergency departments are community emergency departments. What we are really dealing with there is health equity and using strategies to improve the way emergency medicine takes care of people regardless of their ability to pay, regardless of color, regardless of religion.

The second part is the role of telemedicine. During the pandemic, we saw that many people left nursing homes to come into the emergency department to be seen. In the emergency department, they got admitted to the hospital. The hospitals became crowded, but the nursing homes had lots of open beds because everybody moved out of the nursing home. There's an opportunity to use telemedicine to expand our footprint into nursing homes and other places, plus telemedicine or telehealth into rural America. We always felt that the best emergency medicine is physician-led teams, and we always talked about the role of board-certified, residency-trained emergency physicians. With the help of telemedicine, we can bring that to every community in the country and make it possible that board-certified emergency physicians help lead the physician-led team in emergency medicine.

And, of course, pandemic readiness is now a major focus of emergency medicine. I saw the way we shifted our approach to pain and addiction when the pandemic exacerbated the problem with closed pain centers and doctors' offices. I saw the way emergency physicians provided palliative care as they held the hands of those actively dying and helped families communicate over telemedicine. We did more than we ever thought was possible. In many ways, COVID brought out the best in emergency medicine. We can take those parts forward as we improve the safety of the emergency physician in this pandemic and any in the future.

I have assigned objectives related to these three issues to many of ACEP's committees this year. We can take all these great minds and thoughts to work together in an ACEP think tank I like to call the Innovation Center. Within this structure, we can develop ways where we as emergency physicians can better solve these problems in our communities.

As we look at the job opportunities for our residents, I think a lot of it will be outside the bricks-and-mortar of the emergency department and will now allow us to really transcend into communities that we're not even physically in at the time. There is a huge, huge opportunity for us. The future is bright. It's pretty exciting where we're going to go, but it's not a one-year change.

JF: Let's close by getting to know you just a bit better. What is something that the average ACEP member might not know about you personally that would help them understand who you are as a person and as a leader?

MR: When I got into emergency medicine, I really thought that you would be a superhero if you could save a life, and the only specialty that I knew of that would allow us to be superheroes every day was emergency medicine. Every day we set foot in our emergency departments across the country and we make a difference to the patients where we see them, some a small difference, some a major difference. Sometimes it could be just stabilizing somebody who's depressed and suicidal versus somebody who has a cardiogenic shock from a massive [myocardial infarction] and needs to go to the cath lab.

I wanted to be a superhero. I wanted to have that ability. I don't care about people knowing my name. I didn't care about that piece. I cared about coming home and feeling the power that it is when you save a life.

One day, I got called to [labor and delivery]. It was May 25. Why are they calling me to labor and delivery? This is ridiculous. And why do I have to leave the emergency department? I go up to labor and delivery, and they said, "Doc, we need you to resuscitate this newborn. We're doing an emergency C-section right now, and we can't get the neonatologist. You're it."

I was in a small community hospital, and they hand me this pulseless, limp, infant baby, newborn. I had never resuscitated a newborn before, but I trained. I practiced on a mannequin over and over again how to intubate. I knew how to put in lines. I knew everything. Now, I had to do it. I remember looking in the airway, trying to get in the tube, and all of a sudden, things seem to magnify and slow down. And the tube went in and the line went in. By this time, the neonatologist comes in, and Michael Edward was breathing on his own and doing very, very well with a little assistance.

I went down the hallway back to the emergency department, and I'd never, ever in my life felt so good. I was floating. I felt absolutely amazing. And it's that feeling that keeps me going every single day. But there's another part to the story. That was my birthday, and *I always work on my birthday.*

One year later, I'm in the emergency department working on my birthday, and who comes in but 1-year-old Michael Edward. He was bringing balloons to give me a birthday wish, and his mom said, "You were the one who gave him his first breath. We wanted to be here for your birthday." That may only happen once or twice in your career, but you want to know something? I felt like a superhero that day.

What we all have is the inner drive to go toward danger, not away from it, to treat each and every person, regardless of race and gender or anything else, as a person who we can help. When we do, they may turn around at the end of the day and say, "What was that doctor's name again?" And it doesn't matter. They know we were emergency physicians. They know that we were the best thing they saw on their worst day. That's what makes emergency medicine special.

FROM THE EDITOR | CONTINUED FROM PAGE 8

The other major story this year—which would have been the lead story in any other year—was medicine's reckoning with equity, racism, and sexism in medicine. After I accepted the position as Medical Editor in Chief, the *very* first thing I did was to create a recurring column called "Equity Equation." Our article on combatting microagressions in the workplace (written by one of the founding curators of the Equity Equation column, Dr. Uché Blackstock) has quickly become an important online resource.

And while the "Me Too" movement is no longer a new one, our field continues to address those and other systemic issues related to sexism. A powerful piece shining light on the subtle and not-so-subtle disadvantages (entitled "It's Not a Female Resident Problem") faced by women in medicine pairs well with the microaggressions article—and both should be required reading.

Then there's everything else. What could be more representative of emergency medicine as a field than the simple fact that we confronted two major crises *and* still treated our usual complement of patients and their diverse problems? We have to keep up with new literature and stay fresh on bread-and-butter care that we might encounter on any given shift.

The opioid epidemic rages on. With more overdoses comes more naloxone. And with more naloxone comes more precipitated withdrawal. We covered how to manage it humanely. Meanwhile, the year would not be complete without some new literature to muddy the waters on stroke management. As Dr. Ken Milne showed us, the evidence for alteplase for acute ischemic stroke continues to underwhelm—especially when re-analysis takes into account the baseline differences between patients in the control and intervention arm of the major trials.

The award for "article that taught me the most medicine" goes to Dr. Anton Helman's "IV vs. PO: Which Antibiotics Are Better for Common ED Infections?" Sure, I knew that oral antibiotics are safe for a wide variety of infections. But bacteremia? You have to be impressed.

And last but not least, just to drive home the point that emergency physicians must be ready for anything, an article on the finer points of managing fibular fractures. I thought I was smart for remembering that we are supposed to get "manual stress views" for assessing ligament stability in Weber B ankle fractures. But it turns out that gravity and weight-bearing stress radiographs are enough!

What will 2021 teach us? You tell me! My ears and inbox are open to your ideas. Send your suggestions to acepnow@acep.org.

DR. FAUST is an instructor at Harvard Medical School and an attending physician in the department of emergency medicine at Brigham and Women's Hospital in Boston.

UNCONVENTIONAL 2020

In this unprecedented year, ACEP20: Unconventional was an unequivocal success! Although the COVID-19 pandemic meant we couldn't gather in person, thousands of emergency physicians met online for a unique digital experience to learn, network, and celebrate our specialty. Here's a snapshot of the meeting, by the numbers.

TOTAL REGISTERED ATTENDEES
8,059

TOTAL EVENTS VIEWED
1,191,439

AVERAGE TIME SPENT PER VISIT
19 MINUTES

HOW VIEWED

64.54% DESKTOP

32.21% MOBILE

3.15% TABLET

#ACEP20 POSTS ON SOCIAL MEDIA
6,813

#ACEP20 IMPRESSIONS
32,779,175

MOST POPULAR LIVE COURSES

Opening General Session: NIAID Director Dr. Anthony Fauci and Lessons Learned: Global Response to COVID-19
8,309 total views

Critical Update: Coronavirus (COVID-19)
2,307 total views

Acute Decompensated Heart Failure: Time Critical Interventions
2,075 total views

Racial Health Disparities and Inequities in America: Where Do We Go From Here? featuring Ibram X. Kendi
1,848 total views

MOST POPULAR ON DEMAND COURSES

Opening General Session: NIAID Director Dr. Anthony Fauci and Lessons Learned: Global Response to COVID-19
3,412 total views

A Fistful of Fractures
2,370 total views

ACLS Guidelines 2020: What's New and Why
1,936 total views

How Will COVID-19 Affect Our Financial Future? Presented by the Young Physicians Section
1,819 total views

RESIDENCY SPOTLIGHT

UNIVERSITY OF CALIFORNIA SAN FRANCISCO–SAN FRANCISCO GENERAL HOSPITAL EMERGENCY MEDICINE RESIDENCY PROGRAM

Twitter: @ucsfdem

Location: San Francisco

Year founded: 2008

Current number of residents: 57

Program length: Four years

What sets your program apart?

- **Diversity of training institutions and patient populations:** Local residents, referrals from throughout the state, and visitors from all corners of the globe seek care at our institutions. Residents spend half their time at San Francisco General Hospital, which serves as the city and county's only trauma center (Level 1) and is a critical safety-net hospital with approximately 80 percent of patients being uninsured or receiving publicly funded health insurance. Our residents spend the other half of their time at UCSF Health, which consists of UCSF Medical Center at Parnassus and UCSF Medical Center at Mission Bay (where the UCSF Benioff Children's Hospital and Pediatric Emergency Department is located). If it exists, our residents will see it during the course of their training.
- **Award-winning faculty:** Our talented faculty are recognized leaders within education, research, policy, pediatric emergency medicine, toxicology, global health, EMS and disaster medicine, and ultrasound.
- **Diverse and passionate residents:** Our phenomenally talented residents draw strength from their diversity and are staunch and unwavering advocates and allies of the underrepresented, the sick, the vulnerable, and the downtrodden among us.

What unique benefits does your city offer?

The San Francisco Bay Area offers a wide range of neighborhoods, many with their own themed festivals scattered throughout the year in addition to citywide celebrations such as Pride Week and the wackiest foot race in the country, the Bay to Breakers. We have every kind of food you can imagine, world-class sports teams and venues, cultural diversity that is second to none, an incredible variety of arts and entertainment options, and easy access to outdoor activities. Want to surf in the morning and ski the Tahoe slopes in the afternoon? Does dim sum in the morning and Napa or Sonoma Valley wine tasting call to you? How about hiking or mountain biking in the Marin Headlands and returning across the iconic Golden Gate Bridge in time for an incredible Mission District meal?

Recent publications of note

- Degesys NF, Wang RC, Kwan E, et al. Correlation between N95 extended use and reuse and fit failure in an emergency department. *JAMA*. 2020;324(1):94-96.
- Rodriguez RM, Torres JR, Sun J, et al. Declared impact of the US President's statements and campaign statements on Latino populations' perceptions of safety and emergency care access. *PLoS One*. 2019;14(10):e0222837.
- Diaz T, Navarro JR, Chen EH. An institutional approach to fostering inclusion and addressing racial bias: implications for diversity in academic medicine. *Teach Learn Med*. 2020;32(1):110-116.

—Christopher Fee, MD, residency program director

DEADLY DIET DRUG

HYPERTHERMIC DEATH FROM THE DIET PILL DNP

by JESSA BAKER, MD; AND MARK BAKER, MD

The Case

A 22-year-old male arrived in the emergency department at 12:36 a.m., accompanied by his mother. His chief complaint was palpitations and sweating for three hours. He told the triage nurse he was taking "DNP, the fat-burning pill." He had been taking the medication for two weeks and reported taking a "double dose" that evening. Later, he noted palpitations and excessive sweating. Triage vital signs included a pulse of 152, blood pressure of 134/77, oxygen saturation of 99 percent, and temperature of 37.1°C (98.7°F). His weight was 104.8 kg. An ECG showed sinus tachycardia. The patient was put in a treatment room at 12:58 a.m. Initial physical examination was remarkable for an otherwise healthy young man who was diaphoretic and tachycardic and appeared moderately agitated. Laboratory studies, IV fluids, urine toxicology, and a portable chest X-ray were ordered after examination. IV lorazepam was given for agitation. The heart rate did not change despite IV fluids and lorazepam. It was noted by his nurse that it was difficult to keep the cardiac monitor leads on because of profuse sweating.

The patient's nurse learned that he took 1,000 mg of 2,4-Dinitrophenol (DNP) at about 9 p.m. A rapid review of literature done by the physician revealed deaths from hyperthermia from DNP due to decoupling of oxidative phosphorylation. The search also revealed that a typical dose is 200–400 mg. At 2:58 a.m., the physician asked for consultation with poison control and a recheck of temperature, which was 39.4°C (103.0°F). Topical cooling measures with ice packs were started immediately, and IV acetaminophen was ordered.

The physician was connected to the toxicologist at the Rocky Mountain Poison and Drug Center and asked if dantrolene and/or beta blockers would be useful. The toxicologist reported that, theoretically, acetaminophen and dantrolene would not help and suggested that paralysis with cooling measures might be necessary. While the physician was on the phone with the toxicologist, the patient deteriorated and was moved to a resuscitation room.

The patient was now having violent rigors and sweating profusely. The emergency department team prepared for rapid sequence intubation (RSI). The patient was given 2 mg of midazolam followed by 10 mg of vecuronium. There was a brief moment of muscle relaxation insufficient for intubation, followed by the patient's jaw becoming clenched in a closed position. At 3:20 a.m., shortly after vecuronium administration, the patient became asystolic. Chest compressions were started. Asystole had no impact on muscle rigidity. IV placement was confirmed, and an additional 10 mg of vecuronium was given but had no paralytic effect on the patient, who now had whole-body rigidity. The emergency department physician was able to perform nasal intubation blindly with a 6.5 French endotracheal tube, confirmed by breath sounds and capnometer.

The staff hoped the patient would regain a cardiac rhythm by decreasing the core temperature. Aggressive cooling measures were used, including ice and ice water on all exposed skin, ice packs around the neck, IV saline in buckets of ice water, and a cooling blanket. Fans were not available. Despite these cooling measures, at 3:40 a.m., the rectal temperature had increased to 42.1°C (107.8°F). Asystole persisted, and advanced cardiovascular life support measures were continued. Rectal temperatures continued to rise, and at 3:49 a.m. while still covered with ice, the temperature was 42.3°C (108.2°F).

The patient remained in asystole during the entire resuscitation. Near the end of the attempted resuscitation, there was pink frothy fluid coming from the endotracheal tube. At 4:13 a.m., resuscitation efforts were stopped, and the patient was pronounced dead. A postmortem rectal temperature was 42.9°C (109.3°F). The core temperature had continued to rise for almost an hour during attempted resuscitation despite being covered with ice and ice water and infused with IV iced saline.

The Honolulu Police Department and the coroner were contacted. A family member was sent home to retrieve any available medications and returned with a bag, which included caffeine, propranolol, ephedrine with guaifenesin, and n-acetylcysteine (used for weight loss) but no DNP.[1] Family members were not aware of where the patient obtained the drug. The next day the state Department of Health was contacted, which then contacted the US Food and Drug Administration (FDA).

Discussion

DNP is a compound that was first described during World War I. It was initially manufactured to make explosives and has also been used in manufacturing sulfur black dye, pesticides, wood preservatives, and photographic developing chemicals.[2,3] The lethality of DNP was first reported in 1918 after numerous deaths of factory workers in the United States and France were linked to DNP exposure.[4] DNP was studied at Stanford in the 1930s, during which time it was prescribed for weight loss.[5] More side effects were identified, including cataracts, liver failure, and agranulocytosis. It was determined to be unfit for human consumption and was banned by the FDA in 1938.[6]

To understand the impact of DNP on heat production, we review the biochemistry of cellular respiration. Glycolysis is a biochemical process that results in the conversion of glucose into two ATP molecules, two NADH molecules, and two pyruvate molecules. The Krebs cycle follows and produces two more ATP, six NADH and H+ molecules, two FADH2 molecules, and the CO_2 that we exhale. The final phase is oxidative phosphorylation, where the majority of energy is produced; 34 more ATP are created from ADP. With normal oxidative phosphorylation, ATP synthase converts ADP to ATP by adding an inorganic phosphate molecule. DNP interferes with this process by preventing phosphorous uptake into the mitochondria. DNP also allows hydrogen ions to leak across the mitochondrial membrane, thus bypassing ATP synthase.[3] The potential energy that is normally stored during ATP production is released as heat, causing hyperthermia and calorie consumption through further carbohydrate and fat breakdown as cells attempt to create more ATP. This is the characteristic that made it a popular weight loss drug in the 1930s and what continues to make it prevalent today.

DNP causes release of calcium stores from mitochondria and prevents re-uptake; this free intracellular calcium in muscle cells causes unopposed muscle contraction and hyperthermia. The continuous release of calcium following death may also contribute to the rise in body temperature even after cardiopulmonary arrest.[3]

DNP toxicity most commonly presents as hyperthermia, tachycardia, tachypnea, and diaphoresis.[3,6,7] There have been numerous case reports of overdoses on this drug, with rare survivors but no known survivors of cardiac arrest.[6] The drug has a narrow therapeutic window for its "desired effects," and even slight deviations in dosing have been fatal. Case reports document generalized muscular rigidity, making intubation and mechanical ventilation difficult.[7]

DNP is typically sold illegally on the internet. Common names include DNP, Dinosan, Dnoc, Solfo Black, Nitrophen, Aldifen, and Chemox. Websites that sell DNP illegally offer advice on its use; a Google search of "buy DNP" yields pages of results. A typical recommended starting dose is 200 mg per day, and if tolerated, it can be increased to 400 mg daily. Some websites warn users about hyperthermia and recommend exercising in air-conditioned environments, lowering the dose for temperatures over 38.9°C (102°F), taking a cold bath, and ensuring adequate hydration.[8] A vivid description from a patient who took DNP and became hyperthermic can be found on Wikipedia.[9]

Use of the drug for weight loss is making a resurgence. There has been an increasing number of articles describing overdoses resulting in deaths of young body builders and athletes.[6,10] In May 2016, Adam Alden of Bakersfield, California, pled guilty to introducing an unapproved drug into interstate commerce after a customer who purchased DNP via the internet died of DNP ingestion.[11] In 2018, a seller of DNP was convicted of manslaughter in the United Kingdom after selling and marketing DNP as a "fat burner" for human use. A March 2020 retrial confirmed the conviction and a seven-year sentence.[12,13]

A review of the medical literature shows there are no established recommendations for care. Early aggressive management is often recommended, including cooling, fluid resuscitation, early intubation, and admission to an ICU. Acetaminophen theoretically does *not* help lower the temperature. Dantrolene has been discussed in case reports as a potential treatment, but its use remains controversial.[14,15] In a case where dantrolene was reported to have been successful in reducing temperature (in addition to cooling measures being applied), the patient had a temperature of 40.0°C. In a case where dantrolene was unsuccessful, the patient's temperature was 41.5°C.[14] The authors of the latter case state success using dantrolene is biochemically implausible.

Paralysis with intubation should be considered early; however, paralysis may not be possible due to the mechanism of action. DNP affects muscle contraction at the cellular level, whereas paralytic agents impact the neuromuscular junction. Rigidity causing difficult intubations has been reported in numerous case reports. In this patient, blind nasal tracheal intubation was possible and potentially was facilitated by paralysis of the vocal cords in an open position. A surgical airway should also be considered.

Aggressive cooling is likely the best hope for survival. From the authors' perspective, the impact of DNP at the cellular

KEY POINTS

- DNP is a diet drug with a very narrow therapeutic window that causes death by hyperthermia.
- Airway control is compromised by muscle contraction at the cellular level.
- Reversing the hyperthermic effect of DNP is difficult and may be impossible after a certain temperature has been reached.

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level is likely to become irreversible at some point where no amount of cooling or pharmacological intervention will result in survival—a "point of no return." The decoupling of oxidative phosphorylation and the conversion of glucose into heat increase the body temperature, which likely accelerates the rate of reaction, resulting in more heat production, similar to an explosion. Stopping the process before it reaches the point of no return is essential. The question to be answered is how to determine that point of no return. The authors suggest that a core temperature above 38.3°C (101°F) should prompt aggressive treatment, including intubation and aggressive cooling.

Conclusion

DNP is a diet drug that has been banned by the FDA. It has a very narrow therapeutic window, which has resulted in accidental death by hyperthermia of a number of patients, including the young man described in this article. Reversing the hyperthermic effect of DNP is difficult and may be impossible after a certain temperature has been reached. Airway control is compromised by muscle contraction at the cellular level. Death from taking this drug is tragic; those who cared for this patient felt this was a horrific way to die. Efforts to stop distribution of the drug are taking place in some countries and should be increased worldwide.

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TOXICOLOGY Q&A

Don't take a Bite!

PHOTO: JASON HACK (OLEANDER PHOTOGRAPHY)

by JASON HACK, MD, FACEP, FACMT

QUESTION: What are the side effects of chewing this beautiful bloom?

Visit ACEPNow.com for the answer.

DR. HACK is chief of the division of medical toxicology and vice chair for research at East Carolina University in Greenville, North Carolina.

By the Numbers

U.S. COVID-19 Demographics

AS OF NOVEMBER 22, 2020, THE U.S. HAD:

12,028,081 CASES

255,076 DEATHS

CASES

25% Hispanic/Latinx

14.8% Black non-Hispanic

3% Asian

52% FEMALE

DEATHS

MORE THAN 75% OCCUR IN PATIENTS ≥65 YEARS

25% Hispanic/Latinx

19% Black non-Hispanic

4.4% Asian

54% MALE

HISPANIC/LATINX + BLACK PATIENTS ACCOUNT FOR

62% OF DEATHS IN PATIENTS 18–64 YEARS

54% OF DEATHS IN PATIENTS 0–17 YEARS

>60% OF DEATHS IN PATIENTS 0–4 AND >80 YEARS ARE **FEMALE PATIENTS**

>60% OF DEATHS IN PATIENTS 5–74 YEARS ARE **MALE PATIENTS**

HOSPITALIZATION

Age-adjusted hospitalization rates compared to non-Hispanic white patients

4.1X HISPANIC/LATINX PATIENTS

3.7X BLACK PATIENTS

4.0X AMERICAN INDIAN OR ALASKA NATIVE PATIENTS

Compiled by Joshua Niforatos, MD, MTS, an emergency medicine resident at the Johns Hopkins School of Medicine in Baltimore and research editor of Brief19.com. Visit **ACEPNow.com** for the sources of these statistics.

2020 ACEP Council Resolutions

COUNCIL ADDRESSES PPE, TERMINOLOGY, AND MORE

The ACEP Council conducted its meeting virtually this year in advance of ACEP20 Unconventional. The Council consists of members representing ACEP's 53 chapters, 39 sections of membership, the Association of Academic Chairs of Emergency Medicine, the Council of Emergency Medicine Residency Directors, the Emergency Medicine Residents' Association, and the Society for Academic Emergency Medicine.

Using a virtual platform that allowed for feedback and voting, the Council addressed many pressing concerns facing emergency medicine and the College. More than 600 logged in to participate this year, and an additional 250 live-streamed the meeting through the ACEP20 website.

The Council and the Board of Directors adopted non-bylaws resolutions related to the following:

- ACEP Membership and Leadership (as amended)
- Framework to Assess the Work of the College Through the Lens of Health Equity (as amended)
- ACEP Award for Excellence in Innovations in the ED Care of Patients with Behavioral Health and Substance Use Disorder (as amended)
- Medical Society Consortium on Climate and Health
- State Media Training for Emergency Physicians
- 911 Awareness and Policy (as amended)
- Adverse Impact of Healthcare Insurers on Emergency Medicine Reimbursement and Optimal Patient Coverage
- Addressing Systemic Racism as a Public Health Crisis (as amended)
- Attributing the Unqualified Term "Resident" to Physicians (as amended, last 3 resolveds)
- Billing and Collections Transparency in Emergency Medicine (as amended, first 2 resolveds)
- Protection and Transparency (as amended)
- Insurer Accountability/Policy Weakness Disclosure (as amended)
- Public/School Bleeding Control Kit Access and Training
- Supporting the Development of a Seamless Healthcare Delivery System to Include Prehospital Care
- Universal Access to Telehealth Care
- Personal Protection Equipment (as amended)
- Addressing Ethical Challenges of the COVID-19 Pandemic for Emergency Physicians (as amended)
- Creating a Culture of Anti-Discrimination in Our Emergency Departments and Healthcare Institutions (as amended)
- Honoring Employment Contracts for Graduating Emergency Medicine Residents (as amended)
- Strangulation Policy Statement and Educational Resources (as substituted in lieu of Resolution 28 and Resolution 49)
- Support for Expedited Partner Therapy
- Telehealth Disaster Pilot and Educational Resources

The Council referred the following resolutions to the Board of Directors for further discussion:

- Attributing the Unqualified Term "Resident" to Physicians (as amended, first resolved)
- Billing and Collections Transparency in Emergency Medicine (as amended, last 3 resolveds)
- Telehealth Free Choice (as substituted in lieu of Resolution 36 and Resolution 37)
- Due Process in Emergency Medicine (as amended)
- Emergency Licensing and Protection in Disasters (as amended)
- Residency Program Expansion
- The Corporate Practice of Medicine

The Council and the Board of Directors adopted a College Manual amendment replacing by substitution the Procedures for Addressing Charges of Ethical Violations and Other Misconduct and three bylaws resolutions:

- ACEP Committee Quorum Requirement
- Ethics Procedures
- Special Board of Directors Meetings

The Board deferred action on one bylaws resolution, Counting Fellowship Training Time Toward FACEP, to its Jan. 23–24, 2021, meeting, pending clarification from the Bylaws Committee regarding implementation of the resolution.

The Council also adopted three Council Standing Rules amendments:

- Commendation and Memorial Resolutions
- Council Resolution Sponsors and Cosponsors
- Unanimous Consent Agenda.

Council Standing Rules amendments do not require action by the Board of Directors.

ELECTION 2020

EPs HEADED TO CONGRESS

Three emergency physicians won their races for seats in the U.S. House of Representatives in the 2020 election. Congratulations to:

Rep. Mark Green, MD (R, TN-7)

A graduate of West Point, Dr. Green attended Boonshoft School of Medicine at Wright State University and became a flight surgeon, serving tours of duty in the Afghanistan War and Iraq War. Following his military retirement in 2006, Dr. Green founded a hospital emergency department physician group in Tennessee as well as two free clinics.

Dr. Green was first elected to the house in in 2018 and currently serves on the Foreign Affairs, Homeland Security, and Oversight and Reform committees. Dr. Green has sponsored legislation important to emergency medicine, especially in the areas of rural health and access to care.

Rear Admiral (Ret.) Ronny Jackson, MD (R, TX-13)

Dr. Jackson graduated from Texas A&M University at Galveston and then attended medical school at the University of Texas Medical Branch. In 1995, he began his active-duty military career as an officer in the U.S. Navy. In 2001, Dr. Jackson returned to the Naval Hospital in Portsmouth, Virginia, to complete his residency in emergency medicine.

In 2006, while serving in Iraq, Dr. Jackson was selected as a White House physician in the George W. Bush administration. He served in the White House until he retired from the military as rear admiral on Dec. 1, 2019, with his last duty assignment at the White House. This will be his first term in Congress.

Rep. Raul Ruiz, MD, MPH, MPP (D, CA-36)

Dr. Ruiz attended Harvard University in Boston, where he earned his medical degree as well as a masters of public policy from the Kennedy School of Government and a masters of public health from the School of Public Health, becoming the first Latino to earn three graduate degrees from Harvard University.

Dr. Ruiz worked full-time as an emergency physician until he was elected to the U.S. House of Representatives, where he serves on the House Energy & Commerce Committee. Dr. Ruiz has sponsored many bills important to emergency medicine, including surprise medical billing, mental illness care, and veterans' care.

Consider This When Evaluating Mysterious Back Pain

A hemorrhage in the spinal cord can present like cauda equina syndrome

by SANTIAGO LOPEZ, MD; ADAM SCHWARTZ, DO; AND CORMAC SMITH, MD

The Case

A 33-year-old female with a past medical history of anxiety presented to the emergency department complaining of back pain and right lower extremity weakness. The patient denied any recent illnesses, nausea, vomiting, fevers, or chills but reported three days of low back pain, recent onset of right lower extremity weakness, numbness, and tingling. She said that the weakness began suddenly, approximately 20 hours prior to ED arrival.

On arrival, her temperature was 97.9°F, pulse 109 bpm, respiratory rate 20, blood pressure 130/90, and oxygen saturation 98 percent on room air. The physical exam revealed a nonambulatory alert and oriented, well-developed, well-appearing, anxious woman in no acute distress. The patient's musculoskeletal exam was positive for midline tenderness on the lumbar spine located in the L4, L5 region. Neurologically, she had decreased strength (1/5) in the right lower extremity, with decreased sensation down her right lower extremity as well as diminished deep tendon reflexes. The left lower extremity was normal.

Upon further questioning, the patient reported an inability to void for 24 hours. A bedside ultrasound of her bladder demonstrated significant bladder distention. A Foley catheter was placed, and 1 L of urine promptly drained.

The patient was undressed for a detailed integumentary system exam, which did not reveal any insects, insect bites, or rash. All laboratory work was unremarkable and within normal limits. Neurology and neurosurgery were emergently consulted, and the patient was taken for immediate MRI without contrast of the brain, cervical spine, thoracic spine, and lumbar spine.

The MRI demonstrated expansion of the spinal cord, starting at C5 and extending to the T9–T10 level (see Figure 1). The MRI showed areas of hemorrhage in the spinal cord most prominent at the T2 level, with multiple serpentine structures consistent with a spinal cord vascular malformation (sAVM) (see Figure 2). The cord edema and expansion presumably reflected venous congestion/hypertension (see Figure 3). A neurosurgery consultation was obtained, and a catheter angiography was performed, localizing the lesion. At the choice of the patient and her family, the patient elected to transfer to another hospital.

Discussion

Spinal cord arteriovenous malformations account for roughly 20 percent of all spinal masses and 3–4 percent of all space-occupying lesions in the spinal cord.[1,2] The definitive diagnosis and treatment is to perform an angiogram with embolization (which has replaced digital subtraction angiography).[1] Annually, about 300 patients in the United States present with an sAVM requiring hospital treatment, and the average length of related stays decreased from nine to six days between 1995 and 2006.[3]

Classifying sAVM type is essential to decide the best course of treatment (see Table 1).

The patient presented here was diagnosed with a type II sAVM: intramedullary AVM. These typically cause symptoms in patients in their third decade of life. The presentation can be similar as in this case, with sudden onset or loss of neurological function and pain *below* the level of the lesion.[4] The cause of sAVMs is unknown, but it is postulated they might be genetic.[5] Management of sAVMs depends on more than just the type or location but the ability and surgical experience of the neurosurgeon.

Conclusion

Intramedullary sAVMs are a rare cause of acute neurological deficit and back pain that may present similarly to cauda equina syndrome. Although this patient did not suffer from cauda equina, all symptomatology that was appreciated by the patient fit the criteria for said pathology, which promoted the emergent imaging. Emergency physicians must identify and recognize this as possible cause of acute back pain. If any of the usual red flags for back pain are present, an MRI is recommended in conjunction with neurology and neurosurgery consultation. The emergency physician should make a quick decision for imaging to identify life- or function-threatening pathology.

Look for the following when evaluating a patient with back pain:

- Decreased sensation of the lower extremities
- Decreased muscle strength
- Perineal paresthesia
- Urinary or bowel incontinence/retention

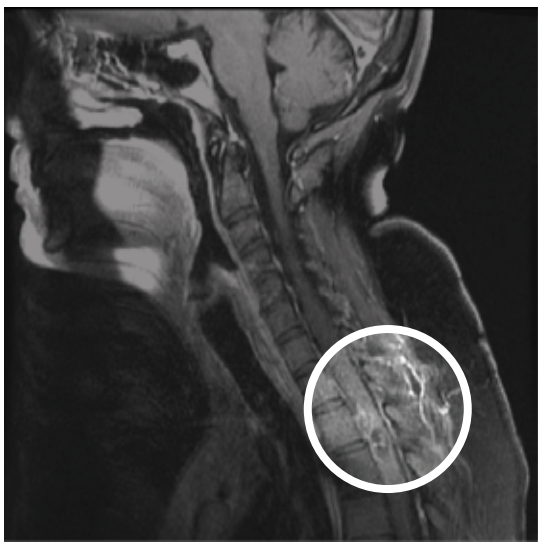

Figure 1: Cervical MRI showing expansion of the cervical cord, originating at the C5 level and extending into the lower thoracic spine. The most prominent areas of hemorrhage are in the T2– T3 levels, with multiple serpentine structures.

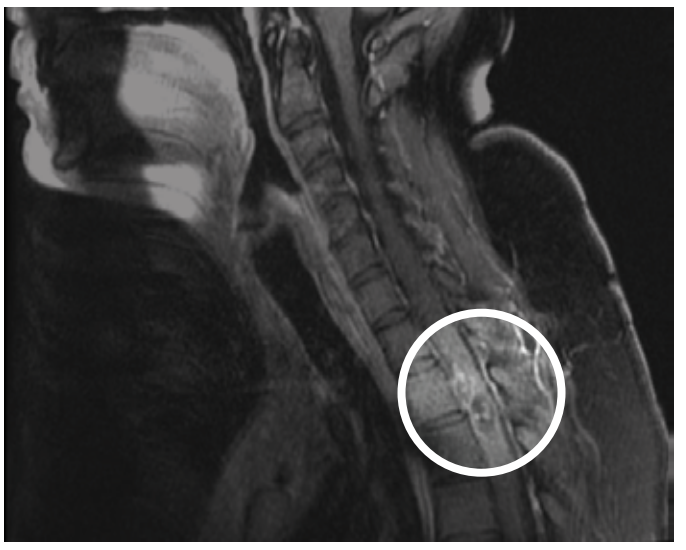

Figure 2: Thoracic MRI showing areas of hemorrhage in the spinal cord most prominent at the T2–T3 level, with multiple serpentine structures, most in keeping with a spinal cord vascular malformation such as an sAVM.

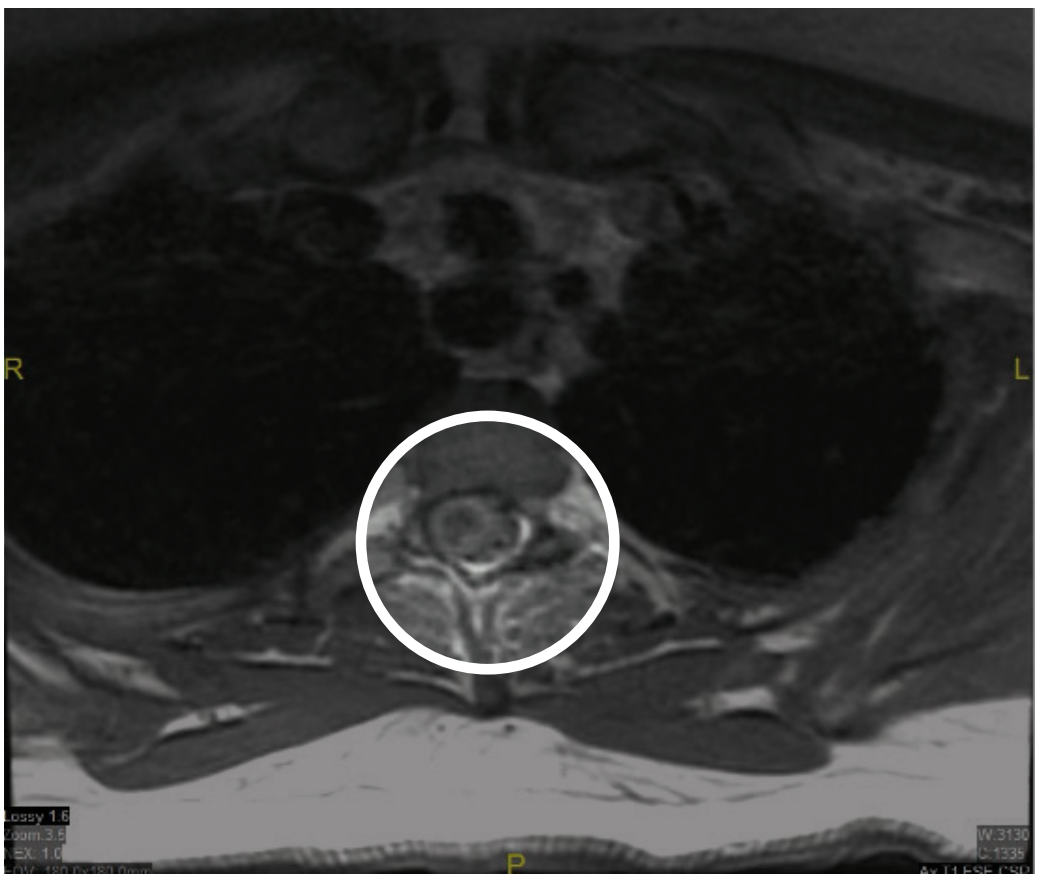

Figure 3: Thoracic MRI expressing cord edema and expansion, presumably reflecting venous congestion/ hypertension. The cord appears to be scalloped due to dilated perivascular vessels.

Table 1: AVM Types

Type I	Spinal Dural Arteriovenous Fistula
Type II	Intramedullary AVM
Type III	Juvenile Malformations
Type IV	Intradural or Premedullary AVM

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Cardiology

High-sensitivity troponin assays have continued to become more commonly used, and the HIGH-US study is one of the most thorough large-scale validations of the rapid rule-out algorithms demonstrated in Europe.[1] This study evaluated two pathways for diagnosis of acute myocardial infarction (AMI), generating consistently mixed results. The most important result from this study is the continued demonstration that a single high-sensitivity troponin below the limit of detection can be sufficient for ruling out AMI. Also, using these new assays for rapid repeat testing is safe, with good sensitivity for AMI. Unfortunately, these assays and algorithms still fail to fully provide clarity, as nearly a third of the patients evaluated still required "continued evaluations" despite the additional precision offered in these tests.

Much has been written about using computed tomography coronary angiography (CTCA) to exclude acute coronary syndrome (ACS) in the initial evaluation of chest pain in the emergency department. Interestingly, there may yet be a role for CTCA even following the diagnosis of ACS. In a study in which CTCA was performed *prior* to invasive coronary angiography in patients with a non-ST segment elevation ACS, nearly a quarter of patients were shown to have coronary stenosis under 50 percent.[2] The implication for downstream management is that resource-intensive and costly procedures might be avoided in a large cohort of patients.

Speaking of avoiding low-value procedures, another study took a population-level look at noninvasive cardiac testing.[3] This study, performed in the Kaiser Permanente Southern California population, tried to tease out an association between receipt of (primarily) early stress testing on subsequent myocardial infarction and mortality. Based on these data, the authors concluded there *may* be a benefit to such testing, but between 200 and 500 tests would need to be performed to inform management to improve the outcome of one additional patient. These data may provide some of the first insights into beneficial effects of follow-up noninvasive testing but clearly demonstrate the need for further studies to elucidate the highest-yield population.

Finally, the last point of curiosity involved physician interpretations of the electrocardiogram (ECG). Many physicians poke fun at the erroneous interpretations of the computer embedded in the ECG machine, but a study collating the accuracy of physician ECG reading was humbling.[4] In a meta-analysis of ECG interpretation skills, after discarding medical students and trainees, pooled performance for physician accuracy sat squarely between 60 and 80 percent. Much depends on the specifics of each included study, but it should be clear there is always work to be done on improving ECG reading skills—and the computers may be better than we thought.

Intra-Abdominal Infections

One of the highest-profile articles published this year concerned the use of antibiotics for appendicitis.[5] Several earlier studies indicated a nonsurgical approach is safe, and a majority of patients have a durable long-term avoidance of appendectomy. However, the proportion of patients who do ultimately require an appendectomy remains nontrivial, leaving many still finding value in an initial surgical strategy. The most important insight from this most recent trial is the role an appendicolith identified on initial imaging plays in treatment failure. Of those who failed an initial nonsurgical approach, 41 percent had an appendicolith compared to only 25 percent of those without. These data further detail the information potentially incorporated into shared decision-making conversations. As antibiotic treatment increases for appendicitis, a decrease in antibiotic use is being seen for diverticulitis. In yet another trial, patients with diverticulitis managed with and without antibiotics showed similar outcomes.[6] This time, the patient population involved those admitted to the hospital with uncomplicated diverticulitis, using a primary outcome of in-hospital length of stay. Although there was no difference in this outcome, and no statistical difference in secondary adverse outcomes, it remains likely that a few patients benefit from antibiotics; figuring out which ones is not so easy though. As with appendicitis, additional data are necessary for teasing out any features of those patients for whom antibiotics play a role.

Advanced Imaging

Yet again, we find there is no clear mechanism to stave off so-called contrast-induced nephropathy (CIN) from CT imaging. The Kompas trial enrolled patients with stage 3 chronic kidney disease undergoing contrast-enhanced CT and found no benefit to the use of sodium bicarbonate infusion as prehydration.[7] The authors conducting the trial concluded that withholding prehydration is safe and cost-effective. These data add yet another piece to the contrast imaging puzzle. The more data showing the futility of any intervention for reducing CIN we gather, the more difficult it becomes to paint a picture of imaging-associated CIN as a true disease entity—at least in the setting of emergency department imaging, where contrast doses are substantially smaller than in other situations, such as interventional radiologic procedures.

This is effectively the new stance adopted by a joint statement by the American College of Radiology and the National Kidney Foundation.[8] In their statement, narrowly focused on patients receiving intravenous contrast for advanced imaging, they described a distinction between contrast-*associated* acute kidney injury and contrast-*induced* acute kidney injury. Contrast-associated acute kidney injury is common, but it's seen as being related to the underlying medical illness rather than *caused* by the contrast administration itself. Their summary described inconsistent evidence supporting the existence of contrast-induced acute kidney injury, noting modern low-osmolar contrast media are less likely to be nephrotoxic than prior-generation products. Only those with the most severe renal impairment are seen as potentially reasonable candidates for gentle volume expansion prior to contrast administration prior to advanced imaging.

Cerebrovascular Disease

Systems of stroke care continue to reorganize in response to access to endovascular intervention (clot retrieval/thrombectomy) and the ever-changing time windows for treatment. Persistent questions remain regarding the necessity of alteplase prior to early endovascular intervention. The DIRECT-MT trial provided some of the most robust evidence to date, suggesting only the smallest advantages in reperfusion from alteplase administration.[9] Reperfusion, however, remains a surrogate for measurably improved clinical outcomes, and once taking adverse events into account, the overall picture appears to favor endovascular intervention alone. It should be considered reasonable to skip alteplase prior to endovascular intervention, but these data may be rendered moot as Tenecteplase (which is given more quickly and thus creates fewer delays) gradually replaces alteplase.

Screening patients for subarachnoid hemorrhage remains a challenge, despite multiple validations of the Ottawa Subarachnoid Hemorrhage Rule. Developed as a zero-miss screening tool, the specificity of this decision instrument creates challenges in implementation. In a recent study, practice patterns were evaluated before and after implementing routine use of the Ottawa rule and a six-hour CT rule.[10] Overall, few differences were observed, likely owing to prestudy familiarity with both changes (ie, many clinicians had already altered their practices prior to any "official" implementation practices). However, a handful of interesting missed cases were noted, including one in a profoundly anemic patient, rendering the Ottawa rule less than zero-miss in some rare circumstances. When using noncontrast CT to exclude subarachnoid hemorrhage, consider contributors to false-negative scans.

See you next year!

The opinions expressed herein are solely those of Dr. Radecki and do not necessarily reflect those of his employer or academic affiliates.

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EMTALA Malpractice?

What is—and isn't—guaranteed under EMTALA can be complex

by ERIC FUNK, MD

This medical malpractice case is high yield for every emergency physician as it covers a subtle but life-threatening diagnosis and highlights the importance of communication at multiple levels. It also provides an opportunity for us to better understand the nuances of EMTALA-related litigation.

The Case

A 30-year-old man presented to the emergency department with a chief complaint of weakness and ankle pain. He was seen in an outpatient clinic and referred to the emergency department for evaluation. The patient had recently returned from a surfing trip to Asia. While on the trip, he reported being bitten by mosquitos multiple times but had not taken any malaria prophylaxis. He also had jumped out of a truck the day before and had twisted his left ankle.

The review of systems was positive for fever, vomiting, myalgias, and headaches.

He was otherwise healthy and up-to-date on his vaccinations.

His triage vitals showed a temperature of 99.5°F, heart rate of 85 bpm, blood pressure of 118/56, respirations of 20 per minute, and oxygen saturation of 97 percent on room air (see Figure 1).

A boilerplate normal examination was documented, including a musculoskeletal note describing "no edema and no tenderness."

The physician noted a differential of "viral syndrome, otitis media, pharyngitis, pneumonia, gastroenteritis, urinary tract infection, and others."

A complete blood count (CBC) was ordered and showed leukocytosis of 14.9, thrombocytopenia of 132. The differential showed 87 percent neutrophils and 5 percent lymphocytes. The comprehensive metabolic panel (CMP) was entirely unremarkable. The urinalysis showed a large amount of blood and occasional bacteria but no white blood cells, leukocyte esterase, or nitrites. An influenza swab was negative, and a malaria smear was also negative (see Figure 2).

An ankle X-ray was ordered and showed "moderate soft tissue swelling" but no fracture or dislocation.

A repeat set of vitals was ordered, and everything was in the normal ranges.

Given the lack of emergency findings and normal vitals, the patient was discharged home. The doctor recommended he take Tylenol or ibuprofen, stay hydrated, and rest. Crutches were provided, and instructions were given to keep the left ankle elevated. A plan to follow up with urgent care the following week for reassessment was recommended.

Commentary

Everything about this case seems straightforward to this point. There is nothing that can be reasonably criticized. The workup is negative.

Figure 1

Vital Signs

Temp	37.5 °C (99.5 °F) JS
Temp src	Oral -JS
Pulse	85 -JS
BP	! 118/56 mmHg -JS
MAP	77 -JS
BP cuff location	Right arm -JS
BP position	Lying -JS
Resp	20 -JS
SpO2	97 % -JS

But this is a medical malpractice column. There has to be a twist.

Recall that the patient was seen in an outpatient clinic and referred to the emergency department. The ED physician was unaware of this. The patient did not volunteer this information, there were no triage notes mentioning it, and no one asked the patient about the preceding medical care.

Shortly before ED arrival, the outpatient clinic documented a blood pressure of 81/38 and a temperature of 100.2°F.

The Case Continues

After being discharged, the patient had an uneventful night. The next morning, he began to feel worse, and two days after the initial visit, he returned to the emergency department. His exam was now notable for "significant edema" at the left ankle, with bruising up the leg. Extreme tenderness was noted, but there was no crepitus.

Vital signs were notable for slight tachycardia at 105 bpm, though his blood pressure, respirations, and pulse remained normal. His CBC and comprehensive metabolic panels were essentially unchanged (see Figure 3).

He was diagnosed with cellulitis and admitted to the hospital due to the severity of the swelling, bruising, and pain. The patient had a penicillin allergy listed and was started on vancomycin monotherapy. The emergency physician wrote a long note, including the reasoning shown below:

> *Consideration for necrotizing fasciitis was done however there is nothing on patient's exam or history to assess that this is present. Patient's had leg pain now for a couple of days and this has not been rapidly worsening the patient did state that it got significantly worse today. Pain is not out of proportion. Patient hasn't had any significant fever and white blood cell count is not significantly elevated.*

In the hospital, the patient developed renal failure, and his vitals worsened. A surgeon was consulted, and the patient was taken to the operating room. There was purulent drainage from the leg, and small areas of necrotic muscle were identified.

Figure 2

MALARIA SMR,THICK/THIN PANEL

Ordering Provider: [redacted] 1239 Order Status:

Resulting Lab: [redacted] Specimen:

Component	Value	Ref Range	Flag
Malaria Stain	Preliminary: No malaria seen. (Thin smear)		
Percent RBC Thin Smear	N/A	%	
Malaria Thick Smear	-		
Result:	No Malaria seen.		

Figure 3

Lab Results

CBC PLT W/AUTO DIFF (Abnormal)

Ordering Provider: [redacted] DO

Resulting Lab: [redacted]

Component	Value
WBC	14.2
RBC	4.52
Hemoglobin	14.7
Hematocrit	42.0
MCV	92.9
MCH	32.6
MCHC	35.1
RDW	12.5
Platelet Count	123
Diff Method	Auto
Neutrophils	92
Lymphs	2

COMP METABOLIC PANEL (Abnorma

Ordering Provider: [redacted] DO

Resulting Lab: [redacted]

Component	Value
Sodium	135
Potassium	4.0
Chloride	101
CO2	25
Anion Gap	9
BUN	11
Creatinine	1.09
Glucose	140
Calcium	9.6
Total Protein	6.7
Albumin	3.3
Globulin	3.4
A/G Ratio	1.0
AST (SGOT)	18
ALT (SGPT)	42
Alk Phos	141
Bilirubin, Total	1.2
GFR (Non-African Amer)	>60

The patient was ultimately transferred to a larger medical center. He underwent several repeat operations for necrotizing fasciitis, ultimately requiring several skin grafts leading to permanent disability of his left leg.

The Lawsuit

The patient filed a lawsuit against the hospital. The plaintiff's attorney alleged EMTALA violations, and therefore the lawsuit was filed in federal court. The specific claim was that the medical screening exam violated EMTALA because it did not lead to the correct diagnosis of necrotizing fasciitis.

The judge ultimately dismissed the lawsuit. In his opinion, he noted that "EMTALA is not a medical malpractice statute, and failing to correctly diagnose Plaintiff's illness does not give rise to [EMTALA] liability." This concept was reiterated throughout his opinion, and elsewhere he stated, "Defendants cannot incur EMTALA liability for what is merely an incorrect diagnosis."

The patient proceeded to sue the hospital and all of the doctors involved in the case in state court. That lawsuit was eventually withdrawn without any mention of a settlement.

Discussion

This case highlights the essential role that communication plays in the care of all patients. The disconnect in the patient's referral at the first ED visit nearly led to a disaster. Awareness of his prior hypotension certainly would have led to a higher level of concern—though not necessarily the correct diagnosis; given his benign workup and vital signs in the emergency department, he may have been discharged home regardless. That the doctor did not realize the patient was referred to the emergency department from an outside facility illustrates the concept of "holes in the Swiss cheese" remarkably well. The clinic did not call the emergency department to notify them of a referred patient, there were no processes in place requiring the triage nurse to ask patients if they had been referred to the emergency department by an outside facility, the patient did not volunteer this information, and the doctor did not think to ask.

This case provides an excellent opportunity to refine our understanding of EMTALA. Just because a medical screening exam does not arrive at the correct diagnosis does *not* mean there was an EMTALA violation. The hospital and emergency physicians involved seem to have prevailed in the legal proceedings, but caution must be taken given the complexity of EMTALA litigation. Specialized attorneys may spend large swaths of their careers dealing with these cases, and even the most well-intentioned emergency physicians are unlikely to have read, let alone understand, its complexities. Just as in medicine, nuanced interpretations are best left to the experts.

SEE THE RECORDS

Visit www.medmalreviewer.com/case-7-ankle-injury/ to review the full medical records or send Dr. Funk an email with your thoughts on the case at admin@medmalreviewer.com.

EM PICS WORTH A THOUSAND WORD

IMAGES IN EM

DR. THOMAS is an attending physician in the emergency department at Kaiser Permanente (Greater Southern Alameda area).

Diversity Should Be a Priority

We can all contribute to increasing inclusion to benefit our patients

by BENJAMIN THOMAS, MD

BENJAMIN THOMAS,

"I have been to the hospital countless times over the last few years, and you are the first Black doctor that I have met to take care of me. Thank you for being here." He was a young Black male paralyzed from the waist down after a gunshot wound to the spine. He had been in and out of the hospital due to complications from his paraplegia. He was trying to get his life together, but reoccurring and new obstacles prevented him from achieving the life he wanted.

I felt a mix of emotions, unsure whether to feel pride or disappointment in what he told me. I said, "You're welcome," and told him I was doing the best job I could, yet I left his room slightly disheartened. Cognitively, I knew that I was among an incredibly small minority of physicians at my hospital and in medicine overall, but hearing his words sparked a better understanding of how important my role as a Black male physician is in emergency medicine and in my community.

One of the attributes that attracted me to emergency medicine was the opportunity to care for patients from all walks of life, no matter their ethnicity, religion, or economic class. As a Black physician, I especially took pride in caring for members of my community, a group that is often underserved. It is well documented that medically underserved populations have increased trust in physicians who are underrepresented in medicine, increased adherence to physician recommendations, and even decreased hospital and ED utilization.[1]

Despite the growth of emergency medicine as a field, we have had lower application rates from women medical students and students underrepresented in medicine than expected from the general population.[2] One documented reason for the lack of diversity in the emergency medicine applicant pool is the lack of diversity among emergency medicine faculty. Currently, approximately 10 to 15 percent of EM faculty are underrepresented minorities.[3] As a trainee, I felt fulfilled by the patients who received our care but often discouraged by the lack of emergency medicine mentors with whom I had shared experiences.

What We Can Do

For our specialty to diversify its physician pool, it is imperative to understand the challenges underrepresented minorities face in medical school matriculation and the factors that motivate interest in emergency medicine. Quantitative and qualitative research cataloging the obstacles to medical school matriculation for minorities includes, but is not limited to, a disproportionate number of minorities educated in school districts with fewer resources, lack of positive role models or sponsors, barriers from bias and stereotyping, the financial cost of higher education, poor socialization to the pre-med process, and a dearth of visible underrepresented minorities in medicine.[4] A recent study also showed that lower interest in emergency medicine was independently correlated with sex and ethnic or racial profile. The odds of underrepresented students in medicine planning careers in emergency medicine were 32 percent lower than their majority peers. Age, level of indebtedness, plans to practice in an underserved area, and advice from mentors were shown to be positive predictors of emergency medicine interest.[5]

I am all too familiar with the obstacles that many minority students face, but I was fortunate to have supportive mentors to help guide me along a path toward medical school and a career in emergency medicine. The data are clear. Emergency physicians who are underrepresented minorities in medicine can have an enormous impact on the trajectory and talent acquisition pipeline of minority students. But we can't do it alone.

Acknowledging the consequences of underrepresentation in emergency medicine, the Society for Academic Emergency Medicine and ACEP have included diversity and inclusion in their mission goals.[1] In 2008, the Council of Emergency Medicine Residency Directors provided national expert recommendations to address the diversity gap in emergency medicine. Unfortunately, these recommendations have not been sufficiently adopted across residency programs. Common reasons include a lack of dedicated resources in some cases, and diversity not even being a priority in others.[6] Identifying local faculty members who can lead these efforts is crucial, as is compensating them for their time, just like any other leadership role.

Our country's demographics are rapidly changing, and our specialty needs to start better mirroring our patient populations. Recent events and tensions have especially highlighted the importance of equity, diversity, and inclusion in medical education and training in emergency medicine. To create change, medical school and residency program leadership across the country needs to engage and make this a priority. Numerous authors, workgroups, and organizations have provided tactics for addressing this issue, including:

- Underserved community outreach and engagement
- Creation and participation in pipeline activities to increase the proportion of underrepresented students, trainees, and faculty
- Holistic review when screening applicants for medical school and residency selection
- Promotion of cultures that nurture productive conversations about diversity
- Strategic recruitment and retainment of underrepresented students, trainees, and faculty[4,7,8]

As a physician of color, I embrace my responsibility to do what I can to reach these goals. For these goals to be accomplished, there must be buy-in from everyone and I invite all of my colleagues to join in this pursuit. This is not only for the benefit of our specialty but most importantly to provide the best care possible to every single one of our patients, regardless of who they are.

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THE END OF THE RAINBOW

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Life Insurance

Do healthy young docs really need it?

by JAMES M. DAHLE, MD, FACEP

Q. Money is tight, and we're young and healthy. Do we really need life insurance?

A. Every now and then, I see an article in a newspaper or on social media about an untimely death of a previously healthy young person. Often it is cancer or trauma—nowadays, COVID-19 as well. At the end of these articles or posts, a GoFundMe account (or similar) started by friends or family members to help the surviving partner and children cope with the financial ramifications of the loss typically appears. These are important community gestures. However, GoFundMe is *not* a life insurance company.

Recently, I saw a post on social media about another untimely death, with the usual link to GoFundMe. It involved a resident who died of eclampsia while giving birth. The baby survived, and the GoFundMe was to help provide for the partner and child. I suppose it is possible that even people expecting a life insurance payout would start a GoFundMe account, but I suspect that it is rare. Besides, a typical GoFundMe drive raises just a few thousand dollars, averaging $2,600. How, I worry and wonder, will the survivors make ends meet?

Aside from personal loss of any loved one, losing the breadwinner of a family can be a catastrophic financial event. Consider the death of a resident who stood to earn $300,000 or more per year for the next 30 years. That is a loss of $9 million in expected income. Given how easy and inexpensive it is to insure against that loss, it is a shame to see those losses go uncovered. Consider that a 28-year-old healthy female can buy a $1 million term life insurance policy for just $15 a month. Two quarters a day. You can't even get coffee at McDonald's for that, much less a decent latte. This investment represents no genuine financial sacrifice whatsoever for a resident physician, even for those making $60,000 per year.

Physicians, even residents, are not invincible. Although the odds of death for someone in their 20s and 30s are low, they're not zero. Approximately one out of 2,000 people of resident age (25–35) dies in any given year. There are about 130,000 resident physicians in the country. That means approximately 65 of our trainees die every year. Of course, some of them do not have any dependents, so as sad as their death is, it does not produce the same financial catastrophe as for those with dependents. However, what if we assume half of them do have at least one dependent? I do not even want to know how many of those physicians never got around to buying a good term life insurance policy. I hope that number is zero. But the GoFundMe drives leave me worried.

How It Works

Term life insurance is not a complicated product. As the policy owner, you will need to pay a premium once a month or once a year to keep the policy active. So long as you pay those premiums, in the event of your death, your designated beneficiary will receive the face value of the policy. They can get the money as soon as they have a copy of your death certificate, and the money comes to them tax-free.

Policies are best purchased from an independent agent, one who can sell you a policy from any company. That will give you lots of options in the event you have any interesting medical problems or adventurous hobbies. Most important, it provides competition that keeps prices low. Rates can vary substantially between companies, and only by having your agent shop around to various companies can you be sure you're getting the best rate on what is, in essence, a commodity.

As a general rule, you want to buy term life insurance that will last until you are financially independent. The idea is that when you have a nest egg large enough to live on for the rest of your life, you no longer need life insurance. If you die, your loved ones will just live on that same nest egg. Because it will likely take a typical physician who remembers to save for retirement 20–30 years to reach financial independence, you should therefore buy a 20- to 30-year level term policy.

Obviously, the longer the term and the higher the face value, the higher the premium will be. Most knowledgeable physicians purchase a policy with a seven-figure face value. Once they add up the cost of paying off a mortgage, sending kids to college, and supporting their partner at least for a few years, they end up with a large sum. Remember, the face value should be approximately equal to the amount of money that would make you financially independent. So $200,000 isn't going to cut it. Most new attendings end up with a $2–$5 million policy, but $1 million seems to be a common amount for residents. Certainly $1 million is far better than the $2,600 that would come from the average GoFundMe.

Some insurance agents push a product called whole life insurance, primarily because the commissions they earn from selling it are much higher than what they get from a term policy. However, whole life insurance is far more expensive than term life insurance for a healthy young person, and young doctors have so many other great uses for their money that selling a whole life policy to a resident is, in my mind, akin to financial malpractice. Although whole life has some niche applications to people in some circumstances, being a doctor is not one of them. Just get a basic, easy-to-understand term policy and don't recommend agents pushing whole life policies to your peers.

When you apply for insurance, you'll have to answer a few questions about your health and hobbies, have your vitals taken, and provide blood and urine samples. Assuming everything checks out, you should be able to finalize the policy with the agent within just a few weeks. It really is a simple process.

Bottom line: If someone else depends on your income, you need to get life insurance in place ASAP. It is more important than saving for retirement, figuring out what to do with your student loans, or buying that new home.

It is my fervent hope that no resident or young physician's family will ever have to resort to a GoFundMe again to meet their basic needs after that person's death.

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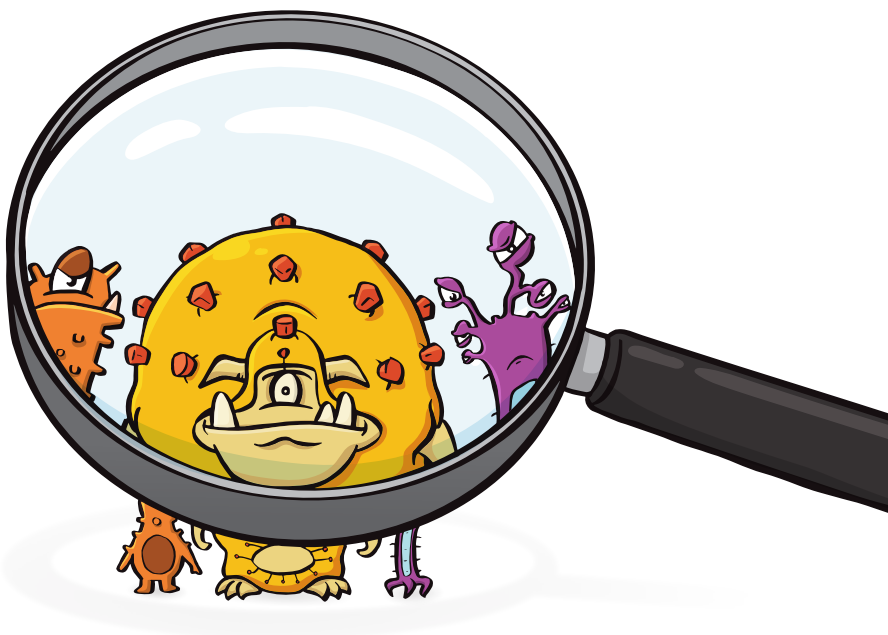

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