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CASE REPORTS

A BLISTERING TALE

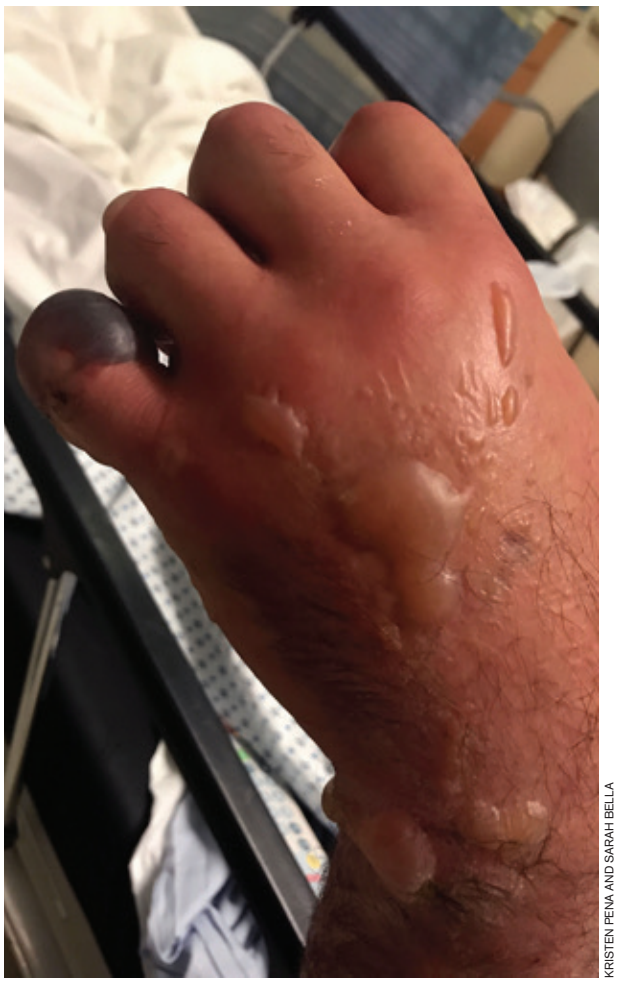
Don't be Bullae'd by bad disease

by KRISTEN PEÑA, DO; AND SARAH BELLA, DO, MPH

The Case

A 60-year-old male with past medical history of anxiety and depression presented to the emergency department via EMS with complaints of pain in the left upper extremity after falling. The patient stated he recently moved into a new apartment, and he tripped and fell forward onto a carpeted surface three days ago. He then developed pain and swelling to the left hand/arm and left eye. He reported loss of consciousness for some time and denied any alcohol or drug use or abuse. The patient noted the redness to his left hand yesterday, and it progressively worsened and started to develop blisters (see Figures 1 and 2). The patient also noted swelling to the left eye upper and lower eyelids and a rash to the left upper abdomen similar in appearance to his hand (see Figures 3 and 4). He admitted to significant pain and stated he could not straighten his fingers. He denied

CONTINUED *on page 11*



KRISTEN PENA AND SARAH BELLA

Figure 1: Rash and blisters on the patient's left hand.

DEADLY SPICE

Tainted synthetic cannabis leads to multistate acquired coagulopathy outbreak

by ARKADY RASIN, MD; JASON DEVGUN, MD; AND THERESA KIM, MD

The Case

After entering the room, it is clear something unusual is going on. This previously healthy 27-year-old has large blood-filled blisters in her mouth. In front of her, she carries a basin into which she is continuously spitting up blood, saliva, and clots.

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She had presented to another emergency department two days earlier with complaints of hematuria and flank pain. After a negative CT scan of her abdomen and pelvis, she was given a provisional diagnosis of urinary tract infection and hematuria and discharged home with a prescription for nitrofurantoin. Apart from the recently prescribed antibiotic, she denies any

CONTINUED *on page 18*

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More Than Just "I Do"

For Dr. Adam Brown and Dr. Steven Farmer, marriage came with a few extra challenges

ADAM BROWN AND STEVE FARMER

When emergency physician N. Adam Brown, MD, MBA, FACEP, met Steven Farmer, MD, while the two were training as physicians, he knew he'd met the person he wanted to spend his life with. However, in the era when the Defense of Marriage Act (DOMA) was still in effect, getting married as a gay couple—and making sure that marriage would be recognized—involved complications that heterosexual couples didn't encounter. The two overcame those hurdles to build a life together as a two-physician couple.

Dr. Brown is currently senior vice president–mid-Atlantic at Envision Physician Services and system

CONTINUED *on page 14*

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Think ELIQUIS–

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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)

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

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NVAF
Indicated to reduce the risk of stroke and systemic embolism in patients with NVAF[1]

DVT/PE
Indicated for the treatment of DVT and PE, and to reduce the risk of recurrent DVT and PE following initial therapy[1]

Learn more about ELIQUIS today at **hcp.eliquis.com**

DVT: deep vein thrombosis; NVAF: nonvalvular atrial fibrillation; PE: pulmonary embolism.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)
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.

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

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (cont'd)
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.
- **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 CATEGORY B
- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Reference: 1. ELIQUIS® Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY.

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

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® (apixaban) 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 and aprotinin) in individuals receiving apixaban, 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 (apixaban) 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 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.

ADVERSE REACTIONS

The following serious 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.
¶ 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 apixaban with diabetes bled more (3.0% 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.

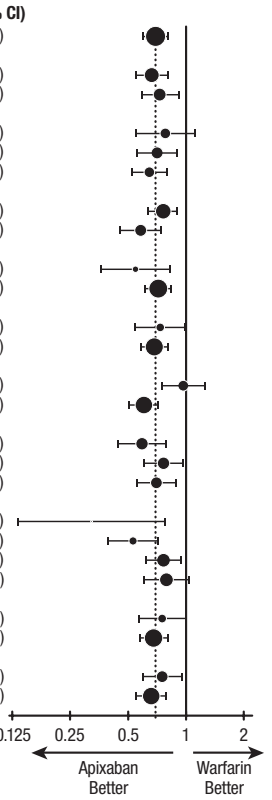
Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

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 apixaban (administered 12 to 24 hours post-surgery).
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (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

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



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 apixaban-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 apixaban-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 (apixaban) 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 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 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. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban 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

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

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 apixaban 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]*.

Marketed by:
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Rev June 2018

432US1801820-04-01

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NEWS FROM THE COLLEGE

UPDATES AND ALERTS FROM ACEP

Winners of ACEP's 50th Anniversary "What's Your Moment?" Contest

We have winners of our 50th anniversary storytelling competition! We received so many excellent submissions from emergency physicians sharing a moment that resonated for them, and we are beyond proud of everyone who submitted. Congratulations to these incredible storytellers. Read their winning entries at www.acep.org/who-we-are/50Years/WhatsYourMoment.

- First place: Stephanie B. Benjamin, MD
- Second place: Eligio S.V. Maghirang, MD, FPCEM
- Third place: Brian K. Sloan, MD, FACEP
- Fourth place: Jeffrey D. Lazar, MD
- Fifth place: Laura Janneck, MD, FACEP

ACEP Responds to *The New York Times* Opinion by Dr. Glenn Melnick

ACEP Immediate Past President Paul Kivela, MD, MBA, FACEP, responded to the Sept. 5, 2018, op-ed by Glenn Melnick, PhD, about emergency departments' contributions to the high cost of health care with corrections on the misinformation presented and hopes for how these issues could be solved. Read the full response at newsroom.acep.org. Here are some highlights from Dr. Kivela's response:

"Insurance companies are taking advantage of hospital emergency departments, because they have a federal mandate to provide care, regardless of insurance coverage or ability to pay, giving negotiating power to the insurance industry.

"Unfortunately, health insurance companies are ignoring a real solution to 'surprise' medical bills and misleading customers and the public when they blame physicians. The Fair Health database, which was developed in response to an insurance company that was fraudulently calculating payments for emergency care, is the best mechanism available to ensure transparency and to make sure insurance companies provide fair payments."

ACEP

Jeffrey Bettinger, MD, FACEP; Randy Pilgrim, MD, FACEP; and Sue Nedza, MD, MBA, FACEP, presenting ACEP's proposed payment model at PTAC meeting.

Federal Advisory Committee Recommends ACEP-Developed Alternative Payment Model to HHS

On Sept. 6, 2018, the Physician-Focused Payment Model Technical Advisory Committee (PTAC) voted in favor of recommending ACEP's proposed alternative payment model, the Acute Unscheduled Care Model (AUCM), to the secretary of the Department of Health and Human Services (HHS) for full implementation. ACEP's model joins only four of the 26 submitted to the PTAC to date that have been recommended for full implementation. The voluntary model aims to improve quality and reduce costs in Medicare by allowing emergency physicians to accept some financial risk for the decisions they make around discharges for certain episodes of acute, unscheduled care. ACEP believes the AUCM has the potential to transform the way emergency care is delivered. While the PTAC recommendation is a victory worth celebrating for emergency medicine, there is still a long road ahead before the model becomes operational. With PTAC's endorsement, ACEP will begin discussions with the Centers for Medicare and Medicaid Services about implementation.

ACEP

Dr. Liferidge (right) with Dr. Kadlec.

ACEP Participates in NASEM Drug Shortage Workshop

On Sept. 6, 2018, ACEP Board member Aisha Liferidge, MD, FACEP, participated in a two-day workshop hosted by the National Academies of Sciences, Engineering, and Medicine (NASEM) on medical product shortages during disasters and discussed the unique challenges facing emergency physicians and their patients during these crises. The workshop was planned after recent disasters and public health emergencies, such as hurricanes Harvey, Irma, and Maria and the Ebola outbreak, highlighting the impact that shortages of commonly used medical supplies, equipment, and pharmaceuticals had on health care delivery and emergency response. Panels explored opportunities to lessen the effects of medical product shortages through information sharing, improved supply-chain infrastructure, and enhanced collaboration among public, private, and nonprofit stakeholders. The United States Assistant Secretary of Preparedness and Response (ASPR) Robert Kadlec, MD, and key members of his staff were in attendance.

Congress Passes Opioid Package

On Oct. 3, Congress passed critical opioid legislation. Included in the package are the "Alternatives to Opioids (ALTO) in the Emer-

CONTINUED *on page 41*

2019 Course Topics

- The ED's Role in Treating Opioid Addiction
- Myths in Emergency Medicine
- Coronary Risk Scores – How Good Are They?
- Sepsis – What's All the Confusion About?
- What the Radiologists Say We Should/Shouldn't Order
- 2018 Stroke Guideline Controversies
- Pearls from *Risk Management Monthly*
- Pearls from *ED Leadership Monthly*
- 2018 Syncope Guidelines
- Serious Diseases, Outpatient Treatment - Part 1
- Serious Diseases, Outpatient Treatment - Part 2
- Diarrheas That You Need to Know About
- ED Issues of Early Pregnancy
- Emergencies in the Bariatric Surgery Patient
- Pediatric Emergency Medicine Pearls - Part 1
- Pediatric Emergency Medicine Pearls - Part 2
- Clinical Consequences of ED Crowding
- Telemedicine in Emergency Care
- 2019 Medicare ED Quality Metrics
- New Evidence Concerning Resuscitation Fluids
- Learning to Love High Sensitivity Troponins
- The Updated Neonatal Fever Evaluation
- Cannabinoid-Related Emergencies
- Geriatric ED Accreditation – What's it Mean?
- What's New in ED Respiratory Support?
- Trauma Care Controversies
- Visual Diagnosis Challenges - Part 1
- Visual Diagnosis Challenges - Part 2
- Important Recent EM Literature - Part 1*
- Important Recent EM Literature - Part 2*
- Optimizing ED Operations*
- Diagnostic and Therapeutic Controversies*

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

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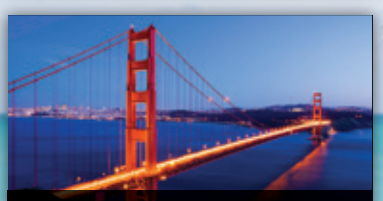
Las Vegas, Nevada
April 1 - 4, 2019



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April 11 - 14, 2019

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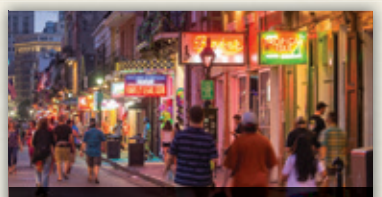
April 15 - 18, 2019 (Easter Week)



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May 1 - 4, 2019 (Jazz Fest)

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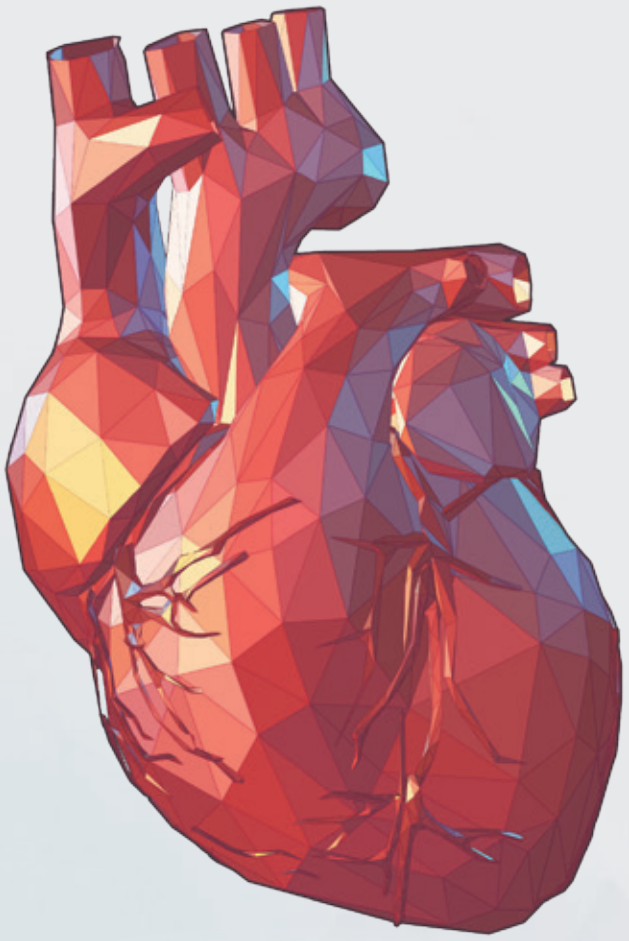
Live from ACEP18

The ACEP18 Closing Celebration, presented by Envision Physician Services, closed the meeting in style with a night in Petco Park, home of the San Diego Padres. Attendees enjoyed food and drinks, music, and games while networking with friends, family, and colleagues on Oct. 3.

JAMES ARONOVSKY



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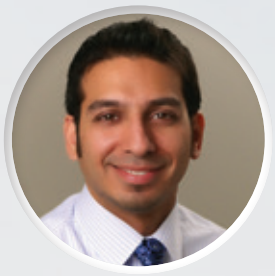

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A Golden Celebration

ACEP18 attendees celebrated ACEP's 50th anniversary by honoring those who shaped the specialty and taking a look back at the five decades of emergency medicine.

ACEP Executive Director Dean Wilkerson, JD, MBA, CAE; ACEP member since 1969 Rudenz "Rudy" T. Douthat, MD, FACEP; ACEP staff member Jana Nelson; and 50th Anniversary Task Force chair Nicholas J. Jouriles, MD, FACEP, at the Museum of Emergency Medicine Ribbon Cutting ceremony. Dr. Douthat stayed behind to cover the emergency department while his colleague George Fink, MD, attended the meeting where ACEP was incorporated.

Exhibits from the History of Military Emergency Medicine.

JAMES ARONOVSKY

Attendees explored the history of the specialty in the Museum of Emergency Medicine.

fever, chills, nausea, vomiting, chest pain, shortness of breath, or similar symptoms in the past. He hadn't taken anything for pain.

Based on his history and physical exam, a CT of the head, maxillofacial, and left hand without contrast were ordered because of concern for necrotizing fasciitis and compartment syndrome. His chemistries were significant for sodium 126 mEq/L, potassium 6.4 mEq/L, blood urea nitrogen 77 mg/dL, creatinine 6.85 mg/dL, glucose 109 mg/dL, total creatinine phosphokinase 11,000 U/L, aspartate aminotransferase 871 U/L, alanine aminotransferase 972 U/L, white blood cell count 13.5 k/mm3 with left shift, hemoglobin 15.2 g/dL, and C-reactive protein (CRP) 249.2mg/L.

The head CT was negative for acute findings. The maxillofacial CT was significant only for soft tissue swelling. The CT of the left hand was notable for osteoarthritis of the left trapezium and first and second metacarpals with some soft tissue swelling with blebs in subcutaneous soft tissues. Plain radiographs of the hand were significant for flexion deformities of the distal phalanges. However, no subcutaneous air or acute fracture or dislocations were noted. X-rays of the right hip and chest were negative for acute findings.

Over the course of his ED visit, the patient became more uncomfortable, and the pain and functionality of his left hand worsened since his arrival. Reexamination showed numbness to the left hand and forearm and a weak radial pulse, both of which were concerning signs for compartment syndrome. Orthopedic surgery was consulted, and the patient was emergently taken to the operating room (OR) for debridement and fasciotomy of the left hand and forearm. Compartment pressures were not measured as the patient exhibited clinical signs of compartment syndrome and delaying definitive treatment to measure compartment pressure is contraindicated. The patient was started on clindamycin, Zosyn, and vancomycin. He was taken to the OR

CONTINUED *on page 32*

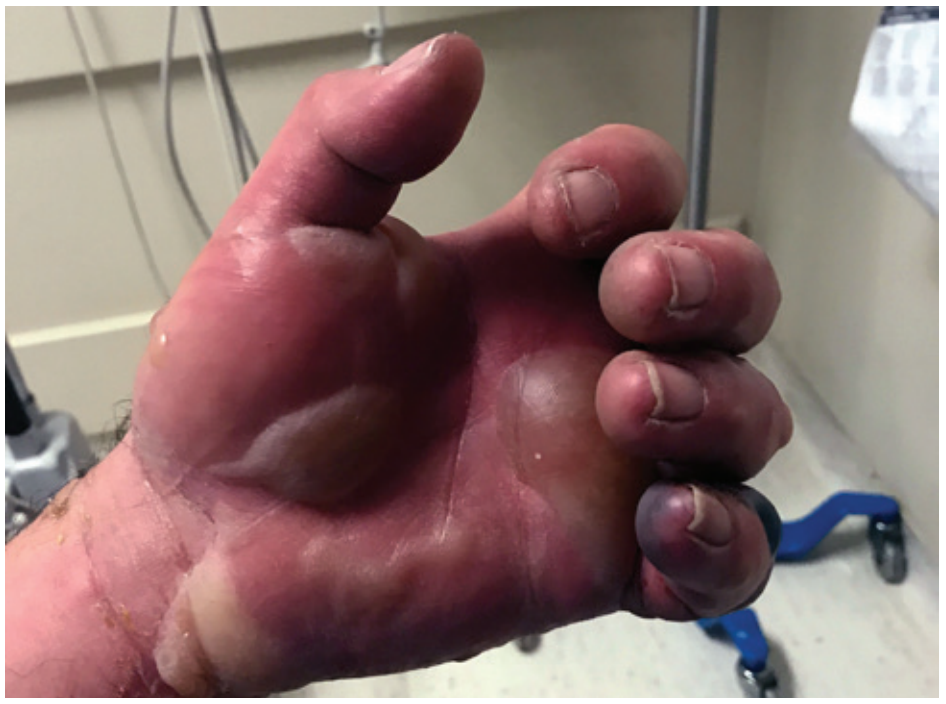

Figure 2: Rash and blisters on the patient's left hand.

Table 1: LRINEC Scoring System[6]

Test	Result	Score
C-reactive protein (mg/L)	<150	0
	≥150	4
White blood cell count (x10,000/µL)	<15	0
	15–25	1
Hemoglobin (g/dL)	>13.5	0
	11–13.5	1
	<11	2
Sodium (mEq/L)	≥135	0
	<135	2
Creatinine (mg/dL)	≤1.6	0
	>1.6	2
Glucose (mg/dL)	≤180	0
	>180	1

TAKE-HOME POINTS

- Rapid recognition of necrotizing fasciitis should be considered in all rapidly progressive soft tissue infections.
- Patients who present with skin infections and the risk factors immunosuppression, drug use, recent surgery, liver disease, traumatic wounds, and diabetes should be ruled out for a necrotizing fasciitis infection.
- In addition to clinical suspicion, the LRINEC scoring system is a helpful tool that may guide provider management in patients presenting with rapidly progressive soft tissue infections.
- CT scan is the most efficient diagnostic tool for necrotizing fasciitis in the emergency department.
- Immediate treatment with antibiotic therapy and surgical debridement is vital to prevent rapid spread of this disease.

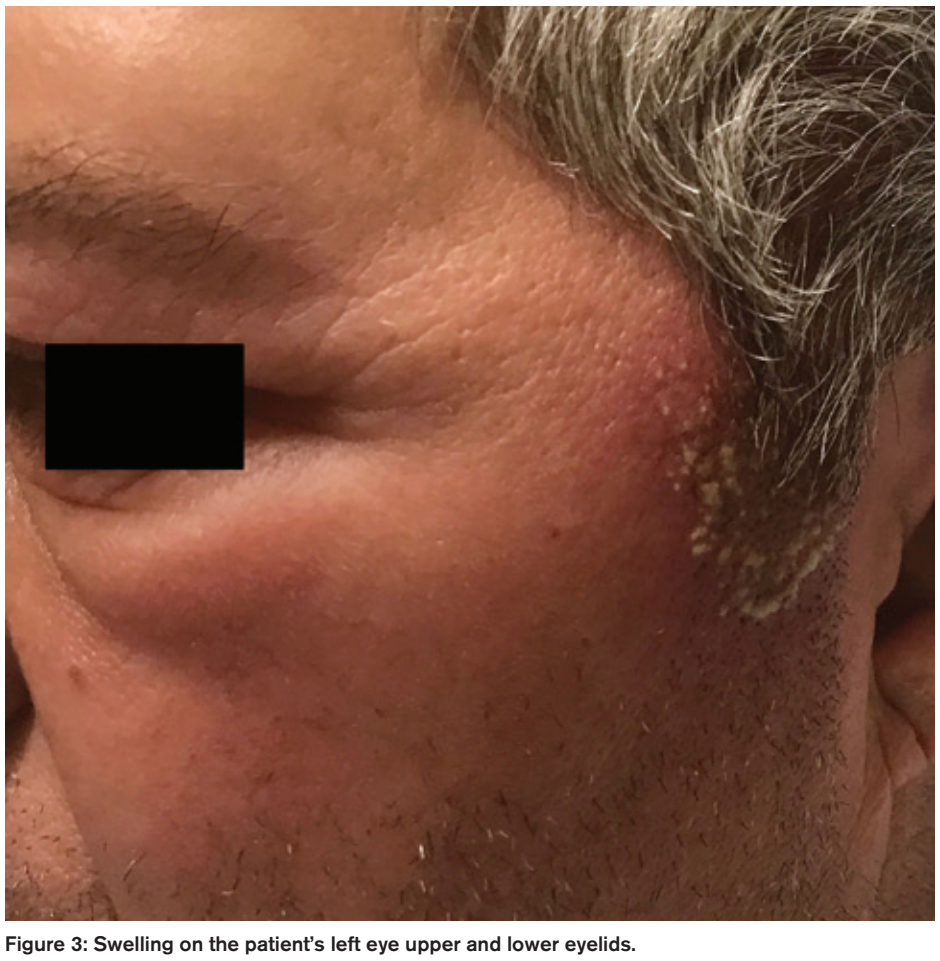

Figure 3: Swelling on the patient's left eye upper and lower eyelids.

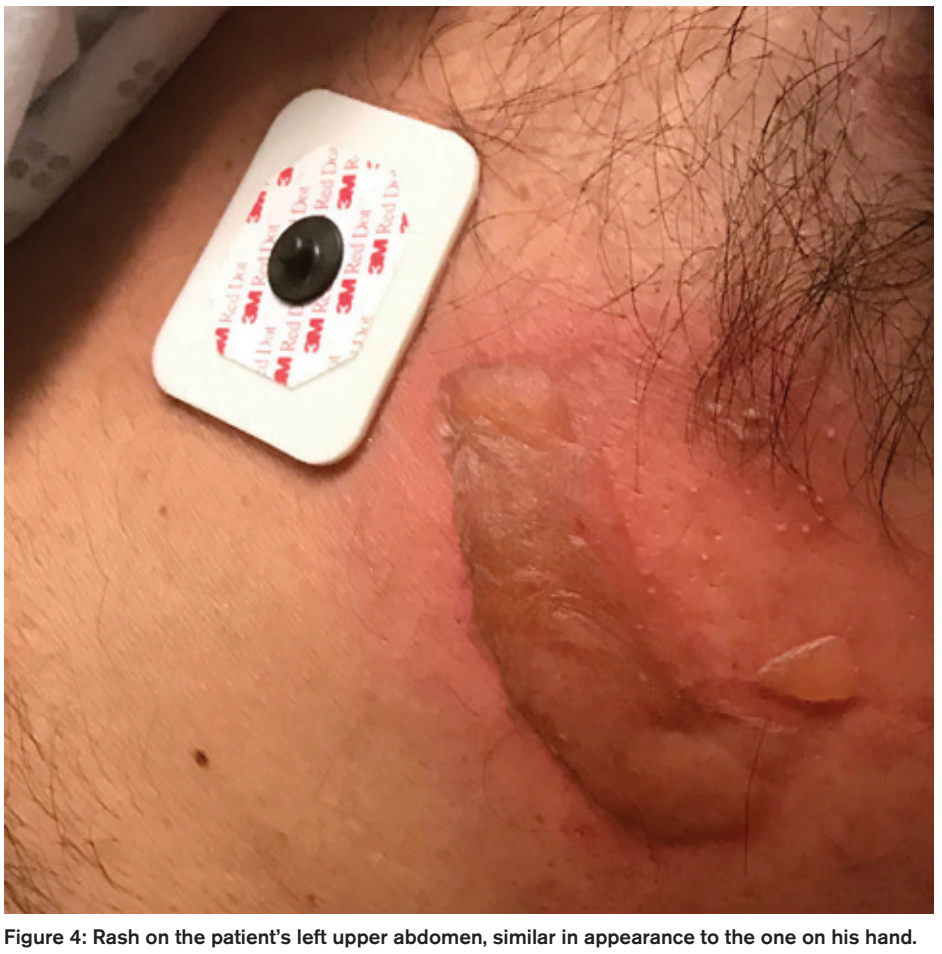

Figure 4: Rash on the patient's left upper abdomen, similar in appearance to the one on his hand.

HOW DOES ACEP'S CODE OF ETHICS APPLY TO ME?

Understanding the code is important for protecting patients, ourselves, colleagues, and EM

BY CHADD K. KRAUS, DO, DRPH, FACEP; KATE ABERGER, MD, FACEP; JAY BRENNER, MD, FACEP; CATHERINE MARCO, MD, FACEP; RAQUEL M. SCHEARS, MD, MPH, MBA, FACEP; JEREMY SIMON, MD, PHD, FACEP

ACEP has a formal procedure for addressing charges of ethical violations among ACEP members under the Code of Ethics for Emergency Physicians. ACEP has published a Code of Ethics (available at www.acep.org/patient-care/policy-statements/code-of-ethics-for-emergency-physicians) which describes principles of ethics, foundations of ethics, and a Policy Compendium.

ACEP addresses complaints related to ACEP's Code of Ethics and to ACEP's Expert Witness Guidelines (available at www.acep.org/patient-care/policy-statements/expert-witness-guidelines-for-the-specialty-of-emergency-medicine) for the specialty of emergency medicine. These two guiding documents describe the role of individuals who are asked to render expert opinion regarding the practice of emergency medicine. The policy states that the expert witness "should review the medical facts in a thorough, fair, and objective manner" and "should not provide expert medical testimony that is false, misleading, or without medical foundation."

The mechanism by which ACEP addresses ethics complaints is detailed in the executive document, Procedures for Addressing Charges of Ethical Violations and Other Misconduct (available at www.acep.org/life-as-a-physician/ethics--legal).

Between 2001 and 2017, 14 ethics charges have been processed. All claims involved alleged unethical expert witness testimony. In addition, there were eight incomplete complaints that were not formally adjudicated by the Ethics Committee due to inadequate information from the complainant.

An understanding of ACEP's Code of Ethics is important for all ACEP members so they can abide by it to protect our patients, ourselves, our colleagues, and the specialty of emergency medicine.

ACEP Expert Witness Guidelines

ACEP has written guidelines for emergency physicians to follow when providing expert witness testimony. These guidelines were originally approved by the ACEP Board of Directors (BOD) in 1990, and revised and approved in 1995, 2000, 2010, and 2015.

As expert witnesses, emergency physicians are asked to opine on standard-of-care questions pertaining to emergency medicine in cases of medical malpractice.

TABLE 1: EXAMPLES OF ETHICAL VIOLATIONS

ETHICAL OBLIGATIONS	EXAMPLES	VIOLATIONS
Personal and Professional Conduct	An emergency physician reviews a record of a patient for whom they have no responsibility with regard to clinical care, education, research, or quality assurance.	Violation of patient confidentiality.
	An emergency physician treats a patient unfairly because of his or her race, color, creed, gender, nationality, or other patient characteristic.	Discrimination evident in provision of patient care.
	An emergency physician commits a crime of moral turpitude, such as sexual misconduct, leaving the scene of an accident, homicide, etc.	Criminal charges and/or convictions.
Clinical Care	An emergency physician records an interaction with a patient without his or her consent.	Commercial recording without consent.
	An emergency physician discloses test results to authorities without due process and chain of custody protections to ensure patient confidentiality.	Cooperation with law enforcement at the expense of the patient.
Commercial Relationships and Interactions with Society	An emergency physician makes a treatment choice based on a gift accepted from industry.	Conflict of interest.

ACEP has established the following criteria to qualify as an expert witness:

- Be currently licensed in the United States as an MD or DO.
- Be certified by a recognized certifying body in emergency medicine.
- Be active in clinical practice for at least three years, outside of training, immediately preceding the date of the events in the case.
- Be chosen on the basis of expertise, not offices or positions held.

ACEP also outlines guidelines for expert witnesses to follow during a case:

- Possess current expertise and ongoing knowledge in area of the testimony.
- Give testimony that reflects the state of medical knowledge at the time of event.
- Review the medical facts in a thorough, fair, and objective manner and not exclude any relevant information.
- Be willing to have the transcripts of depositions and trial testimony subject to peer review.
- Do not provide testimony that is false or misleading, and do not falsely advertise oneself.

- Do not charge a fee contingent on a particular outcome.

Process for Adjudication of Ethics Complaints

There is a process for ACEP members to file a complaint alleging that another member has violated one of the College's policies regarding ethical conduct. The details of the complete process for filing a complaint about a violation of the ACEP Code of Ethics can be found online at www.acep.org/ethicalcomplaints. It is important to note that these policies govern the behavior of ACEP members, and non-members are not subject to those policies. Only a member can report a violation and such alleged violations must be committed by a member.

Who Will Assess the Conduct of the Member Charged with an Ethics Violation?

Usually, this responsibility falls to an Ethics Committee subcommittee after the member filing the complaint (complainant) and the member against whom the complaint is filed (respondent) provide all relevant documentation in support of their respective positions. The subcommittee determines whether the College ethics policies apply and makes a recommendation to the ACEP BOD regarding whether the alleged behavior is a violation of the policies and whether the alleged conduct justifies sanctioning the respondent member. If there is a minority opinion on the case, the dissenting subcommittee members are encouraged to draft their minority opinion for consideration by the BOD, which makes the final determination of whether an ethics violation has occurred and whether disciplinary action is warranted.

Ethical Violations Not Involving Expert Witness Testimony

Table 1 provides examples of violations of ethical obligations, other than giving false or misleading expert witness testimony, contained within the ACEP Code of Ethics and in multiple policies in the ACEP Policy Compendium.

Sanctions of Ethics Complaints

Ethics complaints may result in one of several different sanctions including: censure, suspension, or expulsion.

Censure may be public or private. In a **private censure**, the member receives a letter informing them how their conduct is not in conformity with ACEP's Code of Ethics. The contents of the letter will not be disclosed, but the fact of the letter's issuance and the name of the recipient will be disclosed. The letter will detail expectations of future behavior, including a warning of more serious consequences for continued violation of ACEP's ethical standards. A **public censure** involves a similarly styled letter. However, its contents will be disclosed publicly as part of the disciplinary action.

If a member's behavior is found to warrant **suspension**, the suspension period from ACEP membership is 12 months. After 12 months, the member will be offered reinstatement, and will be processed in the same manner as other lapsed memberships. In extreme cases, **expulsion** may be warranted. The expulsion period is five years, after which the member may petition the BOD for readmission to ACEP.

Matters of suspension and expulsion are much more serious concerns. The dates of suspension or expulsion, whether or not the member was reinstated, and the basis for the action will be publicly disclosed. In addition, ACEP must report suspensions and expulsions to the Boards of Medical Examiners in the states where the physicians are licensed. This, in turn, will likely result in a report to the National Practitioner Data Bank. These reports must be disclosed and explained on most licensure and medical staff applications and renewals of licensure and facility credentials.

Future Directions

Ethics violations and claims have a considerable potential impact on College members, including those not involved with the case. Censure, or other public or private discipline of a College member, can be scandalous to the College and specialty. These consequences may tarnish the reputation of members. Conversely, the College can be strengthened by showing members that maintaining professional and personal integrity by upholding the Code of Ethics is foundational to ACEP's organizational well-being. It is paramount that there be transparent and timely communication and education for members interested in providing expert witness testimony, as well as for those motivated to file ethics complaints through the College.

Communication should ideally be focused on keeping ACEP members up to date on the process and outcomes of ethics charges, while maintaining the integrity of due process and protecting the rights and the privacy of the members involved in an ethics complaint. Additionally, the communication process should aim to avoid tarnishing the reputation of the parties involved, including the member(s) bringing the ethics complaint, those adjudicating the charge, and the individual against whom the complaint has been lodged. This communication should be timely and as complete as possible, while advancing the aforementioned goals.

ACEP's Code of Ethics applies to all members of the College and helps maintain and encourage the ethical practice of emergency medicine. It is important for members to be aware of the policies and procedures governing the College's approach to ethics and ethics complaints.

DR. KRAUS is at Geisinger in Danville, Pennsylvania.

DR. ABERGER is at St. Joseph's Regional Medical Center in Paterson, New Jersey.

DR. BRENNER is at SUNY-Upstate in Syracuse, New York.

DR. MARCO is at Wright State University in Dayton, Ohio.

DR. SCHEARS is the chair of the ACEP Ethics Committee.

DR. SIMON is at Columbia University in New York City. All authors are members of the ACEP Ethics Committee.

chief of emergency medicine at Sentara Northern Virginia Medical Center in Woodbridge. Dr. Farmer is a cardiologist at George Washington University in Washington, D.C.

The couple recently sat down with *ACEP Now* Medical Editor-in-Chief Kevin Klauer, DO, EJD, FACEP, to discuss the challenges of getting married as a gay couple before it was legal nationwide in the United States and of being in a two-physician marriage.

KK: Tell us about yourselves.

AB: I'm from North Carolina, born and raised. I went to medical school at East Carolina University in Greenville and then did residency at Thomas Jefferson University in Philadelphia. That's where Steve and I met. I started working for EmCare at the time; now I work for Envision Healthcare. I work clinically at a hospital here in northern Virginia, but most of my time is spent working administratively.

SF: I was born in London in the United Kingdom and lived in multiple cities around the world, domestically and internationally. I attended medical school back east at Yale, and then I did my residency and fellowship all at the University of Pennsylvania in Philadelphia. I also have a PhD in health policy.

KK: How did you two meet, and when did you get married?

AB: I was in my last year of residency at Jefferson, and Steve was in his first year of fellowship at Penn. Our first date was at The Continental in downtown Philly. After that date, there was really no question this was the person I was going to be with; that was 11 years ago. We got married seven years ago on July 9 in Montreal, Canada.

With Steve being a dual citizen, we wanted to make sure that our marriage would be recognized in the United Kingdom. The United States, at that point, did not have marriage equality across the country, and while we had considered getting married in a place like Massachusetts or Washington, D.C., where marriage was legal, it was not recognized in the United Kingdom, but a marriage in Canada would be recognized. They would recognize international gay marriages, which is kind of an odd way to choose your marriage destination, but that was a calculation we had to make.

SF: It wasn't that we could have gotten married in Chicago, Massachusetts, or some other location that allowed gay marriage, but if you got married in one of those places and then you moved from that place to another state, they may not have the same technical definition of a gay marriage, and you would have to get divorced in the first state and then remarried in the second. This is all pre-DOMA, the Defense of Marriage Act, being revoked.

Although we got married in Montreal, we essentially became incorporated when we moved to Chicago. We became this very complicated legal entity, which established many but not all of the equivalencies of marriage through legal contract.

AB: There are a lot of challenges that I don't think that most people recognize. Those were some of the hoops that we needed to jump through to make sure that we were fully recognized as a married couple. We flew back to Chicago after Montreal and then eventually we moved to DC. Marriage equality hadn't passed, and so our marriage was valid in the District, however, as soon as we crossed the Potomac River into Virginia, the marriage wasn't valid.

In 2015 when the Defense of Marriage Act was overturned by the Supreme Court, that was a big day for us.

KK: In some conversations with you, Adam, I've gained some understanding of the complexities of being a gay man in health care. What challenges and obstacles have you encountered?

AB: I think one of the biggest challenges is the implicit bias, or the assumptions that are made, if someone doesn't know that I'm gay. Something that actually happened recently was I was doing a promo video for our company. I was sitting at a desk, and the assumption by the people that were doing the video was that I would have a wife and kids. They had a picture on the desk of my face superimposed on the picture that was what they envisioned my family would look like. I was with a wife, two kids, and a white fluffy dog. I questioned them, "Where did you get this picture because my face is superimposed over the male picture, and secondly, I don't have a white dog. My dog is gray, and of course, I don't have kids either."

That was illustrative of some of the biases that take place. I know that happens with other minority groups. Once I actually do tell people that I'm gay, then there is the immediate worry or fear that people will think of me in a different light. Will they see me as a certain stereotype? Will they think of me in a sexualized manner? Once you tell someone you're gay, you're telling them what you like sexually. That is something that I think in a heterosexual or heteronormative environment does not happen.

Every time I have a conversation with someone about my family, I'm having a "coming out" type of moment if someone didn't see me in that light. That can be difficult because I have to guess if that person is going to be supportive. Are they going to turn away? Are they going to think of me in a negative fashion?

ADAM BROWN AND STEVE FARMER

TOP: Dr. Farmer (left) and Dr. Brown.

ABOVE & OPPOSITE PAGE: Dr. Brown and Dr. Farmer on a recent vacation in Barcelona.

KK: Steve, did you see the picture of Adam's alternative family?

SF: I did see it, and I had some real questions for Adam when I got home.

It did prompt a lot of conversation. Lots of other people saw that nationally, and they know Adam. People did question if something had changed.

KK: Steve, what about your experiences?

SF: Well, I think in residency and fellowship as a cardiologist, it's much more conservative than emergency medicine. I had a real concern because I didn't know any other people nationally who were gay and a cardiologist.

I was very careful about not revealing my sexuality while in training because I didn't want it to prevent my getting a fellowship at Penn and I didn't want it to impact my job search. When I did apply for jobs, I was very explicit that I was gay because I didn't ever want to be in a situation where I joined a group that was in any way uncomfortable with it.

It frequently happens that patients will speak with me and make assumptions about my being married because they see my ring or for other reasons. In DC, I have a lot of African American patients, and maybe I'm coming back at them with my own biases, but my sense is that gay men are less acceptable in the African American culture than they are in some other groups. I usually deflect the question or ignore it. It's kind of awkward, clinically speaking, because I never really say who I am, which I think is an impediment to being authentic with patients.

KK: What are some of the challenges and struggles you go through together as a couple with your busy schedules and your relationship?

AB: I think we consciously have to work hard not to allow for constant shop talk. With both of us being very interested in health policy and both of us working as physicians, we have the tendency to bring a lot of our work home. Luckily, we are in different specialties; that has helped.

We have done a lot of planning for going on trips together. We go to the gym together, exercise together, etc., and that has made a huge difference toward ensuring that we keep some level of balance and reality to the world that we live in.

KK: Steve, what are some of the unique characteristics, positive or negative, of being married to an emergency physician?

SF: Well, the first thing I would say is that a noninvasive cardiologist and an emergency physician are pretty much the opposite extremes of the decision-making processes. Adam makes decisions very quickly with limited information, and that's the nature of his personality and his job. As a cardiologist, nearly every decision that I make is a decade-long decision, where I'm trying to optimize long-term outcomes, which is the complete opposite mindset.

I've found that Adam's and my decision-making styles complement each other tremendously. We both benefit from joint decision making because I will bring in more considerations into some decisions that we make together, and he pushes me to make a decision.

KK: Do you have any words of advice for emergency physicians or their significant others or life partners about how to make relationships work?

SF: You have to compromise, and you have to talk. Sometimes, you have to give, and other times, you get the benefit of support from your partner. I think those are features of any solid relationship.

AB: Understanding that everything that Steve does, whether I agree with it or disagree with it, I know he loves me and he loves our relationship. I know that he wants what's best for me, and he knows that I want what's best for him, and we want what's best for us. That's so important.

KK: Adam and Steve, I really appreciate your time, and thank you for your openness.

CLEVIPREX® (clevidipine) injectable emulsion

Included in the

2018 AHA/ASA AIS GUIDELINES*[1]

Blood pressure reduction with

TITRATABLE CONTROL

CLEVIPREX® (clevidipine) is a calcium channel blocker that provides blood pressure reduction when oral therapy is not feasible or not desirable[2]

2-4 MIN onset of action[2]

~89% of acute severe hypertension patients achieved target BP[3]

~1 MIN HALF-LIFE with full BP recovery 5-15 minutes after infusion is stopped in most patients[2]

Indication

CLEVIPREX® (clevidipine) is a dihydropyridine calcium channel blocker indicated for the reduction of blood pressure (BP) when oral therapy is not feasible or not desirable.

Important Safety Information

CLEVIPREX® (clevidipine) Injectable Emulsion is contraindicated in patients with:

- Allergies to soybeans, soy products, eggs, or egg products;
- Defective lipid metabolism seen in conditions such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia; and
- Severe aortic stenosis.

CLEVIPREX® is intended for intravenous use. Use aseptic technique and discard any unused product within 12 hours of stopper puncture.

Hypotension and reflex tachycardia are potential consequences of rapid upward titration of CLEVIPREX®. If either occurs, decrease the dose of CLEVIPREX®. There is limited experience with short-duration therapy with beta-blockers as a treatment for CLEVIPREX®-induced tachycardia. Beta-blocker use for this purpose is not recommended.

CLEVIPREX® contains approximately 0.2 g of lipid per mL (2.0 kcal). Lipid intake restrictions may be necessary for patients with significant disorders of lipid metabolism.

Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure. Monitor heart failure patients carefully.

CLEVIPREX® is not a beta-blocker, does not reduce heart rate, and gives no protection against the effects of abrupt beta-blocker withdrawal. Beta-blockers should be withdrawn only after a gradual reduction in dose.

Patients who receive prolonged CLEVIPREX® infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped.

There is no information to guide use of CLEVIPREX® in treating hypertension associated with pheochromocytoma.

Most common adverse reactions for CLEVIPREX® (>2%) are headache, nausea, and vomiting.

Please see Brief Summary on next page.

*Select patients only. CLEVIPREX is not indicated for the prevention or treatment of acute ischemic stroke.

For more information, please visit **Cleviprex.com**

Chiesi
People and ideas for innovation in healthcare

CLEVIPREX® (clevidipine) injectable emulsion

Brief Summary

CLEVIPREX® (clevidipine) injectable emulsion, for intravenous use

Brief Summary of Prescribing Information

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
CLEVIPREX is a dihydropyridine calcium channel blocker indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable.

CONTRAINDICATIONS
Known Allergy - CLEVIPREX is contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products.

Defective Lipid Metabolism - CLEVIPREX is contraindicated in patients with defective lipid metabolism such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia.

Severe Aortic Stenosis - CLEVIPREX is contraindicated in patients with severe aortic stenosis because afterload reduction can be expected to reduce myocardial oxygen delivery.

WARNINGS AND PRECAUTIONS
Need for Aseptic Technique - Use aseptic technique and discard any unused product within 12 hours of stopper puncture *[see Dosage and Administration (2.3)]*.

Hypotension and Reflex Tachycardia - CLEVIPREX may produce systemic hypotension and reflex tachycardia. If either occurs, decrease the dose of CLEVIPREX. There is limited experience with short-duration therapy with beta-blockers as a treatment for CLEVIPREX-induced tachycardia. Beta-blocker use for this purpose is not recommended.

Lipid Intake - CLEVIPREX contains approximately 0.2 g of lipid per mL (2.0 kcal). Lipid intake restrictions may be necessary for patients with significant disorders of lipid metabolism. For these patients, a reduction in the quantity of concurrently administered lipids may be necessary to compensate for the amount of lipid infused as part of the CLEVIPREX formulation.

Negative Inotropy - Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure. Monitor heart failure patients carefully.

Beta-Blocker Withdrawal - CLEVIPREX is not a beta-blocker, does not reduce heart rate, and gives no protection against the effects of abrupt beta-blocker withdrawal. Beta-blockers should be withdrawn only after a gradual reduction in dose.

Rebound Hypertension - Patients who receive prolonged CLEVIPREX infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped.

Pheochromocytoma - There is no information to guide use of CLEVIPREX in treating hypertension associated with pheochromocytoma.

ADVERSE REACTIONS
The following risk is discussed elsewhere in the labeling: Hypotension and Reflex Tachycardia *[see Warnings and Precautions (5.2)]*.

Clinical Trials Experience
CLEVIPREX clinical development included 19 studies, with 99 healthy subjects and 1307 hypertensive patients who received at least one dose of clevidipine (1406 total exposures). Clevidipine was evaluated in 15 studies in hypertensive patients: 1099 patients with perioperative hypertension, 126 with severe hypertension and 82 patients with essential hypertension.

The desired therapeutic response was achieved at doses of 4-6 mg/hour. CLEVIPREX was infused for <24 hours in the majority of patients (n=1199); it was infused as a continuous infusion in an additional 93 patients for durations between 24 and 72 hours.

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.

Perioperative Hypertension
The placebo-controlled experience with CLEVIPREX in the perioperative setting was both small and brief (about 30 minutes). Table 2 shows treatment-emergent adverse reactions and the category of "any common adverse event" in ESCAPE-1 and ESCAPE-2 where the rate on CLEVIPREX exceeded the rate on placebo by at least 5% (common adverse reactions).

Table 2. Common adverse reactions in placebo-controlled perioperative studies.

	ESCAPE-1		ESCAPE-2	
	CLV N=53 (%)	PBO N=51 (%)	CLV N=61 (%)	PBO N=49 (%)
Any common adverse event	27 (51%)	21 (41%)	32 (53%)	24 (49%)
Acute renal failure	5 (9%)	1 (2%)	—	—
Atrial fibrillation	—	—	13 (21%)	6 (12%)
Nausea	—	—	13 (21%)	6 (12%)

Three randomized, parallel, open-label studies called ECLIPSE, with longer exposure in cardiac surgery patients define the adverse reactions for patients with perioperative hypertension. Each ECLIPSE study compared CLEVIPREX (n=752) to an active comparator: nitroglycerin (NTG, n=278), sodium nitroprusside (SNP, n=283), or nicardipine (NIC, n=193). The pooled mean maximum dose in these studies was 10 mg/hour and the mean duration of treatment was 8 hours.

There were many adverse events associated with the operative procedure in the clinical studies of CLEVIPREX and relatively few plausibly related to the drugs used to lower blood pressure. Thus, the ability to differentiate the adverse event profile between treatments is limited. The adverse events observed within one hour of the end of the infusion were similar in patients who received CLEVIPREX and in those who received comparator agents. There was no adverse reaction that was more than 2% more common on CLEVIPREX than on the average of all comparators.

Serious Adverse Events and Discontinuation – Perioperative Hypertension Studies

The incidence of adverse events leading to study drug discontinuation in patients with perioperative hypertension receiving CLEVIPREX was 5.9% versus 3.2% for all active comparators. For patients receiving CLEVIPREX and all active comparators the incidence of serious adverse events within one hour of drug infusion discontinuation was similar.

Severe Hypertension
The adverse events for patients with severe hypertension are based on an uncontrolled study in patients with severe hypertension (VELOCITY, n=126).

The common adverse reactions for CLEVIPREX in severe hypertension included headache (6.3%), nausea (4.8%), and vomiting (3.2%). The incidence of adverse events leading to study drug discontinuation for CLEVIPREX in severe hypertension was 4.8%.

Less Common Adverse Reactions in Patients with Severe or Essential Hypertension
Adverse reactions that were reported in <1% of patients with severe or essential hypertension included:

Cardiac: myocardial infarction, cardiac arrest

Nervous system: syncope

Respiratory: dyspnea

Post-Marketing and Other Clinical Experience
Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or to establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-approval use of CLEVIPREX: increased blood triglycerides, ileus, hypersensitivity, hypotension, nausea, decreased oxygen saturation (possible pulmonary shunting) and reflex tachycardia.

DRUG INTERACTIONS
No clinical drug interaction studies were conducted. Clevidipine and its major dihydropyridine metabolite do not have the potential for blocking or inducing any CYP enzyme.

USE IN SPECIFIC POPULATIONS
Pregnancy: Pregnancy Category C - There are no adequate and well-controlled studies of CLEVIPREX use in pregnant women. In animal studies, clevidipine caused increases in maternal and fetal mortality and length of gestation. CLEVIPREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There was decreased fetal survival when pregnant rats and rabbits were treated with clevidipine during organogenesis at doses 0.7 times (on a body surface area basis) the maximum recommended human dose (MRHD) in rats and 2 times the MRHD in rabbits.

In pregnant rats dosed with clevidipine during late gestation and lactation, there were dose-related increases in maternal mortality, length of gestation and prolonged parturition at doses greater than or equal to 1/6 of the MRHD based on body surface area. When offspring of these dams were mated, they had a conception rate lower than that of controls. Clevidipine has been shown to cross the placenta in rats *[see Nonclinical Toxicology (13.3)]*.

Labor and Delivery: CLEVIPREX in the labor and delivery setting has not been established as safe and effective. Other calcium channel blockers suppress uterine contractions in humans. Pregnant rats treated with clevidipine during late gestation had an increased rate of prolonged parturition.

Nursing Mothers: It is not known whether clevidipine is excreted in human milk. Because many drugs are excreted in human milk, consider possible infant exposure when CLEVIPREX is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of CLEVIPREX in children under 18 years of age have not been established.

Geriatric Use: Of the 1406 subjects (1307 with hypertension) treated with CLEVIPREX in clinical studies, 620 were ≥65 years of age and 232 were ≥75 years of age. No overall differences in safety or effectiveness were observed between these and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, for an elderly patient doses should be titrated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE
There has been no experience of overdosage in human clinical trials. In clinical trials, doses of CLEVIPREX up to 106 mg/hour or 1153 mg maximum total dose were administered. The expected major effects of overdose would be hypotension and reflex tachycardia.

Discontinuation of CLEVIPREX leads to a reduction in antihypertensive effects within 5 to 15 minutes *[see Clinical Pharmacology (12.2)]*. In case of suspected overdosage, CLEVIPREX should be discontinued immediately and the patient's blood pressure should be supported.

Please see Full Prescribing Information at www.cleviprex.com.

References: 1. Powers WJ, Rabinstein AA, Ackerson T, et al; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-e110. **2.** CLEVIPREX® (clevidipine) Prescribing Information. 2017. **3.** Pollack CV, Varon J, Garrison NA, Ebrahimi R, Dunbar L, Peacock WF. Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. *Ann Emerg Med*. 2009;53(3):329-338.

CLEVIPREX®
(clevidipine)
injectable emulsion

ILLUSTRATION: CHRIS WHISSEN & SHUTTERSTOCK.COM

The poison center has been receiving reports across the state of people with a history of synthetic cannabinoid use presenting with severe acquired coagulopathy presumed to be secondary to long-acting coumarin rodenticides, otherwise known as superwarfarins.

DEADLY SPICE

CONTINUED FROM PAGE 1

other medications or supplements.

Her physical exam reveals a pale, ill-appearing, and uncomfortable female. Large hemorrhagic bullae fill her mouth, particularly around the gingiva and sides of the tongue. Cutaneous findings include scattered ecchymoses and an oozing abrasion on her right upper extremity. The rest of the physical exam is unremarkable.

Initial labs are normal other than a hemoglobin and hematocrit that are slightly elevated. Similarly, liver function tests are unremarkable. The coagulation study results are taking much longer than expected. A urine toxicology screen is negative for opioids, benzodiazepines, phencyclidine, and cannabis.

Additional social history reveals she smokes marijuana daily, but because she is trying to find employment, she recently switched to smoking synthetic cannabinoids (ie, "spice") to avoid detection on pre-employment urine drug screens. She denies any other recreational drug use.

She reports that spice is sold under a variety of names in small sealed packets she buys from several corner markets throughout the city. The packaging varies, and she reports smoking multiple brands. Sometimes they are labeled as other substances such as Kratom, but the patient states it is a well-known fact these packages actually contain synthetic marijuana. The spice is clearly different from the regular marijuana she used to smoke. She noted a brief, more intense high and found herself smoking synthetic cannabinoids multiple times daily.

Finally, her coagulation results come in: Her activated partial thromboplastin time is 92 seconds, her prothrombin time (PT) is >120 seconds, and her international normalized ratio (INR) is >20. She is given four units of fresh frozen plasma (FFP) and 10 mg of IV vitamin K1.

Despite a negative past medical history or anticoagulant use, coumarin anticoagulant poisoning is suspected. Oral vitamin K1 (50 mg three times daily) is started, consistent with management from previous reports of intentional warfarin overdoses.[1]

The poison center has been receiving reports across the state of people with a history of synthetic cannabinoid use presenting with severe acquired coagulopathy presumed to be secondary to long-acting coumarin rodenticides, otherwise known as superwarfarins. Her serum subsequently tests positive for brodifacoum, and her urine is positive for two popular synthetic cannabinoids. With the FFP and vitamin K1, her PT and INR rapidly correct, and her bleeding symptoms resolve over the course of the next couple of days. She is ultimately discharged on 50 mg oral vitamin K1 twice daily.

Discussion

In March 2018, the Illinois Poison Center became aware of multiple patients presenting to emergency departments across the state with profoundly elevated INRs with various bleeding complaints. The aforementioned patient is actually a composite of multiple patients to illustrate the typical presentation according to our bedside experience.

Early on when working with the Illinois Department of Public Health, the common thread through these cases was synthetic cannabinoid use. This correlation was confirmed by performing a detailed interview, urine and serum testing for various popular synthetic cannabinoids, and serum testing for several long-acting anticoagulants. The case count grew rapidly to include multiple states with 165 cases and three fatalities, as was published in the May *Morbidity and Mortality Weekly Report* (MMWR).[2] Since that May report, many additional cases have presented to hospitals across multiple states.

Sporadic case reports exist of patients exposed to brodifacoum through smoking crack cocaine, marijuana, and tobacco.[3,4] There are lay press reports of police seizures of synthetic cannabinoids laced with rodenticides.[5] However, experience with inhalational exposure to brodifacoum is limited because most previously reported cases of brodifacoum poisoning have been oral ingestions.

Coumarin rodenticides work by blocking quinone reductase and epoxide reductase to prevent the conversion of vitamin K epoxide to vitamin K hydroquinone (K1), which is required for the synthesis of activated factors II, VII, IX, and X and factors C, S, and Z. Brodifacoum is a derivative of 4-hydroxycoumarin that adds a halogenated side chain. Compared to warfarin, it features greater affinity for K1-2,3-epoxide reductase, disrupts the K1-epoxide cycle at multiple points, and causes hepatic accumulation and profoundly longer biological half-lives due to prolonged lipid solubility and enterohepatic circulation.[1]

The elimination half-life of brodifacoum reportedly ranges from 16 to 36 days, with case

reports of up to 270 days in intentional chronic exposures.[6,7] Treatment with vitamin K1 provides active cofactor, bypassing the inhibited enzymes. However, considering the lack of regeneration of spent cofactor to vitamin K1, poor oral absorption of vitamin K1, and the long elimination half-life of many superwarfarins, patients must take regular large doses of vitamin K1 for a prolonged course to continue to produce clotting factors.

Diagnosis and Treatment

Suspect brodifacoum in patients presenting with unexplained bleeding, particularly hematuria and flank pain. Because brodifacoum is a superwarfarin, patients will present with a markedly elevated prothrombin time and INR. A history of synthetic cannabinoid or other illicit substance use may strongly support the diagnosis, especially in the setting of a cluster of cases. A thorough history addressing other causes of genetic or acquired coagulopathy is vital. Calling your local poison center may prove crucial in facilitating initial stabilization, long-term management, and coordination with the local health department.

Faced with a large-scale outbreak and the need to properly utilize available resources, we developed a treatment protocol that started with 10 mg of IV vitamin K1 and Kcentra, FFP, or factor eight inhibitor bypassing activity (FEIBA) for major bleeding. All patients who could tolerate oral delivery without active gastrointestinal bleeding were also started on oral vitamin K1 at 50 mg three times a day and then titrated every 48 hours to maintain an INR below 2.

Once patients were on a stable minimum dose, they were discharged. Every patient required reliable outpatient follow-up and access to vitamin K, which was complicated by the cost of vitamin K1, the large doses required, and the anticipated prolonged duration of treatment.

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DR. RASIN is a toxicology fellow at Toxikon Consortium in Chicago.

DR. DEVGUN is a clinical instructor and attending at the University of Illinois at Chicago.

DR. KIM is an attending physician at NorthShore University HealthSystem in Evanston, Illinois.

Highlights from *Annals of Emergency Medicine*

Can 911 Triage Nurses Improve Care and Save Money?

by MAURA KELLY

The following is a summary of "DC's New 911 Nurse Triage Program" from the October issue of **Annals of Emergency Medicine**. *Visit www.annemergmed.com to read the complete article.*

In April, triage nurses began working with the 911 call center in Washington, D.C., responding to callers with milder symptoms and, when appropriate, directing them away from emergency departments to urgent care centers, walk-in clinics, and primary care physicians. This new initiative was designed to ease the load on D.C.'s overburdened emergency departments and ambulance corps and to help establish a better pattern of care for patients.

At least six other similar initiatives are currently operating in the United States; D.C. consulted with a few of those programs before launching its effort. D.C. was able to get health insurers to agree to provide nonemergency medical transportation on a same-day basis when directed to do so by triage nurses, thereby overcoming what might have been a significant hurdle to implementation.

Strategies like D.C.'s seem to save payers a bundle. Reno, Nevada, calculated that between October 2013 and June 2016, its nurse triage program reduced medical care costs by nearly $6 million. So why aren't more jurisdictions in the United States trying out similar initiatives? One argument is that most entities that oversee emergency medical services get paid per ambulance ride rather than per patient. Therefore, there isn't much incentive to change. Another critic complains that if you were to take a nuanced look at the entire course of treatment, nurse triage programs, in total, would likely end up costing more. What's more, nurse triage programs represent a perceived risk that patients in need of urgent care might be diverted erroneously. Although programs in places like Reno, Las Vegas, and Fort Worth, Texas, report that they've had no adverse outcomes, there are no randomized studies on 911-based triage nurses fielding low-acuity emergency calls.

MS. KELLY is a special contributor to *Annals News & Perspective*.

The Roots of Burnout: Part 2

DR. CHRISTINA MASLACH DISCUSSES HOW OUR UNDERSTANDING OF BURNOUT CAN BE USED TO COMBAT IT

When Christina Maslach, PhD, started her psychology research career in the early 1970s, she didn't know her work would lead to the Maslach Burnout Inventory, a measure for professional burnout still being used today. She first published the inventory with coauthor Susan E. Jackson in 1981. Dr. Maslach, who is professor of psychology at the University of California, Berkeley, has researched and published extensively about burnout throughout her career and has helped to define the way we discuss and understand the combination of stress, exhaustion, and powerlessness that endangers the careers—and lives—of many emergency physicians.

ACEP Now Medical Editor-in-Chief Kevin Klauer, DO, EJD, FACEP, recently sat down with Dr. Maslach to discuss the early research that led to her developing the Maslach Burnout Inventory, and what she's learned from decades of talking to people about burnout. Here is Part 2 of their conversation. Part 1 appeared in the September issue.

KK: I'm noticing people moving away from the term "burnout" and moving toward "resiliency." What are your thoughts on that?

CM: On the one hand, I think it's a good strategy to focus on what are the positive goals we could move toward. People are going to be more highly motivated to make things better—let's improve the situation—rather than simply focusing on the negative. In fact, we did that in our research earlier when we started focusing on what we were calling engagement as the opposite of what we were seeing in terms of burnout.

Where I would disagree a little bit is that resilience is really focusing on individual characteristics such as how well you cope, how well you take care of yourself, etc. The biggest challenge I find right now is that people keep thinking of burnout as a personal problem, and how do we get people to fix themselves? What that means is, we're not paying attention to all of the causes of the problem.

Years ago, there was a cartoon showing a medical doctor in a white lab coat running on a treadmill really fast, with a huge fire and flames licking at his heels. Resiliency is directed at how to make you run faster, be stronger, last longer, etc., but it's not doing a thing about the fire. At some point, we really need to make sure that we're looking at both, but being healthy, getting enough rest, meditating, and doing yoga aren't going to solve the problem. I'm a believer in what's happening upstream is causing this problem.

KK: Do you recall either a specific time or a specific individual where you thought your interaction with somebody saved a life?

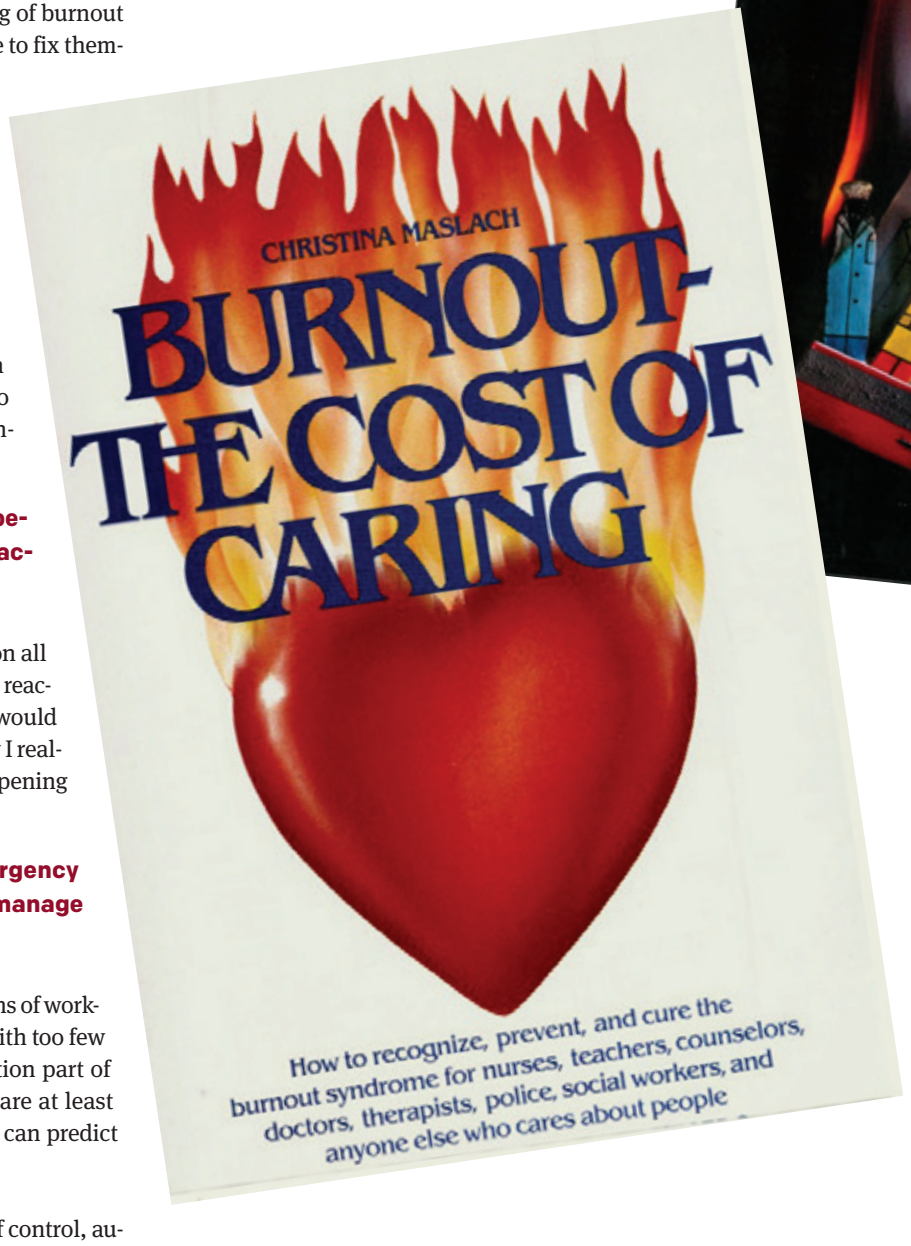
CM: I will go back to that very first article based on all the interviews I did, where I spoke with people. The reaction that I got to that paper was huge, and people would write or call and say, "I read your article, and now I realize I have a different understanding of what's happening and what I need to do."

KK: Do you have any suggestions for emergency physicians to avoid burnout, recognize it, manage it?

CM: Everybody thinks of burnout primarily in terms of workload. The demands are way too high combined with too few resources, etc. That is a predictor of the exhaustion part of burnout. The research is showing us that there are at least five other areas between people and the job that can predict burnout, or greater engagement with work.

1. The workload issue.
2. The extent to which you have some sort of control, autonomy, or discretion over how you do your job.
3. Reward, which is positive feedback, getting positive feedback when you've done good work. What we're finding is that it's not so much salary or benefits; it's social reward and recognition.
4. Community, which is the workplace community (eg, your colleagues, bosses, the people you supervise, anybody who you come in contact with on a regular basis). If there is a toxic work environment where people don't trust each other, don't feel that everybody has their back and they have theirs, there's no support. There's destructive competition—it is deadly.
5. Fairness. Whatever the rules are, there should be a fair way in which they are administered to avoid issues of discrimination and not treating people fairly and well.
6. Values. It's what is driving you to do that kind of work, your passion. I see that in health care when we get into how many minutes can you spend with each patient, getting the beds turned, the financial pressure that is eating into the quality of care that they're providing. That can also be a great source of burnout.

KK: Absolutely, and knowing those domains is critically important. Some call it health care reform, but I think it's really payment reform. Spending less time with patients and providing less value, that sixth component, is putting a lot of pressure on us, which is weakening our resilience, and making burnout worse. Thank you so much for your time and your wonderful work. You truly have benefited emergency medicine.



PHOTOS: CHRISTINA MASLACH

TOP: Dr. Christina Maslach

ABOVE: Image from the cover of the issue of *Human Behavior* magazine where Dr. Maslach published her first article in 1976.

LEFT: Cover of *Burnout: The Cost of Caring,* published in 1982.

ACEP Council Elects Board Members, President-Elect

ACEP

Two New Board Members Elected, Two Incumbents Re-Elected

The ACEP Council elected L. Anthony Cirillo, MD, FACEP (Rhode Island, left) and John T. Finnell, MD, FACEP, FACMI (Indiana, second from right) to the ACEP Board of Directors. Christopher S. Kang, MD, FACEP, FAWM (incumbent, Washington, second from left) and Mark Rosenberg, DO, FACEP (incumbent, New Jersey, right) were re-elected for their second terms.

William Jaquis, MD, FACEP, of Fort Lauderdale, Florida, was elected President-Elect Sunday during the ACEP Annual Meeting in San Diego, California. He was elected by ACEP's Council to serve a 1-year term and will assume ACEP's presidency at next year's meeting in Denver, Colorado.

ACEP

President-Elect, Dr. William Jaquis

"The past five years have brought significant changes in health policy, market consolidation, and the role of social media to emergency medicine," said Dr. Jaquis. "Failure to address issues such as prudent layperson and fair coverage will lead to broad-based changes to access to care for millions of emergency patients."

Dr. Jaquis currently serves as the senior vice president of Envision Health's East Florida Division. He's also an attending physician at Aventura Medical Center in Aventura, Florida. He was voted to ACEP's Board in 2012 and 2015. Dr. Jaquis has previously served as the organization's Vice-President. Prior to that, he served as an active member of the Maryland ACEP Chapter for 16 years, including a term as President.

Dr. Jaquis earned his medical degree at the Medical College of Ohio and completed his residency at Case Western–Mt. Sinai Medical Center in Cleveland, Ohio.

ACEP Council Reviews Social Issues and More at Annual Meeting

The 2018 ACEP Council considered several resolutions during its annual meeting this week, including proposals related to social issues and physician wellness.

This year's 421-member Council represents all 53 chapters, 37 ACEP sections of membership, the Emergency Medicine Residents' Association (EMRA), the Association of Academic Chairs in Emergency Medicine, the Council of Emergency Medicine Residency Directors, and the Society of Academic Emergency Medicine.

The resolutions adopted by the Council do not become College policy until they are reviewed and approved by the ACEP Board of Directors on Thursday.

Social issues were a point of focus and debate throughout the meeting; after much discussion, the Council passed an amended version of a resolution about separating migrating children from caregivers.

The Council also adopted resolutions related to:

- Codifying the Leadership Development Advisory Committee
- Nominating committee revision to promote diversity
- Growth of the ACEP Council
- Diversity of ACEP Councillors
- No more emergency physician suicides
- Verification of training
- Adequate resources for safe discharge requirements
- Addressing mental health treatment barriers created by the Medicaid institutions for mental diseases exclusion
- Advocating for Centers for Medicare and Medicaid Services policy restraint to avoid restricting quality emergency care
- ED copayments for Medicaid beneficiaries
- Funding for medication-assisted treatment programs
- Funding of substance use intervention and treatment programs
- Naloxone layperson training
- Payment of opioid sparing pain treatment alternatives
- Physician orders for life-sustaining treatment forms
- Separation of migrating children from their caregivers
- Violence is a health issue
- Antimicrobial stewardship
- Care of the boarded behavioral health patient
- Care of individuals with autism spectrum disorder in the emergency department
- Emergency department and emergency physician role in the completion of death certificates
- Firearm safety and injury prevention policy statement
- Inclusion of methadone in state drug and prescription databases
- Support for extreme risk protection orders to minimize harm
- Law enforcement information gathering in the emergency department policy statement
- Supporting medication for opioid use disorder
- Recording in the emergency department

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

- Generic injectable drug shortages
- ACEP policy related to immigration
- Expert witness testimony

ABEM's New President on Continuous Certification

Dr. Robert Muelleman tackles today's EM issues for *ACEP Now*

ABEM

The future of certification is exciting, according to Robert L. Muelleman, MD, FACEP, new President of the American Board of Emergency Medicine (ABEM), who was elected in July and will serve for the 2018–2019 term.

Dr. Muelleman is professor and past chair of the department of emergency medicine at the University of Nebraska Medical Center in Omaha. He has been a member of the ABEM Board of Directors since July 2011 and was elected to the Executive Committee in 2015.

Dr. Muelleman recently responded in writing to *ACEP Now*'s questions about his goals as ABEM President and the future of certification.

Given your long involvement in academic emergency medicine, what would you like ACEP members to know about you?

Until two years ago, I was an academic department chair at the University of Nebraska Medical Center. My practice and teaching focus is in the heartland of America. Much of my academic interest revolves around the challenges of providing emergency care in rural America. That brings a unique, somewhat nontraditional focus within academic emergency medicine.

While I was the chair of the Residency Review Committee for Emergency Medicine, I tried to find practical approaches to residency training that would serve physicians who ultimately went to work in community settings. Because most ABEM-certified physicians are community physicians, I want them to know that I am committed to having ABEM serve their needs.

Finally, I'm an avid wine grape grower in Nebraska. Because ACEP Immediate Past President Paul Kivela is a wine maker, I think we will have some fun, non-emergency medicine–related conversations during the upcoming year.

As the President of ABEM, what do you see as the biggest challenges for the specialty?

Emergency medicine has been described as the hub of the U.S. health care system, and I think the wheel is starting to squeak. Although we have high self-expectations and need to keep up with medical advances, we are being pummeled from every side with additional rules and requirements. We want to take some of the pressure away from emergency physicians. We want ABEM certification to be the only credential that an emergency physician will need beyond a medical license. It's a delicate balance to increase the value of ABEM certification, with its rigorous standards, without burdening physicians with unnecessary work. We know that certification is valuable and is associated with greater levels of income, more career opportunities, and a lower risk of state medical board disciplinary actions. We are constantly seeking ways to make it even more valuable.

How will the "Vision Commission" that the American Board of Medical Specialties (ABMS) is conducting affect ABEM and our specialty?

The Vision Commission was established by ABMS to suggest ways to redesign continuing certification (Maintenance of Certification [MOC]). What's important for emergency medicine is that we have had a voice on the commission. ABEM Executive Director Earl J. Reisdorff, MD, FACEP, serves on the commission. The commission heard testimony from John C. Moorhead, MD, FACEP, the Chair of ABMS, but, importantly, a past President of both ACEP and ABEM. Testimony from other emergency physicians, including Janet G. H. Eng, DO, FACEP, and Kim M. Feldhaus, MD, FACEP, provided perspectives on the day-to-day realities of emergency physicians; they really portrayed our specialty favorably.

The Vision Commission will soon submit a report to ABMS with recommendations to improve the continuing certification process. I'll be surprised if ABEM will need to make many adjustments to our planned modifications.

What can you share from your survey to all ABEM-certified physicians about continuing certification?

We conducted the survey because we felt it was extremely important to hear the voice of all ABEM-certified physicians as we developed modifications to the continuing certification process. I was pleased by the high response rate. We received almost 13,000 responses (36 percent) on a survey that was open for only two weeks. More than 70 percent of respondents thought that some assessment of medical knowledge should be part of continuing certification, and more than 90 percent prefer the general idea of shorter, more frequent open-book assessments. This information will help guide our path. For me, the biggest takeaway is a sense of gratitude to everyone who took the time to share their ideas so that together we can change the future of our specialty.

Tell us about the future of ABEM's Continuing Certification Program.

In short, it's really exciting. Our biggest challenges are defining the content and detailed design of the new testing format, MyEMCert, and meeting our self-imposed 2020 deadline for the pilot. We're also exploring the best parts of our current program, such as the Lifelong Learning and Self-Assessment, to see if we can leverage that learning experience within MyEMCert. With O. John Ma, MD, leading a taskforce of very talented and creative individuals, I'm confident it will be a high quality product.

We are also trying to find ways to identify new developments within the specialty and incorporate them into the new testing format in a timely manner. One of the criticisms we received is that we don't focus on the most recent and relevant advances in the specialty. I think that will change.

The flip side of this effort is to not lose the validity of the current ConCert Exam. Research shows that the ConCert is a valid assessment of cognitive skill.

What's been happening with the anti-MOC legislation?

Most anti-MOC legislation has failed. Among the bills that passed, most prohibit using MOC or certification as a requirement for medical licensure. I find that ironic since no ABMS Board has ever suggested that certification should be a requirement for a medical license. There are states, such as Texas, Georgia, and Tennessee, where the legislation has been more substantial.

Much anti-MOC activity has been born out of a hostility within other specialties. We are fortunate that, within emergency medicine, there has been open communication, even when there is not always agreement about the best approach. We think there is a growing awareness that anti-MOC legislation would injure professional self-regulation, which is the publicly stated opinion from our colleagues at the American College of Surgeons. We would welcome ACEP joining us with a similar position. The medical profession has already lost a lot of ground on cost control, access to care, and quality improvement, and now some physicians are trying to legislate away our ability to regulate ourselves. We believe that emergency medicine has an opportunity to be a leader in revising continuing certification and helping emergency physicians become even better doctors while showing a united front in preserving professional self-regulation.

EM LITERATURE OF NOTE

PEARLS FROM THE MEDICAL LITERATURE

DR. RADECKI is an emergency physician and informatician at Kaiser Permanente NW and affiliated with the McGovern Medical School at UTHealth. He blogs at Emergency Medicine Literature of Note and can be found on Twitter @emlitofnote.

How to Save the Dead

Challenging common practices of advanced life support

by RYAN PATRICK RADECKI, MD, MS

There's a big difference between patients who are mostly dead and all dead. Mostly dead is, by logical extension, slightly alive. Slightly alive we can work with.

However, this leads to a question: Which application of the medical sciences is best for the slightly alive?

Two important questions have remained controversial for decades: the use of epinephrine in cardiac arrest and the type of advanced airway management provided. This year has brought to light several new studies concerning these topics, but they seem to provide only minimal illumination.

Epinephrine Research

ARAMEDIC2, a randomized, double-blinded, placebo-controlled trial of epinephrine in adults with out-of-hospital cardiac arrest (OHCA), was conducted in the United Kingdom's prehospital system.[1] This study used the contemporary dose of 1 mg intravenously repeated every three to five minutes as indicated by advanced cardiac life support protocols. The primary outcome? Survival at 30 days.

So the unqualified answer favors epinephrine, but the details are a little more complicated. Of the 8,014 patients randomized into this trial, survival at 30 days was 3.2 percent in the epinephrine group versus 2.4 percent in the placebo group. Dismal numbers, but incrementally less dismal when treated with epinephrine.

The catch—and there's always a catch—is the entirety of excess patients surviving to 30 days in the epinephrine cohort were all gravely disabled. In these small cohorts of survivors, 31 percent of those randomized to epinephrine were gravely disabled at follow-up compared with only 17.8 percent of those randomized to placebo. In short, as we parse these results down to the most important patient-oriented outcomes, the differences disappear.

But wait: When we dig into these results more closely, the differences are actually magnified. A full 36.3 percent of patients in the epinephrine cohort had some return of spontaneous circulation during prehospital transport compared with only 11.7 percent of those randomized to placebo. Initial treatment in the hospital sheared another chunk off the top of each group, but still nearly three times as many patients survived to hospital admission in the epinephrine cohort as compared to the placebo group.

We can interpret this as either an advantage or a disadvantage. When no reliable difference appears regarding favorable neurological outcomes, short-term survival can be seen as a substantial cost and burden to the health system absent long-term benefit. However, the survival advantage associated with epinephrine is still massive.

Potential interventions such as early coronary angiography, targeted temperature management, and other potential physiologic and neuroprotective interventions may yet generate clear separation between the two groups with regard to neurologically intact survival. In sum, the decisions we make today regarding the use of epinephrine may be quite different than those a few years from now.

Airway Management Studies

Two trials, AIRWAYS-2 and PART, compared endotracheal intubation (ETI) with the placement of a supraglottic airway (SGA).[2,3] The larger trial, AIRWAYS-2, was conducted in England, enrolling 9,296 people in its intention-to-treat population. In this trial, individual paramedics at four emergency medical services (EMS) were randomized to use ETI or SGA as their initial method of securing the airway. For SGA, they used the i-gel device (chosen because it is the most commonly used device in England), and all intubation attempts utilized direct laryngoscopy. Their primary outcome was a good outcome on the modified Rankin Scale, measured as a score ≤3 at hospital discharge or 30 days.

Again, as expected with cardiac arrest not seen on television, overall outcomes were dismal. Survival in the first 72 hours was 13.1 percent in the ETI cohort and 13.6 percent with SGA, and a good outcome was observed in 6.8 percent and 6.4 percent, respectively. Unlike the epinephrine trial, however, outcomes remained essentially parallel at all time points in the study.

This study featured several interesting quirks. Patients treated by paramedics randomized to the ETI cohort were far less likely to have any advanced airway attempted, with almost 25 percent of those in the ETI cohort simply receiving no airway attempt compared with 14 percent of those in the SGA group. These patients were managed with bag-valve-mask ventilation as indicated, and the overall rate of good outcome in these patients measured approximately 17 percent. Only 2.3 percent of those in whom an ETI was attempted had a good outcome compared with only 3.2 percent of those in whom SGA was attempted.

Caution: Beware imagining a causal relationship between attempting an advanced airway and poorer outcomes. It is far more likely individual patient factors associated with a better prognosis led to the difference in management strategies, but these data cannot definitively answer questions regarding the necessity of an advanced airway.

The PART study, conducted in the United States and enrolling 3,004 patients, was similar, although with minor differences in design. Rather than randomizing at the individual paramedic level, randomization occurred at the EMS agency level and included crossover periods for each. Additionally, the SGA device used was a laryngeal tube, the most commonly used SGA in the United States.

These authors observed outcomes similar to AIRWAYS-2, with a 72-hour survival of 15.4 percent in the ETI cohort compared to 18.3 percent with SGA. Neurological survival also favored SGA, with good outcomes occurring in only 5 percent of those randomized to ETI compared with 7.1 percent for SGA.

This study is also full of quirks relating to the individual agencies and the devices used. A handful of agencies were made up of EMS providers with only basic life support training. Patients randomized to ETI enrolled by these cohorts received noninvasive ventilation while awaiting the arrival of an advanced life support provider. Additionally, the overall rate of initial airway success was only 51.6 percent with ETI compared to 90.3 percent with SGA. Only one attempt was mandated, but any potential delay or interruption of resuscitative efforts may be interpreted to have deleterious effects on outcomes for the ETI cohort.

So what should we do for the airway based on the results from these 12,000 total patients? Although there is more than enough room for debate, it seems the *least* favorable position would be to support prehospital ETI. ETI cannot conclusively be shown to result in *harm* compared to SGA, but it is challenging to consider it the best strategy.

A better question may be whether *any* advanced airway is routinely necessary. A small trial in France could not reach a conclusion regarding the utility of ETI compared to bag-valve-mask ventilation even though that trial utilized physicians for airway procedures in the prehospital setting.[4]

I believe the current evidence favors conserving limited health care resources by omitting epinephrine and using primarily SGA, if any airway is even needed. However, it would be just as reasonable for a medical director to draw up protocols using both epinephrine and ETI as it would be to omit both. At the end of the day, we are a little closer to definitive answers, but we have many new questions.

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4. Jabre P, Penaloza A, Pinero D, et al. Effect of bag-mask ventilation vs endotracheal intubation during cardiopulmonary resuscitation on neurological outcome after out-of-hospital cardiorespiratory arrest: a randomized clinical trial. *JAMA*. 2018;319(8):779-787.

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Choose the only NOAC with...

Extensive safety and efficacy data in the most patients studied with ***NVAF*** at a higher risk* of stroke[1-5]

AND

A major bleeding rate as low as aspirin with superior efficacy in recurrent ***DVT/PE*** risk reduction†[6]

†After 6 months initial treatment.

*$CHADS_2$ scores 3 to 6 in pivotal NOAC phase 3 trials: ROCKET AF (N=12,402), ARISTOTLE (N=5502), ENGAGE-AF (N=~11,200), and RE-LY (N=5882).

INDICATIONS

XARELTO® is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.

XARELTO® is indicated for the treatment of deep vein thrombosis (DVT). XARELTO® is indicated for the treatment of pulmonary embolism (PE). XARELTO® is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

IMPORTANT SAFETY INFORMATION

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

A. Premature discontinuation of XARELTO® increases the risk of thrombotic events

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

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO® 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 non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants, *see* Drug Interactions**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery**
- **Optimal timing between the administration of XARELTO® 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 for thromboprophylaxis.

DVT = deep vein thrombosis; NOAC = non-vitamin K antagonist oral anticoagulant; NVAF = nonvalvular atrial fibrillation; PE = pulmonary embolism.

Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit www.XareltoHCP.com/PI.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO® in patients with active pathological hemorrhage.
  - A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable.
  - Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant 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. To reduce the potential risk of bleeding associated with the concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next XARELTO® dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.
- **Use in Patients With Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation of XARELTO® in patients who develop acute renal failure while on XARELTO®.
  - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.
  - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue the treatment.
- **Use in Patients With Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO® in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use With P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A4 inhibitors. Avoid concomitant use of XARELTO® with drugs that are known combined P-gp and strong CYP3A4 inducers.
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients With Prosthetic Heart Valves:** The safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO® is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients/Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO® is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A4 inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding.
- Combined P-gp and strong CYP3A4 inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase the risk of bleeding.
- Avoid concurrent use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO® for the mother and possible risks to the fetus when prescribing XARELTO® to a pregnant woman.
  - Fetal/Neonatal adverse reactions: Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.
  - Labor or delivery: The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of XARELTO® in this setting.
  - There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage.
- **Lactation:** Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XARELTO® and any potential adverse effects on the breastfed infant from XARELTO® or from the underlying maternal condition.
- **Females and Males of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

OVERDOSAGE

- Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of XARELTO® overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable.

ADVERSE REACTIONS IN CLINICAL STUDIES

- The most common adverse reactions with XARELTO® were bleeding complications.

Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit www.XareltoHCP.com/PI.

References: 1. Patel MR, Mahaffey KW, Garg J, et al; and the ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. **2.** Granger CB, Alexander JH, McMurray JJV, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. **3.** Connolly SJ, Ezekowitz MD, Yusuf S, et al; and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. **4.** Giugliano RP, Ruff CT, Braunwald E, et al; for the ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. **5.** Savaysa® [prescribing information]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015. **6.** Weitz JI, Lensing AWA, Prins MH, et al; for the EINSTEIN CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222.

083074-171026

Xarelto® rivaroxaban tablets

Janssen Pharmaceuticals, Inc.

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Brief Summary of Prescribing Information for XARELTO® (rivaroxaban)

XARELTO® (rivaroxaban) tablets, for oral use
See package insert for full Prescribing Information

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

A. Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO 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 (2.3, 2.8), in full Prescribing Information, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO 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 non-steroidal 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 XARELTO and neuraxial procedures is not known**

***[see Warnings and Precautions and Adverse Reactions]*.**

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 for thrombo-prophylaxis *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

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

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1) in full Prescribing Information]*.

Treatment of Deep Vein Thrombosis: XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

Treatment of Pulmonary Embolism: XARELTO is indicated for the treatment of pulmonary embolism (PE).

Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism: XARELTO is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions]*
- severe hypersensitivity reaction to XARELTO (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 XARELTO, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO 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 (2.3, 2.8) and Clinical Studies (14.1) in full Prescribing Information]*.

Risk of Bleeding: XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors.

Concomitant use of drugs that are known combined P-gp and strong CYP3A4 inhibitors increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions]*.

Reversal of Anticoagulant Effect: A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant 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 *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of XARELTO and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (i.e., 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. The next XARELTO dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO for 24 hours.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

Use in Patients with Renal Impairment: Nonvalvular Atrial Fibrillation: Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly *[see Dosage and Administration (2.4) in full Prescribing Information]*. Consider dose adjustment or discontinuation of XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations]*.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population *[see Use in Specific Populations]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations]*.

Use in Patients with Hepatic Impairment: No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations]*.

Use with P-gp and Strong CYP3A4 Inhibitors or Inducers: Avoid concomitant use of XARELTO with known combined P-gp and strong CYP3A4 inhibitors *[see Drug Interactions]*.

Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A4 inducers *[see Drug Interactions]*.

Risk of Pregnancy-Related Hemorrhage: In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Patients with Prosthetic Heart Valves: The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy: Initiation of XARELTO is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation *[see Boxed Warning and Warnings and Precautions]*
- Bleeding risk *[see Warnings and Precautions]*
- Spinal/epidural hematoma *[see Boxed Warning and 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 clinical practice.

During clinical development for the approved indications, 18560 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 6962 patients who received XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily to treat DVT or PE (EINSTEIN DVT, EINSTEIN PE), 10 mg or 20 mg orally once daily (EINSTEIN Extension, EINSTEIN CHOICE) to reduce the risk of recurrence of DVT and/or PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

Hemorrhage: The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF trial.

Table 1: Bleeding Events in ROCKET AF*- On Treatment Plus 2 Days

Parameter	XARELTO N=7111 n (%/year)	Warfarin N=7125 n (%/year)	XARELTO vs. Warfarin HR (95% CI)
Major Bleeding†	395 (3.6)	386 (3.5)	1.04 (0.90, 1.20)
Intracranial Hemorrhage (ICH)‡	55 (0.5)	84 (0.7)	0.67 (0.47, 0.93)
Hemorrhagic Stroke§	36 (0.3)	58 (0.5)	0.63 (0.42, 0.96)
Other ICH	19 (0.2)	26 (0.2)	0.74 (0.41, 1.34)
Gastrointestinal (GI)¶	221 (2.0)	140 (1.2)	1.61 (1.30, 1.99)
Fatal Bleeding#	27 (0.2)	55 (0.5)	0.50 (0.31, 0.79)
ICH	24 (0.2)	42 (0.4)	0.58 (0.35, 0.96)
Non-intracranial	3 (0.0)	13 (0.1)	0.23 (0.07, 0.82)

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

‡ Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.

XARELTO® (rivaroxaban) tablets

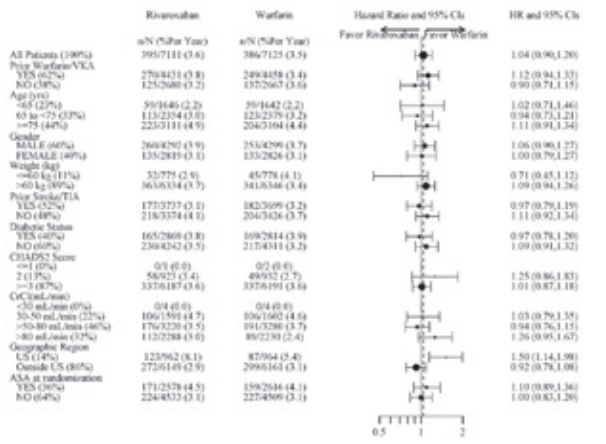
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.

Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Figure 1 shows the risk of major bleeding events across major subgroups.

Figure 1: Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF – On Treatment Plus 2 Days



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). 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.

Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE): EINSTEIN DVT and EINSTEIN PE Studies: In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

Parameter	XARELTO† N=4130 n (%)	Enoxaparin/ VKA† N=4116 n (%)
Major bleeding event	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2 g/dL	28 (0.7)	42 (1.0)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28.0)

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

Reduction in the Risk of Recurrence of DVT and/or PE: EINSTEIN CHOICE Study: In the EINSTEIN CHOICE clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1% for XARELTO 10 mg, 2% for XARELTO 20 mg, and 1% for acetylsalicylic acid (aspirin) 100 mg. The mean duration of treatment was 293 days for XARELTO 10 mg-treated patients and 286 days for aspirin 100 mg-treated patients.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN CHOICE study.

Table 3: Bleeding Events* in EINSTEIN CHOICE

Parameter	XARELTO† 10 mg N=1127 n (%)	Acetylsalicylic Acid (aspirin)† 100 mg N=1131 n (%)
Major bleeding event	5 (0.4)	3 (0.3)
Fatal bleeding	0	1 (<0.1)
Non-fatal critical organ bleeding	2 (0.2)	1 (<0.1)
Non-fatal non-critical organ bleeding§	3 (0.3)	1 (<0.1)
Clinically relevant non-major (CRNM) bleeding¶	22 (2.0)	20 (1.8)
Any bleeding	151 (13.4)	138 (12.2)

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule: XARELTO 10 mg once daily or aspirin 100 mg once daily.

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥ 2 units of whole blood or packed red blood cells.

¶ Bleeding which was clinically overt, did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

In the EINSTEIN CHOICE study, there was an increased incidence of bleeding, including major and CRNM bleeding in the XARELTO 20 mg group compared to the XARELTO 10 mg or aspirin 100 mg groups.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N=4487 n (%)**	**N=4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N=3281 n (%)**	**N=3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N=1206 n (%)**	**N=1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.

† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions: Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies are shown in Table 5.

Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies

Body System Adverse Reaction		
EINSTEIN DVT Study	**XARELTO 20 mg N=1718 n (%)**	**Enoxaparin/VKA N=1711 n (%)**
Gastrointestinal disorders		
Abdominal pain	46 (2.7)	25 (1.5)
General disorders and administration site conditions		
Fatigue	24 (1.4)	15 (0.9)
Musculoskeletal and connective tissue disorders		
Back pain	50 (2.9)	31 (1.8)
Muscle spasm	23 (1.3)	13 (0.8)
Nervous system disorders		
Dizziness	38 (2.2)	22 (1.3)
Psychiatric disorders		
Anxiety	24 (1.4)	11 (0.6)
Depression	20 (1.2)	10 (0.6)
Insomnia	28 (1.6)	18 (1.1)
EINSTEIN PE Study	**XARELTO 20 mg N=2412 n (%)**	**Enoxaparin/VKA N=2405 n (%)**
Skin and subcutaneous tissue disorders		
Pruritus	53 (2.2)	27 (1.1)

* Adverse reaction with Relative Risk >1.5 for XARELTO versus comparator

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

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Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

Body System Adverse Reaction	XARELTO 10 mg N=4487 n (%)	Enoxaparin† N=4524 n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication

† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of XARELTO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury)

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

General Inhibition and Induction Properties: Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Combined P-gp and strong CYP3A4 inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A4 inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.

Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Interaction with Combined P-gp and Strong CYP3A4 Inhibitors: Avoid concomitant administration of XARELTO with known combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with XARELTO as the change in exposure is unlikely to affect the bleeding risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Interaction with Combined P-gp and Moderate CYP3A4 Inhibitors in Patients with Renal Impairment: XARELTO should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and NSAIDs/Aspirin: Coadministration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: The limited available data on XARELTO in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO for the mother and possible risks to the fetus when prescribing XARELTO to a pregnant woman *[see Warnings and Precautions]*.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations: *Disease-Associated Maternal and/or Embryo/Fetal Risk:* Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Pregnant women with thromboembolic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrauterine growth restriction, placental abruption and early and late pregnancy loss.

Fetal/Neonatal Adverse Reactions: Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.

Labor or Delivery: All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery *[see Warnings and Precautions]*. The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of XARELTO in this setting.

Data: *Human Data:* There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage. In an *in vitro* placenta perfusion model, unbound rivaroxaban was rapidly transferred across the human placenta.

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Animal Data: Rivaroxaban crosses the placenta in animals. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg during the period of organogenesis. This dose corresponds to about 14 times the human exposure of unbound drug. In rats, peripartal maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

Lactation: Risk Summary: Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Rivaroxaban and/or its metabolites were present in the milk of rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XARELTO and any potential adverse effects on the breastfed infant from XARELTO or from the underlying maternal condition *(see Data)*.

Data: *Animal data:* Following a single oral administration of 3 mg/kg of radioactive [^{14}C]-rivaroxaban to lactating rats between Day 8 to 10 postpartum, the concentration of total radioactivity was determined in milk samples collected up to 32 hours post-dose. The estimated amount of radioactivity excreted with milk within 32 hours after administration was 2.1% of the maternal dose.

Females and Males of Reproductive Potential: Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In EINSTEIN CHOICE, approximately 39% were 65 years and over and about 12% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14) in full Prescribing Information]*.

Renal Impairment: In pharmacokinetic studies, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Patients with End-Stage Renal Disease on Dialysis: Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study *[see Clinical Pharmacology (12.2, 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 ROCKET AF.

Treatment of DVT and/or PE and Reduction in the Risk of Recurrence of DVT and/or PE : In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery: The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Hepatic Impairment: In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products.

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Q&A ABOUT OUR LITTLEST PATIENTS

KIDS KORNER

DR. JONES is assistant professor of pediatric emergency medicine at the University of Kentucky in Lexington.

DR. CANTOR is professor of emergency medicine and pediatrics, director of the pediatric emergency department, and medical director of the Central New York Regional Poison Control Center at Upstate Medical University in Syracuse, New York.

by LANDON JONES, MD, AND RICHARD M. CANTOR, MD, FAAP, FACEP

The best questions often stem from the inquisitive learner. As educators, we love, and are always humbled by, those moments when we get to say, "I don't know." For some of these questions, you may already know the answers. For others, you may never have thought to ask the question. All questions, comments, concerns, and critiques are encouraged. Welcome to the Kids Korner.

Stylet In or Out?

Question 1: For pediatric lumbar punctures (LPs), does advancement of the LP needle without a stylet (ie, stylet out) increase the odds of a successful LP?

Advancement of the LP needle without a stylet has been reported in the adult medical literature since the 1960s.[1] After puncturing through the epidermis and subcutaneous tissue with the stylet in place, does advancement with the stylet out allow for earlier recognition of the subarachnoid space, or would the soft pediatric bony structures more easily facilitate materials occluding the needle?

A 17-month prospective observational study in 2006 by Baxter et al evaluated 594 pediatric LPs in children age 12 months or younger in a tertiary pediatric emergency department.[2] Of 594 pediatric LPs, data were collected on 428 (72 percent), of which 377 were performed by residents and included in their analysis.

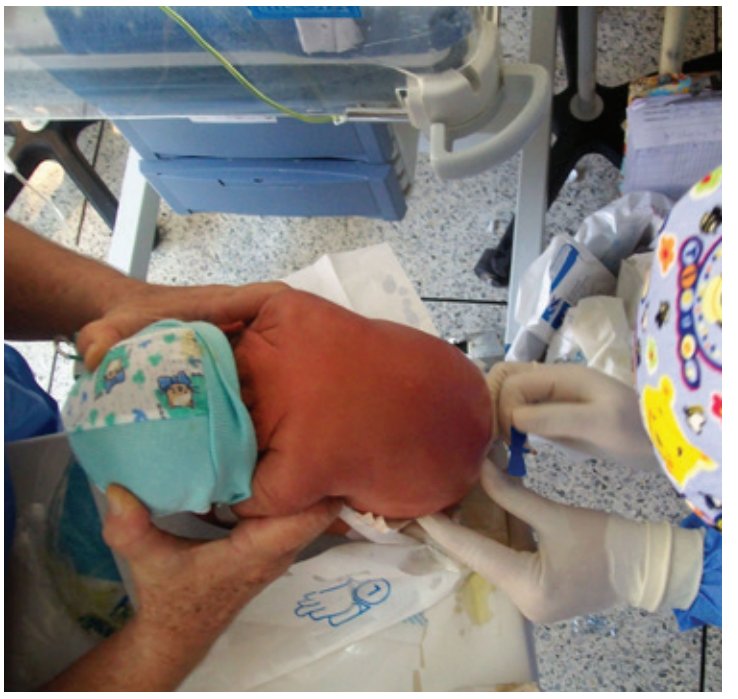
The authors were interested in resident-performed LPs. LP kits included a form for recording several intraprocedural data elements such as patient age, use of anesthetics, use of paper drapes, experience of the person performing the LP, early stylet removal, and number of attempts. The primary outcome was the ability of the resident to successfully perform an LP. Failure was defined as more than 1,000 red blood cells (RBCs)/mm^3, inability of the resident to get cerebrospinal fluid (CSF), or inability to get enough volume for a CSF cell count (ie, adequate volume for a CSF culture but not enough for a cell count).

When analyzing all children age 12 months or younger, the success of LP with early stylet removal was not significant—the final adjusted odds ratio (OR) was 1.9 (95% CI; 0.95–3.9). When evaluating children younger than 12 weeks of age, the OR for successful completion of the procedure using early stylet removal was 2.4 (95% CI; 1.1–5.2), which *was* significant, suggesting that early stylet removal might be beneficial in LP success in this young group.

A prospective observational study in 2007 by Nigrovic et al evaluated 1,459 pediatric LPs (ages 0 to 22 years) over a 19-month period at a tertiary pediatric emergency department.[3] Data collection forms were prospectively obtained and included performer experience, anatomical landmark identification, patient characteristics, local anesthesia, sedation, early stylet removal, and patient movement. The primary outcome was successful LP on first attempt with further analysis by age (3 months or less versus older than 3 months of age). Failure was defined as more than 10,000 RBCs/mm^3, the inability to get CSF on the first attempt, or the inability to get enough volume for a CSF cell count (ie, adequate volume for a CSF culture but not enough for a CSF cell count).

The stylet-out LP technique was performed in 29 percent of these first LP attempts. For all children, the stylet-in technique demonstrated an adjusted OR of 1.8 (95% CI; 1.3–2.7) for failure. For kids age 3 months or younger, failure was significantly associated with stylet in, with an OR of 1.4 (95% CI; 1.02–2.0), suggesting that stylet out improves LP success.

Summary: After insertion of the LP needle through the epidermis and subcutaneous tissue with the stylet in, advancing stylet out appears to improve LP success in children.



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Herpes and Erythema Multiforme

Question 2: In pediatric cases of erythema multiforme (EM) minor, is herpes simplex virus (HSV) a common cause?

Traditionally, EM had been classified as part of a continuum alongside Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), but this is no longer the case. Currently, EM minor and major are believed to be separate pathological entities from SJS and TEN. EM minor typically involves cutaneous lesions alone, while EM major additionally involves mucosal surfaces. These EM lesions are immune-mediated reactions and are most commonly described as target lesions located predominantly on the extremities and less on the torso and back.

A 1992 prospective study of 20 pediatric patients (ages 1 to 16 years) by Weston et al evaluated HSV involvement in cases of EM.[1] Ten patients had associated oral mucosal lesions, a history of recent preceding HSV labial lesion, or a positive HSV culture from a labial lesion that occurred after the EM rash; this group was designated "herpes-associated EM." Ten separate EM cases involved cutaneous lesions only without a history of HSV-associated lesions, and they were designated "idiopathic EM."

Cutaneous lesions from both groups were sampled, and polymerase chain reaction was performed. In the herpes-associated EM group, eight of 10 lesion samples were positive for HSV DNA. In the idiopathic EM group, eight of 10 cutaneous lesions demonstrated HSV DNA.

Weston further clarified, "No HSV could be detected in a biopsy of normal uninvolved skin of a child in whom HSV was present in lesional skin."

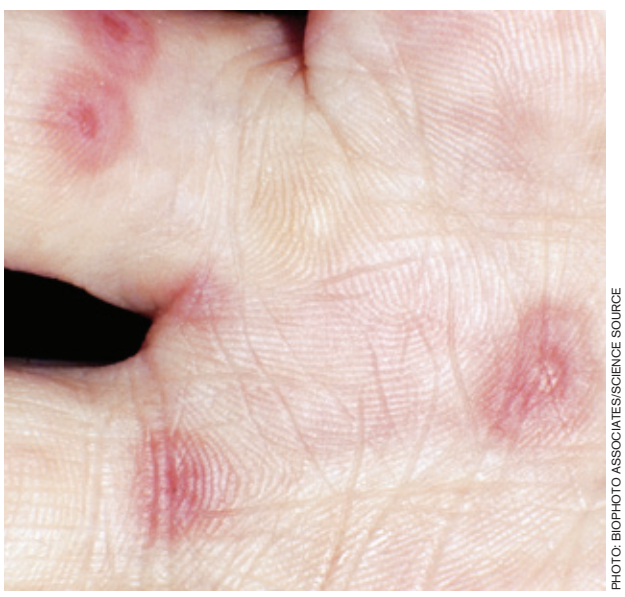

PHOTO: BIOPHOTO ASSOCIATES/SCIENCE SOURCE

Control specimens of bullous skin diseases were negative for HSV DNA. The study does not mention how many children had oral lesions at the time of specimen collection. The idiopathic EM group appeared to be EM minor, and these results suggest HSV might be a common cause of EM minor in children.

A 14-year study by Siedner-Weintraub published in 2017 retrospectively evaluated children (n=30) 4 to 18 years old with EM.[2] Of these 30 children, common etiologies included idiopathic (15 of 30), nonspecific febrile illness (11 of 30), history of past HSV infection (seven of 30), new medication (five of 30), and mycoplasma pneumonia (four of 14). In this study, a direct association with HSV was not found because no cases had a recent history of an HSV infection in the preceding weeks. However, only eight of these children were tested for HSV.

A three-year retrospective study published in 2017 by Read and Keijzers identified nine pediatric patients with EM of whom zero had mucosal involvement.[3] Of these patients, the causes were designated as upper respiratory tract infection (three of nine), otitis media (three of nine), nonspecific viral illness (two of nine), and immunizations (one of nine). There was no identified HSV involvement in these cases, but blood work was drawn in only one patient, and all were treated conservatively.

Other reported causes of EM minor aside from HSV include mycoplasma pneumonia, chlamydia pneumonia, anti-epileptics, and antibiotics (particularly penicillins and sulfonamides).[4,5]

Summary: HSV infection has a potential association with EM minor in children, but it appears to be more commonly associated with adult EM cases

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TIPS FOR BETTER PERFORMANCE

SPECIAL OPs

DR. WELCH is a practicing emergency physician with Utah Emergency Physicians and a research fellow at the Intermountain Institute for Health Care Delivery Research. She has written numerous articles and three books on ED quality, safety, and efficiency. She is a consultant with Quality Matters Consulting, and her expertise is in ED operations.

Falling for You!

Tips for reducing falls in your ED through process and design changes

by SHARI WELCH, MD, FACEP

PHOTO: SHUTTERSTOCK.COM

The cost of patient falls in elderly persons is expected to reach $32.4 billion dollars in 2020.[1] Patients fall most often in their bedrooms, followed by the bathroom; this holds true both at home and in the hospital. Fortunately, a growing body of research surrounding falls in the hospital helps us understand some of the conditions and circumstances that contribute to falls.

Identify and Communicate

Process and design changes exist that can reduce the risk of falls for emergency department patients. One important process change is identifying patients who are fall risks; checklists at intake can help identify them. Risk factors for falling include:

- History of recent falls
- Decreased level of consciousness
- Use of a walking aid
- Difficulty rising from a chair
- Balance problems
- Hypotension/orthostasis
- Presence of:
  - » Foley catheter
  - » Brace or cast
  - » Feeding tube
  - » IV or heparin lock
- Certain diseases such as stroke, seizures, or Parkinson's
- Taking three or more medications
- Visual or hearing impairment

Once falling risk factors have been identified, how do you effectively communicate that information to all members of the emergency department team? Noting the patient is a fall risk in the chart has become commonplace, and using more visual cues is gaining momentum. Some organizations use color-coded booties (typically red), and these booties often include nonskid design elements. These brightly colored booties are readily identifiable by staff, including transport techs, radiology techs, and ED techs, who may have only brief encounters with the patient and inadvertently put the patient at risk. Commercial products such as the Patient Care Sign allow staff to use sign icons on the patient door such as Fall Risk, NPO, Isolation, etc.

The point: Identification alone will not reduce falls if the risk is not conveyed to staff and there are not policies and procedures in place to reduce the risk.

Design Changes

So what are some of the procedures and policies that have become part of effective fall-reduction programs? Use of a low-rise bed, easy access to call lights, nonskid slippers or floor mats, alarm mats that chime when the patient gets out of bed, and decreased clutter in patient rooms all can reduce falls.

Other design features have demonstrated potential for reducing falls as well. Slippery floors (the proverbial polished linoleum) contribute to falls, and there is much experimentation afoot using antibacterial carpet tiles with nonskid surfaces. Adding floor lighting to improve visibility for visually impaired patients and installing adequate railings can improve safety in clinical areas.

The direction a bathroom door opens can increase or decrease patient falls. When the door opens into the bathroom, the patient becomes crowded into the sink or commode and can fall, so it is best for the restroom door to swing outward. In some new modular designs, the commode folds down from the wall right next to the patient's bedside so the patient does not travel far. New room designs include a family space to encourage family members to monitor their loved ones for safety.

The height of furniture, especially beds and toilets, can be tricky. You will often read that these should be low for ill patients, but that is not entirely correct. Research from the Center for Health Design suggests beds and toilets be high so that patients, whose limb girdle muscles are the first to weaken during illness, do not have to lower themselves a long way down to the furniture. On the other hand, lower beds and commodes are associated with less severe injuries when the patient does fall.

A final design change associated with decreasing fall rates is one still not widely popular with nurses: decentralized nurse stations. Clinical units are being designed with work stations scattered throughout the department to allow nurses more opportunity to do paperwork while observing patients. Decentralization offers other advantages, too, including decreased noise levels, which is critical to patient satisfaction, and decreased amounts of walking for nurses who have to work from multiple sites.

The Potential

How much can these kinds of process and design changes reduce falls? The Center for Health Design estimates design changes alone can reduce patient falls by as much as 17 percent. Methodist Hospital in Indianapolis, Indiana, ramped up its fall-reduction program with rigorous procedures and design changes that included a family space in every patient room and decentralized nurse stations. These efforts resulted in a reduction of patient falls from six per 1,000 patients to two per 1,000 patients in a cardiac care unit.[2]

As many emergency departments consider adding geriatric service lines to their departments, the issue seems even more relevant than in the past. Shouldn't we apply some of these strategies in the emergency department?

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ONE MORE REASON NOT TO ORDER AN X-RAY

SOUND ADVICE

DR. NAGDEV is director of emergency ultrasound at Highland General Hospital in Oakland, California.

MR. LUFTIG is a PA in the department of emergency medicine at Highland General Hospital.

DR. MANTUANI is assistant director of emergency ultrasound at Highland General Hospital.

How to Effectively Block an Acutely Fractured Distal Radius

An ultrasound-guided nerve block adapted for the emergency department

by ARUN NAGDEV, MD; JOSH LUFTIG, PA; AND DANIEL MANTUANI, MD

Distal radius fractures (commonly called Colles' or Smith's fractures) are often encountered in the emergency department, with options for analgesia revolving around either a hematoma block, intravenous opioids, or procedural sedation, particularly for closed reduction. A novel single-injection nerve block technique known as the retroclavicular approach to the infraclavicular region (RAPTIR) may be the ideal method for excellent pain control, allowing for nearly painless closed reduction and lasting analgesia.[1,2]

Clinical Conundrum

There are many locations to block the brachial plexus as it emerges from the cervical column and then travels down the neck, underneath the clavicle, and into the arm. In our 10-year ED-clinical experience, blocks of the proximal portion of the brachial plexus (superior to the clavicle) offer better analgesia for injuries to proximal structures (ie, shoulder and upper arm), whereas blocks of the distal portion of the brachial plexus (inferior to the clavicle) offer better analgesia for distal structures (ie, elbow, forearm, wrist, and hand). Unfortunately, when performing brachial plexus blocks above the clavicle, we have noticed inconsistent analgesia for distal radius fractures.

The upper extremity regional blocks that most emergency physicians may be familiar with include the interscalene and supraclavicular blocks.[3] However, both of these blocks target the proximal portion of the plexus. They provide excellent analgesia to the shoulder and upper arm, but they commonly fail to provide analgesia adequate for closed reduction of distal radius fractures. Also, when placing anesthetic in locations adjacent to the phrenic nerve, there is concern for ipsilateral diaphragmatic paralysis.

Performing a block in the distal region of the brachial plexus, specifically below the clavicle, maximizes distal upper extremity anesthesia while minimizing phrenic nerve blockade. The classic blocks in this region include the infraclavicular block (ICB) in the chest wall above the axilla and the axillary block (AXB) on the medial aspect of the upper arm at the axilla. Unfortunately, these blocks historically have been difficult to perform for two reasons.

First, when performing a traditional ICB with the patient in the position of comfort (shoulder adducted, elbow flexed, and the fractured wrist resting at their side or on their chest/abdomen), the clavicle forces the operator to enter the skin at a very steep angle, significantly decreasing ultrasound visualization of the needle tip during the procedure and increasing the risk of iatrogenic pneumothorax. Second, in order to bring the brachial plexus out from under the clavicle, these blocks are commonly performed with significant upper extremity manipulation. Directly following an injury, abducting and externally rotating the shoulder is often not possible, limiting the generalizability of these infraclavicular approaches to the brachial plexus.

RAPTIR is a novel block that targets the same distal portion of the brachial plexus while correcting for the major challenges associated with traditional ICB and AXB. The patient is allowed to remain in the position of comfort during the procedure, and the needle angle is kept flat relative to the ultrasound probe, markedly increasing needle tip visualization and avoiding a trajectory deep into the thoracic cavity. Additionally, the needle path avoids the nearby cephalic vein and thoracoacromial artery, and only one injection is required to block the entire distal extremity.

We have successfully performed the RAPTIR in numerous patients in our emergency department, facilitating dense anesthesia and ideal pain control for closed reductions. When compared to procedural sedation, we have noted two specific benefits from using the RAPTIR. First, when attempting to optimize closed reduction (and potentially avoid subsequent open reduction and internal fixation), we often require repeat radiographs to confirm proper alignment. RAPTIR allows for essentially painless repeat reduction attempts (if needed) without worry of a prolonged sedation. Second, because we use a long-acting anesthetic for the block, patients can be sent home with excellent pain control, starting an oral analgesic before the block wears off.

Procedure

Visit www.highlandultrasound.com/raptir for a video demonstration of this technique.

Pre-assessment: Patients with a short, poorly mobile neck; thick chest wall; or deformed clavicle, such as from prior fracture, are poor candidates for RAPTIR, and another technique should be considered. We recommend a pre-block survey scan to determine if the axillary artery is clearly visible **(see Figure 1)**.

Positioning: Place the patient in a semi-recumbent supine position with the affected extremity adducted in a position of comfort. Rotate the patient's head away from the injured limb and put a folded blanket under the upper back (ipsilateral to the injury). Stand at the head of the bed with the ultrasound system in direct line of sight (on the same side as the

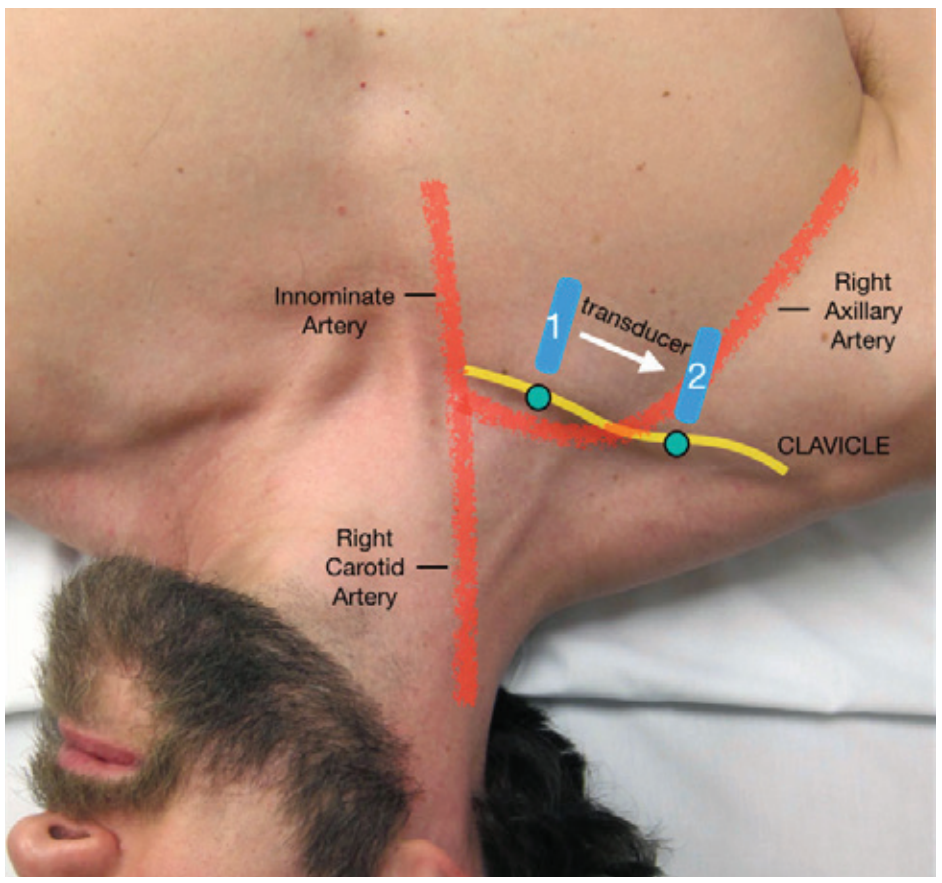

FIGURE 1: Overview of the initial and final probe position when performing the block. Slide the transducer (blue solid line) from mid-clavicle region to the deltopectoral groove. The probe marker (green dot) should face cephalad. The goal is to visualize the subclavian/axillary artery as it exits below the clavicle.

FIGURE 2: Stand above the patient with the ultrasound screen in clear view. Note the transducer is located in the deltopectoral groove with the needle entering above the clavicle.

injured extremity) **(see Figure 2)**.

Survey scan: Place a high-frequency linear transducer in the infraclavicular region with the cephalad portion of the probe resting on the medial portion of the clavicle **(see Figure 3A)**. The transducer should be in parasagittal orientation with the probe marker facing cephalad. Slide the transducer laterally along the inferior portion of the clavicle **(see Figure 3B)**. While sliding laterally, sonographically visualize the axillary artery in cross section as it emerges from under the clavicle **(see Figure 3C)**, traverses the second rib, then courses away from the thoracic cage, appearing on ultrasound to be moving farther and farther from the clavicle. Fix the probe at the position where the axillary artery is 2–3 cm from the clavicle on the ultrasound **(see Figure 3D)**. At this location, identify the injection target, which lies just posterior to the artery.

Anesthetic: For a 70 kg patient, use 35–40 mL of 0.25% bupivacaine, 0.5% ropivacaine, or 1% lidocaine with epinephrine. Always adhere to weight-based lidocaine dosing guidelines.

Needle type: Use a Tuohy 20g, 90 mm epidural needle (block needle) and a 25–27g hypodermic needle (for the local anesthetic skin wheal needle).

Injection setup: We commonly use a two-person technique to perform this block. One operator is advancing the needle under ultrasound visualization with the second operator slowly injecting the anesthetic while frequently aspirating to prevent inadvertent vascular puncture.

Injection: The primary challenge of the RAPTIR is passing the block needle through the "blind zone" created by the acoustic shadow of the clavicle during the initial portion of needle insertion. Keeping the transducer fixed over the injection target and aligned in the parasagittal plane, identify a block needle insertion site aligned with the long axis of the ultrasound beam and approximately 2 cm cephalad to the clavicle **(see Figure 4A)**. This will ensure a safe needle path and allow adequate room for the needle to clear the posterior surface of the clavicle without angling posteriorly. Probing the insertion site with a gloved finger and seeing transmitted tissue motion on the ultrasound view help the operator get a feel for the needle insertion path and help determine if the insertion site is posterior enough to clear the clavicle.

Place a local anesthetic skin wheal at the insertion site using a 25–27g needle, then insert the block needle through the skin wheal and advance the needle beneath the clavicle toward the ultrasound beam at an angle parallel to the gurney **(see Figure 4A)**. The patient should be prompted to alert the operator of any paresthesia in the shoulder while the needle advances, as the suprascapular nerve lies in the vicinity; this is a very uncommon occurrence. If the patient reports paresthesia of the shoulder, the needle should be withdrawn, and a slightly different needle path should be used. Also, when passing through the blind zone created by the clavicle, the needle should never be angled posteriorly, as this increases the risk of pneumothorax. However, the entire needle can be posteriorly deflected by applying pressure to the shaft at the insertion site while maintaining the same flat angle of approach, similar to the method used to get past the clavicle for a blind subclavian central line.

After insertion through the approximately 3 cm blind zone, use subtle needle and transducer adjustments to locate the clearly visualized needle emerging from beneath the clavicle **(see Figure 4B)**. Continue advancing with in-plane ultrasound guidance toward the target location just posterior to the axillary artery, typically at or slightly past the six o'clock position relative to the artery **(see Figure 4C)**. Aspirate to check for inadvertent vascular puncture and then inject small aliquots of normal saline. Anechoic anesthetic fluid should be seen spreading just posterior to the axillary artery and deflecting the artery toward the probe, confirming needle tip location within the axillary sheath **(see Figure 4D)**. The sheath surrounds both the brachial plexus and the axillary artery. Thus, fluid injected into the sheath bathes the plexus. It is not necessary to visualize the nerves of the plexus. Once satisfied with the needle position, gradually inject local anesthetic until a total of 35–40 mL is deposited within the sheath. Total needling time is usually less than five minutes, and dense arm anesthesia develops within 30.

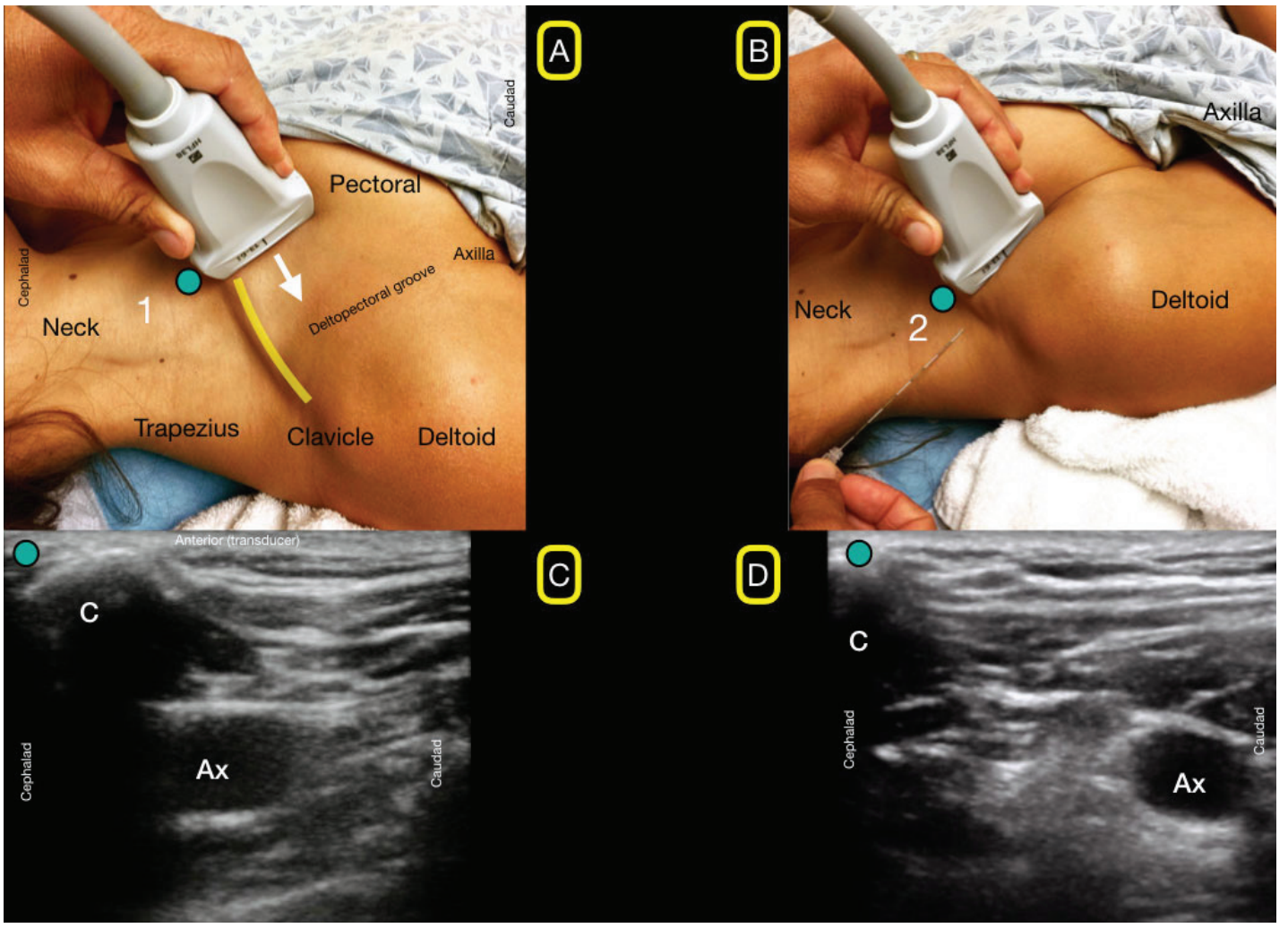

FIGURE 3A: The ultrasound probe is placed in the initial position (1) with the probe marker facing cephalad. **3B:** Slide the ultrasound transducer along the inferior aspect of the clavicle until close to the deltopectoral groove (2). **3C:** Note that in the initial position (1) the axillary artery (Ax) may be visible just under the clavicle (C). **3D:** In the second position (2), the axillary artery (Ax) is visible and away from the pleura.

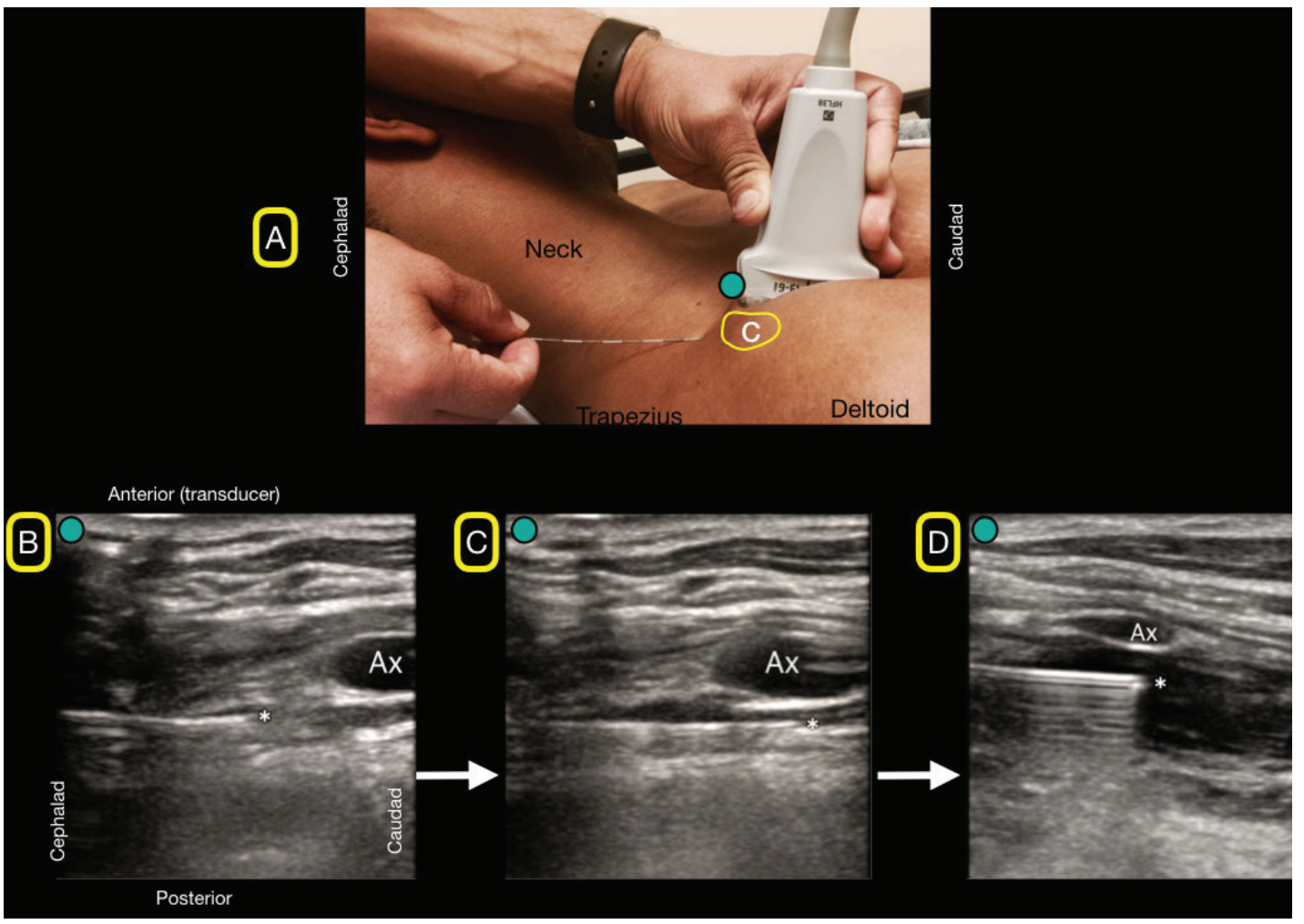

FIGURE 4A: A flat needle angle will be used to traverse under the clavicle (C). **4B:** The bock needle will have to pass under the clavicle and will not be visualized. Note the needle tip as it emerges from under the clavicle and can be easily seen because of its flat angle. **4C:** The block needle is advanced until placed just under the axillary artery (Ax). **4D:** Anechoic anesthetic fluid is injected under the axillary artery (Ax) for a successful block.

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the following day for a second debridement, and a muscle biopsy was performed of the left volar region, identifying viable skeletal muscle tissue with mild reactive changes. The patient underwent hemodialysis for acute renal failure secondary to rhabdomyolysis. The patient had a long, complicated hospital course. Ultimately, he improved and was discharged to a rehabilitation facility on day 20.

Background

Necrotizing fasciitis is a category of soft tissue infection that is described as fulminant deep tissue destruction with systemic signs of toxicity and a high mortality rate.[1,2] There are two types of necrotizing fasciitis: polymicrobial (anaerobic and aerobic) and group A *Streptococcus*.[1] Patients typically present with erythema, swelling, pain out of proportion to the exam, crepitus, and skin breakdown with bullae that can begin acutely and rapidly progress and spread.[1-3] Risk factors include immunosuppression, drug use, recent surgery, liver disease, traumatic wounds, and diabetes.[1-3]

In patients who present to the emergency department with these symptoms and risk factors, it is also important to consider other similarly presenting complications such as acute compartment syndrome (ACS). ACS occurs when fascial compartment pressures surpass capillary perfusion pressures, leading to tissue ischemia and necrosis. ACS is a limb-threatening diagnosis that can occur acutely after fracture or soft tissue injury and requires immediate clinical suspicion and intervention. Both necrotizing fasciitis and ACS are rare diagnoses, and a few case studies have shown that they can occur simultaneously in patients who present with severe extremity pain and signs of a systemic inflammatory response.

To help providers better recognize necrotizing fasciitis in the emergency department, the laboratory risk indicator for necrotizing fasciitis (LRINEC) scoring system was developed based on six laboratory results: total white cell count, hemoglobin, sodium, glucose, serum creatinine, and CRP (see Table 1). Patients with a score of 6 or above should be seriously considered for necrotizing fasciitis.[4,5] For example, in the case presented above, the patient's LRINEC score was 8 for elevated CRP, hyponatremia, and elevated creatinine, which reinforced our suspicion for necrotizing fasciitis and need for emergent treatment.

CT scan is the most helpful imaging modality for detecting necrotizing fasciitis in the deeper soft tissue layers in the emergency department in a timely manner.[1,7] However, the only way to definitively diagnose necrotizing fasciitis is surgical exploration and early wound debridement of necrotic tissue.[1,7] Surgical exploration should not be delayed, and wound cultures should be obtained. The wound should also be evaluated 24 hours later in the OR and aggressively debrided again if necrotic tissue is present. Broad-spectrum antibiotic therapy should be started and continued until no additional debridement is needed and the patient's condition improves.[7]

Necrotizing fasciitis is associated with a high mortality rate and should be treated immediately upon identification in the emergency department. Patients may present with different clinical histories and physical exam findings, but it is important that necrotizing fasciitis be ruled out in cases of rapidly progressive soft tissue infections.

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DR. PEÑA is an emergency medicine resident at St. Joseph's University Medical Center in Paterson, New Jersey.

DR. BELLA is an emergency medicine resident at Morristown Medical Center in Morristown, New Jersey.

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THE END OF THE RAINBOW

DR. DAHLE is the author of *The White Coat Investor: A Doctor's Guide to Personal Finance and Investing* and blogs at http://whitecoatinvestor.com. He is not a licensed financial adviser, accountant, or attorney and recommends you consult with your own advisers prior to acting on any information you read here.

The 10 Biggest Financial Mistakes Doctors Make

AND HOW YOU CAN AVOID THEM

by JAMES M. DAHLE, MD, FACEP

Q. In medicine, it is best to learn from the mistakes of others, as evidenced by morbidity and mortality conferences. What are the big mistakes doctors make when it comes to their finances?

A. Physicians earn relatively high incomes, but that doesn't make them immune to financial missteps. Avoid these 10 errors:

1. Financial Illiteracy

The biggest mistake doctors make is simply not paying sufficient attention to their finances. In our 401(k) world, we each have a second job as a pension fund manager, whether we like it or not and whether we've been trained to do it or not. You (together with your partner) are your family's chief financial officer(s). Your family is like a business, with various sources of income and various expenditures. If you manage it well, it will be profitable and will support you long after you've stopped working. If you do a poor job, you will reap the consequences. The cavalry isn't coming. It's up to you.

2. Growing Into Income Too Quickly

This is a real problem for emergency physicians, who generally hit their maximum lifetime income shortly out of residency. If their spending grows just as quickly as their income, they have missed out on the very best way to build wealth as a doctor—that is, living like a resident for the first two to five years out of residency and using the difference between attending and resident incomes, and the accompanying lifestyle, to pay off student loans, save for a down payment on a dream house, and catch up to their college roommates with their retirement savings.

3. Not Saving Enough

Even after the "live like a resident" period, a typical physician should save approximately 20 percent of their gross income for retirement. No amount of fancy investing can make up for inadequately funding the portfolio. An adequately funded portfolio, on the other hand, can make up for a plethora of investing mistakes.

4. Inadequate Insurance

Physicians should insure well against financial catastrophes, such as professional and personal liability, illness, injury, disability, death, and loss of expensive property. Too many physicians with family members relying on them financially carry inadequate term life and disability insurance. Too many doctors only carry the state-required minimums on their auto liability policies. Bad things happen regularly, and they can happen to you.

5. Mistaking Whole Life Insurance for an Investment

Nearly every physician will have whole life insurance pitched to them at some point in their career. All too often, the physician falls for it. Although there are some niche uses for this insurance product, it was inappropriately sold to the vast majority of physicians who have purchased it. The ongoing high premiums prevent these doctors from utilizing better investments, paying off their student loans, and sometimes even carrying an adequate amount of term life insurance! Treat the purchase of whole life insurance like you would evaluate a potential spouse. It's either until death do you part, or it's going to cost a lot of money to get out.

> Remember that business school professors refer to bad investments as "deals that can only be sold to doctors."

6. Choosing the Wrong Adviser

Most physicians want and need at least some assistance from a high-quality financial adviser. However, the key is to get good advice at a fair price. Good advice comes from a competent fiduciary, fee-only adviser who understands the unique financial situations physicians find themselves in. A fair price is a four-figure amount per year. If you are paying more than that, know that high-quality advice is available for less than you are paying. Keep looking until you find it, even if your current adviser is a good friend or family member.

7. Not Understanding Their Retirement Accounts

It is critical you become an expert in the retirement accounts available to you. If you are an employee or in a partnership, actually read the 401(k) plan document the employer is required to provide you if asked. Know how the plan works, whether there is an employer match, what the investment options are, and what fees you can expect to pay. Your employer may provide other retirement accounts such as a 403(b), 457(b), or defined benefit/cash balance plan. Also become familiar with a personal and spousal backdoor Roth IRA and a health savings account. Independent contractors and those who moonlight should use an individual 401(k) instead of a SEP-IRA and can even consider using a personal defined benefit/cash balance plan. These retirement accounts lower your taxes, boost investing returns, facilitate estate planning, and, in most states, protect your assets from creditors.

8. Buying Individual Stocks

Investing in individual stocks is an example of uncompensated risk. Any risk that can be eliminated through diversification is by definition uncompensated. Mutual funds provide diversification (plus liquidity and professional management) and therefore less risk than individual stocks. Physicians are very unlikely to select stocks well enough to beat the market averages in the long run and are generally best served by using low-cost, broadly diversified mutual funds.

9. Using Actively Managed Mutual Funds

The literature is quite clear that, over the long run, a low-cost, passively managed (index) mutual fund will outperform 80–90 percent or more of its actively managed peers. Trying to beat the market is a loser's game; you actually win by not playing. Each year, some mutual fund managers will beat the market, but you are just as unlikely to succeed at choosing those managers a priori as they are to repeat their past performance.

10. Getting Burned by Exotic Investments

Physicians, as accredited investors by virtue of their high income, can invest in many investments not available to the general public. Each investment must be evaluated carefully on its own merits. A physician need not stray from boring old stock and bond index mutual funds to succeed financially, but should you do so, the principles of cautious due diligence and diversification still apply. If it sounds too good to be true, it probably is. Remember that business school professors refer to bad investments as "deals that can only be sold to doctors."

Learning from and avoiding the mistakes of others can speed you along your way to achieving your financial goals. Make sure you help your colleagues and trainees by sharing your mistakes with them.

Richard T. Logue

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DR. KAUFMAN is a board-certified geriatric pharmacist, a pharmacist at NewYork-Presbyterian/Lower Manhattan Hospital, and a freelance medical writer and editor.

Suboxone 101

Everything you need to know about this medicated-assisted treatment drug

by MICHELE KAUFMAN, PHARMD, BCGP

Suboxone is a sublingual (SL) film dosage form containing a partial opioid agonist (buprenorphine) and an opioid antagonist (naloxone) for treating opioid dependence.[1] It is a Schedule III Controlled Substance that was originally approved by the U.S. Food and Drug Administration (FDA) in August 2010. It should be used as part of a complete treatment plan that includes psychosocial support and counseling.

Prescribing Suboxone is limited under the Drug Addiction Treatment Act (DATA), which states that prescription use of Suboxone to manage opioid dependence is limited to health care providers who meet certain qualifying requirements, have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence, and have been assigned a unique identification number that must be included on every prescription.[2,3]

Administration

Suboxone is administered sublingually or buccally as a single daily dose, which should not be cut, chewed, or swallowed. One film should be placed under the tongue close to the base on the left or right side and allowed to completely dissolve. For buccal administration, the film should be placed on the inside

CONTINUED *on page 37*

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A Clinical Guide to Buprenorphine Products

Suboxone, Butrans, Zubsolv, Probuphine, Sublocade, Buprenex—enough!

by ERIC KETCHAM, MD, MBA, FACEP, FASAM, FACHE

There are multiple forms for buprenorphine (commonly called bupe), and this can prove confusing. Although we may never use most of these formulations in the emergency department, we should be familiar with them.

Sublingual Tablets and Film Strips

This is the primary formulation used in the emergency department and hospital as well as the most common form for those prescribed bupe for the treatment of opioid use disorder (OUD) and for patients who are prescribed bupe for pain. The film strips are preferred by my patients because they dissolve fast and tend to not taste too bitter.

The naloxone is included to prevent drug abusers from crushing the tab or strip and inhaling it or dissolving and injecting the medication. Naloxone has a very poor sublingual (SL) and oral bioavailability (less than 2 percent). However, naloxone has a very high intranasal and IV bioavailability, which is a deterrent to misuse of the medication. Patients and health care providers are often confused by the combination of bupe and naloxone because buprenorphine can precipitate withdrawal in opioid-dependent patients. However, buprenorphine-precipitated withdrawal is a feature of the pharmacology of bupe itself and has nothing to do with the naloxone component of Suboxone. When Suboxone is taken sublingually as intended, the naloxone has no bioavailability and no effect.

Bupe also has poor oral bioavailability—only about 15 percent if swallowed. Furthermore, it is important to remember that bupe tabs or strips must be placed sublingually, not anywhere else in the mouth; it's not an oral dissolving tablet like ondansetron.

There is also a SL bupe mono-product, the most common brand name of which is Subutex, produced by Indivior, the same company that makes Suboxone. Subutex is only produced in tablet form. It is generally available in 2 mg and 8 mg strengths. Most generic forms are in the same dose formulations as the Suboxone or Subutex products (eg, 8 mg/2 mg or simply 8 mg, respectively).

When is the bupe mono-product indicated instead of the dual product? The most common clinical indication is pregnancy because the safety of routine naloxone exposure during pregnancy remains somewhat in question. However, recent small studies suggest the dual product is safe in pregnancy.[1,2]

The other common use of Subutex is in clinics, hospitals, etc., where the medication is administered by a nurse and there is no worry it will be crushed and injected. In my clinic and emergency department, we use only the generic mono-product bupe (administered by a nurse) because it is less expensive. We stock 8 mg and 2 mg SL tablets.

Many patients buy bupe, administering their own medication-assisted treatment. When patients speak of treating their symptoms or self-medicating with "strips," they are usually speaking of 8 mg/2 mg bupe/naloxone film strips. Clearly, bupe does have street value. However, the street value of bupe is far less than that of other prescription opioids.

Injectable Buprenorphine

Buprenex, the common brand of injectable bupe, comes in 0.3 mg/1 mL vials. Bupe is a potent analgesic, and as an analgesic, bupe 0.3 mg IV is equivalent to about 7.5 mg of IV morphine. However, it has a much longer half-life. Of note, although the half-life of bupe as an analgesic is only about eight hours, its half-

CONTINUED *on page 37*

SUBOXONE 101 | CONTINUED FROM PAGE 36

of the left or right cheek and allowed to completely dissolve.

Dosing

To avoid precipitating withdrawal, induction with Suboxone should be undertaken when clear and objective withdrawal signs are evident.[1,4] Whether the patient's opioid dependence is with long-acting or short-acting drugs should be considered.

Initially, Suboxone should be given in divided doses. In patients dependent on short-acting opioids, start with up to 8 mg/2 mg (buprenorphine/naloxone) on Day 1 in divided doses. On Day 2, give a single dose of up to 16 mg/4 mg. For methadone or long-acting opioid dependence products, induction onto SL buprenorphine monotherapy is initially recommended for Days 1 and 2.

For maintenance treatment, the target Suboxone dosage is usually a single dose of 16 mg/4 mg. From Day 3 onward, doses should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg to a level that suppresses withdrawal.

Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up. Patients should be monitored at least weekly for the first month. Once the patient has achieved a stable dosage and their assessment (eg, urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. There is no maximum recommended duration of maintenance treatment. Patients may need to remain on treatment indefinitely.

Drug Safety

Buprenorphine-containing transmucosal products for the treatment of opioid dependence (BTOD) for the risk evaluation and mitigation strategy (REMS) program is an FDA-required program designed to ensure informed risk-benefit decisions prior to beginning treatment and during treatment with BTOD drugs.[5] This product's REMS is to decrease the risk of abuse, addiction, misuse, overdose, and drug interactions leading to respiratory depression. Other adverse reactions include transaminitis, hypotension, hypersensitivity reactions, and central nervous system (CNS) depression.

Additionally, it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking BTODs.

Buprenorphine/Naloxone Products List[4]

Buprenorphine/naloxone products include:

- Suboxone SL film in strengths of buprenorphine 2 mg/naloxone 0.5 mg, buprenorphine 4 mg/naloxone 1 mg, buprenorphine 8 mg/naloxone 2 mg, and buprenorphine 12 mg/naloxone 3 mg
- Bunavail buccal film in strengths of buprenorphine 2.1 mg/naloxone 0.3 mg, buprenorphine 4.2 mg/naloxone 0.7 mg, and buprenorphine 6.3 mg/naloxone 1 mg
- Zubsolv SL tablet in strengths of buprenorphine 0.7 mg/naloxone 0.18 mg, buprenorphine 1.4 mg/naloxone 0.36 mg, buprenorphine 2.9 mg/naloxone 0.71 mg, buprenorphine 5.7 mg/naloxone 1.4 mg, buprenorphine 8.6 mg/naloxone 2.1 mg, and buprenorphine 11.4 mg/naloxone 2.9 mg
- Buprenorphine/naloxone generic SL tablet, in strengths of buprenorphine 2 mg/naloxone 0.5 mg, buprenorphine 8 mg/naloxone 2 mg, buprenorphine 12 mg/naloxone 3 mg, and buprenorphine 16 mg/naloxone 4 mg

Price[4]

Sixty pouches of Suboxone SL film cost approximately $328 (2 mg/0.5 mg), $587 (4 mg/1 mg and 8 mg/2 mg), and $1,174 (12 mg/3 mg), according to Lexi-Drugs. Thirty generic SL tablets of buprenorphine/naloxone cost approximately $175 (2 mg/0.5 mg) and $313 (8 mg/2 mg).

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BUPRENOPHINE | CONTINUED FROM PAGE 36

life when treating OUD is much longer (about 36 hours) but is dose-dependent.

The IV form of bupe is not commonly used in the United States but has been used as an IV analgesic in other parts of the world since the 1980s. The use of injectable bupe is growing in American veterinary medicine. Due to its much higher affinity for the mu receptor, IV bupe has also been used in some emergency departments to reverse acute opioid overdoses.[3]

Transdermal Buprenorphine Patches

Butrans is the brand name of the transdermal bupe patches used to treat chronic pain. While Butrans may be effective in treating OUD, it is not usually prescribed for OUD, and it has a U.S. Food and Drug Administration (FDA) indication only for chronic pain in the "opioid-experienced" patient. Generally, patients are switched to Butrans patches after developing a tolerance to traditional opioids.

The patches come in dosing strengths of 5, 7.5, 10, 15, and 20 mcg/hour and are changed every seven days. The 10 mcg/hour patch is approximately equianalgesic to 80 mg/day of oral morphine. Note that bupe patches, intended for the opioid-dependent patient, release much fewer mcg/hour of buprenorphine than fentanyl patches do of fentanyl.

Implantable Buprenorphine

Probuphine is a long-term implantable form of buprenorphine that delivers a continuous, stable blood level of bupe for the treatment of OUD. Four implants inserted subdermally in the upper arm (in an office procedure) release a total dose of bupe similar to a daily sublingual 8 mg dose for six months. The dose equivalent of only 8 mg/day SL is lower than the effective dose for most patients treated for OUD with bupe SL. This low equivalent dose along with the cost and the need to obtain insurance approval are factors that prevent more widespread use.

Depot Subcutaneous Buprenorphine

Sublocade is the newest long-acting form of bupe on the market, FDA-approved in late 2017 for treating OUD. This depot form of bupe is injected monthly in 100 mg and 300 mg doses into the abdominal subcutaneous tissue to continuously release a dosage equivalent to 8–24 mg/day of SL bupe. Although more patients with OUD could more easily remain compliant in bupe medication-assisted treatment, the number of patients receiving Sublocade remains low. The cost and the need to obtain insurance approval are factors that prevent more widespread use.

There may be a future role for depot injectable forms of bupe in the emergency department to ensure sustained opioid withdrawal management for patients after discharge from the emergency department or to serve as a longer bridge of sobriety for referral to an opioid addiction treatment clinic.

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DR. KETCHAM is medical director of the opioid addiction treatment service via New Mexico Treatment Services in Farmington, co-medical director of EMS agencies of San Juan County, and a staff emergency physician at San Juan Regional Medical Center in Farmington and Los Alamos Medical Center.

DR P. MARAZZI/SCIENCE SOURCE

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BOB has congenital hemophilia with inhibitors.

Indications and Usage

NovoSeven® RT (Coagulation Factor VIIa [Recombinant]) is a coagulation factor indicated for:

- Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets
- Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia

Important Safety Information

WARNING: THROMBOSIS

- Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported.
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT.
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis.

Warnings and Precautions

- Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance.
- Exercise caution when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications, such as those with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, uncontrolled post-partum hemorrhage, history of coronary heart disease, liver disease, post-operative immobilization, in elderly patients, in neonates, or in patients receiving concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates).

novo nordisk®

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A.

 Printed in the U.S.A. US18NSVN00054 September 2018

Bleeds happen[1]:

Take control with NovoSeven® RT

Experience: >30 years of research and long-term clinical experience[3,a]

Effectiveness: Proven efficacy in bleed resolution and surgery across 4 indications—more than any other product[2]

Speed: Rapid reconstitution and administration leading to rapid activity[2,4]

Portability: Room temperature stable for rapid access to treatment[2]

Safety: Recombinant safety and low rate of thrombotic adverse events[2,5,b]

Administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.
[a]1989: compassionate use initiated in the United States; 1999: FDA approval received for congenital hemophilia with inhibitors (CHwI).[5]
[b]0.2% of bleeding episodes in patients with CHwI.[2,5]

Visit NovoSevenRTpro.com today to learn more

Warnings and Precautions *(cont'd)*

- Hypersensitivity reactions, including anaphylaxis, have been reported with NovoSeven® RT. Administer only if clearly needed in patients with known hypersensitivity to NovoSeven® RT, any of its components, or mouse, hamster, or bovine proteins. Should symptoms occur, discontinue NovoSeven® RT and administer appropriate treatment.
- Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity (FVII:C). If FVII:C fails to reach the expected level, or PT is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.
- Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis.

Adverse Reactions

- The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® RT in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia.

Drug Interactions

- Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII.

Please see Brief Summary of Prescribing Information on the following pages.

References: 1. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818 and appendix. **2.** NovoSeven RT [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2017. **3.** Hedner U. History of rFVIIa therapy. *Thromb Res*. 2010;125:S4-S6. **4.** Bysted BV, Scharling B, Moller T, Hansen BL. A randomized, double-blind trial demonstrating bioequivalence of the current recombinant activated factor VII formulation and a new robust 25°C stable formulation. *Haemophilia*. 2007;13(5):527-532. **5.** Abshire T, Kenet G. Safety update on the use of recombinant factor VIIa and the treatment of congenital and acquired deficiency of factor VIII or IX with inhibitors. *Haemophilia*. 2008;14(5):898-902.

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Rx only

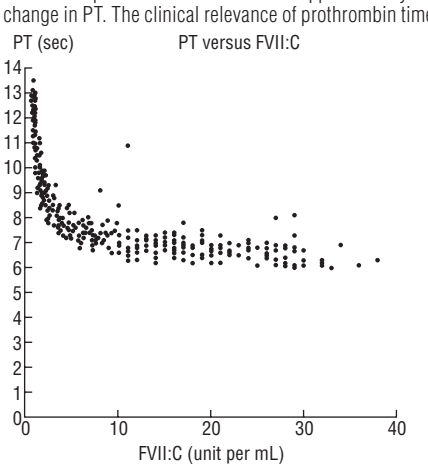
BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: THROMBOSIS: Serious arterial and venous thrombotic events following administration of NovoSeven® RT have been reported. *[See Warnings and Precautions]* Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. *[See Warnings and Precautions]* Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. *[See Warnings and Precautions]*

INDICATIONS AND USAGE: NovoSeven® RT, Coagulation Factor VIIa (Recombinant), is indicated for: Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets; Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia.

CONTRAINDICATIONS: None known.

WARNINGS AND PRECAUTIONS: Thrombosis: Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) and uncontrolled post-partum hemorrhage have an increased risk of developing thromboembolic events due to circulating tissue factor (TF) or predisposing coagulopathy *[See Adverse Reactions and Drug Interactions]*. Exercise caution when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with NovoSeven® RT should be weighed against the risk of these complications. Monitor patients who receive NovoSeven® RT for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, reduce the dose of NovoSeven® RT or stop the treatment, depending on the patient's condition. **Hypersensitivity Reactions:** Hypersensitivity reactions, including anaphylaxis have been reported with NovoSeven® RT. Administer NovoSeven® RT only if clearly needed in patients with known hypersensitivity to NovoSeven® RT or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins. Should symptoms occur, discontinue NovoSeven® RT, administer appropriate treatment and weigh the benefit/risks prior to restarting treatment with NovoSeven® RT. **Antibody Formation in Factor VII Deficient Patients:** Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NovoSeven® RT. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. **Laboratory Tests:** Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven® has been shown to produce the following characteristics: PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 units per mL. For FVII:C levels > 5 units per mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NovoSeven® RT administration is unknown.



INR: NovoSeven® has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of NovoSeven® on bleeding times/volume in models of clinically-induced bleeding in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have normalized. aPTT: While administration of NovoSeven® shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds. FVIIa:C: FVIIa:C levels were measured two hours after NovoSeven® administration of 35 micrograms per kg body weight and 90 micrograms per kg body weight following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 units per mL for the two dose levels, respectively.

ADVERSE REACTIONS: The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven® in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia. **Clinical Trials Experience:** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice. Adverse reactions outlined below have been reported from clinical trials and data collected in registries. Hemophilia A or B Patients with Inhibitors: In two studies for hemophilia A or B patients with inhibitors treated for bleeding episodes (N=298), adverse reactions were reported in ≥2% of the patients that were treated with NovoSeven® for 1,939 bleeding episodes (see Table 3 below).

Table 3: Adverse Reactions Reported in ≥2% of the 298 Patients with Hemophilia A or B with Inhibitors

Body System Reactions	**# of adverse reactions** (n=1,939 treatments)	**# of patients** (n=298 patients)
Body as a whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Fibrinogen plasma decreased	10	5
Cardiovascular		
Hypertension	9	6

Serious adverse reactions included thrombosis, pain, thrombophlebitis deep, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and abnormal hepatic function. The serious adverse reactions of DIC and therapeutic response decreased had a fatal outcome. In two clinical trials evaluating safety and efficacy of NovoSeven® administration in the perioperative setting in hemophilia A or B patients with inhibitors (N=51), the following serious adverse reactions were reported: acute post-operative hemarthrosis (n=1), internal jugular thrombosis adverse reaction (n=1), decreased therapeutic response (n=4). *Immunogenicity:* There have been no confirmed reports of inhibitory antibodies against NovoSeven® or FVII in patients with congenital hemophilia A or B with alloantibodies. The incidence of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NovoSeven® RT with the incidence of antibodies to other products may be misleading. Congenital Factor VII Deficiency: Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that 75 patients with Factor VII deficiency had received NovoSeven®: 70 patients for 124 bleeding episodes, surgeries, or prophylaxis; 5 patients in the pharmacokinetics trial. The following adverse reactions were reported: intracranial hypertension (n=1), IgG antibody against rFVIIa and FVII (n=1), localized phlebitis (n=1). *Immunogenicity:* In 75 patients with factor FVII deficiency treated with NovoSeven® RT, one patient developed IgG antibody against rFVIIa and FVII. Patients with factor VII deficiency treated with NovoSeven® RT should be monitored for factor VII antibodies. The incidence of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NovoSeven® RT with the incidence of antibodies to other products may be misleading. Acquired Hemophilia: Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven® for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 6 patients experienced 8 serious adverse reactions. Serious adverse reactions included shock (n=1), cerebrovascular accident (n=1) and thromboembolic events (n=6) which included cerebral artery occlusion, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Three of the serious adverse reactions had a fatal outcome. Glanzmann's Thrombasthenia: Data collected from the Glanzmann's Thrombasthenia Registry (GTR) and the HTRS registry showed that 140 patients with Glanzmann's thrombasthenia received NovoSeven® RT for 518 bleeding episodes, surgeries or traumatic injuries. The following adverse reactions were reported: deep vein thrombosis (n=1), headache (n=2), fever (n=2), nausea (n=1), and dyspnea (n=1). **Postmarketing Experience:** The following adverse reactions have been identified during post approval use of NovoSeven®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

Table 4: Post Marketing Experience

MedDRA System Organ Class	**Preferred Term**
Immune system disorders	Hypersensitivity (including anaphylactic shock, flushing, urticaria, rash, angioedema)
Vascular disorders	Thromboembolic events (including hepatic artery thrombosis, myocardial infarction, cerebral infarction, intestinal infarction, intracardiac thrombus, peripheral ischemia, portal vein thrombosis, myocardial ischemia, renal artery thrombosis)

DRUG INTERACTIONS: Avoid simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates. The risk of a potential interaction between NovoSeven® RT and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies. Do not mix NovoSeven® RT with infusion solutions. Thrombosis may occur if NovoSeven® RT is administered concomitantly with Coagulation Factor XIII.

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: There are no adequate and well-controlled studies using NovoSeven® RT in pregnant women to determine whether there is a drug-associated risk. Treatment of rats and rabbits with NovoSeven® in reproduction studies has been associated with mortality at doses up to 6 mg per kg body weight and 5 mg per kg body weight respectively. At 6 mg per kg body weight in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg per kg body weight, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg per kg body weight of NovoSeven® gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven®. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. **Lactation:** Risk Summary: There is no information regarding the presence of NovoSeven® RT in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NovoSeven® RT and any potential adverse effects on the breastfed infant from NovoSeven® RT or from the underlying maternal condition. **Pediatric Use:** Clinical trials enrolling pediatric patients were conducted with dosing determined according to body weight and not according to age. Hemophilia A or B with Inhibitors: During the investigational phase of product development NovoSeven® was used in 16 children aged 0 to <2 years for 151 bleeding episodes, 27 children aged 2 to <6 years for 140 bleeding episodes, 43 children aged 6 to <12 for 375 bleeding episodes and 30 children aged 12 to 16 years for 446 bleeding episodes. In a double-blind, randomized comparison trial of two dose levels of NovoSeven® in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors 20 children aged 0 to <12 and 8 children aged 12 to 16 were treated with NovoSeven® in doses of 35 or 70 micrograms per kg dose. Treatment was assessed as effective (definite relief of pain/tenderness as reported by the patient and/or a measurable decrease of the size of the hemorrhage and/or arrest of bleeding within 8 hours [rated as excellent = 51%], within 8-14 hours [rated as effective = 18%] or after 14 hours [rated as partially effective = 25%]) in 94% of the patients. NovoSeven® was used in two trials in surgery. In a dose comparison 22 children aged 0 to 16 years were treated with NovoSeven®. Effective intraoperative hemostasis (defined as bleeding that had stopped completely or had decreased substantially [rated as effective = 86%] or bleeding that was reduced but continued [rated as partially effective = 9%]) was achieved in 21/22 (95%) patients. Effective hemostasis was achieved in 10/10 (100%) patients in the 90 mcg/kg dose group and 10/12 (83%) in the 35 mcg/kg dose group at 48 hours; effective hemostasis was achieved in 10/10 (100%) in the 90 mcg/kg dose group and 9/12 (75%) in the 35 mcg/kg dose group at 5 days. In the surgery trial comparing bolus (BI) and continuous infusion (CI) 6 children aged 10 to 15 years participated, 3 in each group. Both regimens were 100% effective (defined as bleeding has stopped completely, or decreased substantially) intra-operatively, through the first 24 hours and at day 5. At the end of the study period (Postoperative day 10 or discontinuation of therapy) hemostasis in two patients in the BI group was rated effective and hemostasis in one patient was rated as ineffective (defined as bleeding is the same or has worsened). Hemostasis in all three patients in the CI group was rated as effective. Adverse drug reactions in pediatric patients were similar to those previously reported in clinical trials with NovoSeven®, including one thrombotic event in a 4 year old with internal jugular vein thrombosis after port-a-cath placement which resolved. Congenital Factor VII deficiency: In published literature, compassionate use trials and registries on use of NovoSeven® in congenital Factor VII deficiency, NovoSeven® was used in 24 children aged 0 to <12 years and 7 children aged 12 to 16 years for 38 bleeding episodes, 16 surgeries and 8 prophylaxis regimens. Treatment was effective in 95% of bleeding episodes (5% not rated) and 100% of surgeries. No thrombotic events were reported. A seven-month old exposed to NovoSeven® and various plasma products developed antibodies against FVII and rFVIIa [*see Adverse Reactions and Overdosage*]. Glanzmann's Thrombasthenia: In the Glanzmann's Thrombasthenia Registry, NovoSeven® was used in 43 children aged 0 to 12 years for 157 bleeding episodes and in 15 children aged 0 to 12 years for 19 surgical procedures. NovoSeven® was also used in 8 children aged >12 to 16 years for 17 bleeding episodes and in 3 children aged >12 to 16 years for 3 surgical procedures. Efficacy of regimens including NovoSeven® was evaluated by independent adjudicators as 93.6% and 100% for bleeding episodes in children aged 0 to 12 years and >12 to 16 years, respectively. Efficacy in surgical procedures was evaluated as 100% for all surgical procedures in children aged 0 to 16 years. No adverse reactions were reported in Glanzmann's thrombasthenia children. **Geriatric Use:** Clinical studies of NovoSeven® RT in congenital factor deficiencies and Glanzmann's thrombasthenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

OVERDOSAGE: Dose limiting toxicities of NovoSeven® RT have not been investigated in clinical trials. The following are examples of accidental overdose. One newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven® (single dose: 800 micrograms per kg body weight). Following additional administration of NovoSeven® and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported. One Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms per kg body weight (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke). One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms per kg body weight and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms per kg body weight to 986 micrograms per kg body weight on five consecutive days. There were no reported complications in either case.

More detailed information is available upon request.

For information contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536, USA
1-877-NOVO-777
www.NovoSevenRT.com

Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark
License Number: 1261

US18NSVN00053 8/18

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

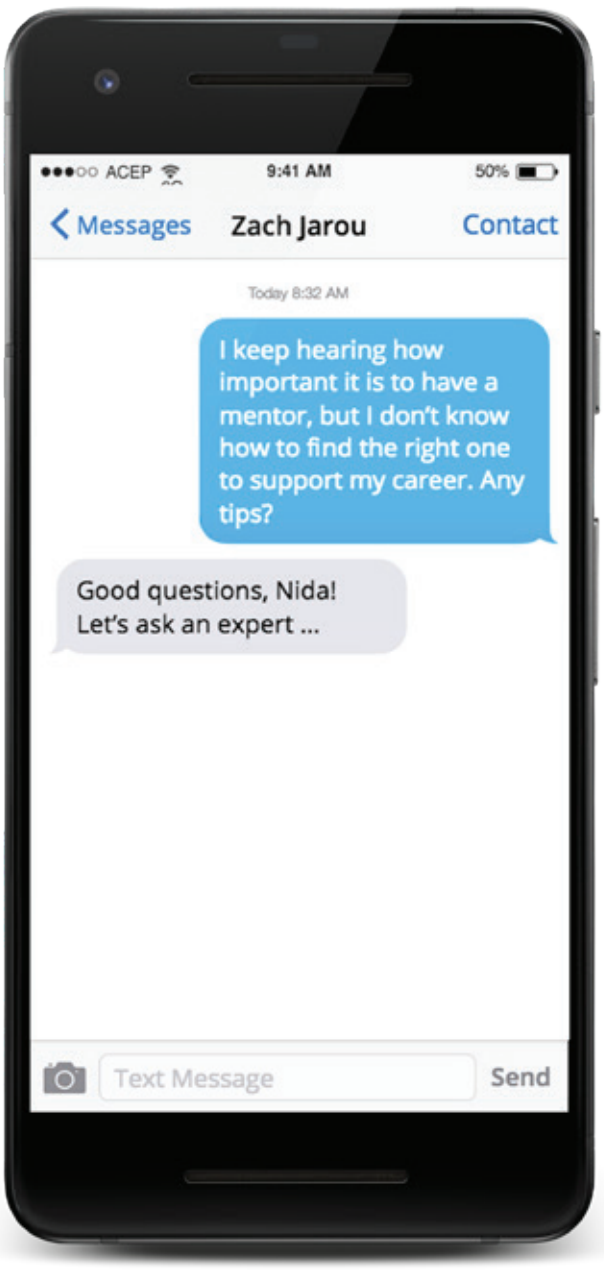
AVOID THE HAZARDS OF EM PRACTICE: FAQs FROM YOUNG PHYSICIANS

WHAT I WISH I KNEW...

DR. AKUNYILI is the facility medical director at Waterbury Hospital and in the TeamHealth Emergency Medicine, Northeast Group in Waterbury, Connecticut.

Selecting the Right Mentor

How to build a community of mentors to support your career



by IJE AKUNYILI, MD, MPA, FACEP

Thirteen years ago, I embarked on a career in medicine as a nontraditional student. I had a career before medicine, a five-month-old baby, and limited networks and resources. I knew I wanted to be an emergency physician and leader but had no idea how my goals would intersect with practice, medical school, and residency. I needed a mentor. Over the years, I have invested in surrounding myself with a community of mentors. These are people who share my passion for changing the world through medicine. A community of mentors also guarantees their mentee a collective advantage of years of experiences and even mistakes. My career and life journey have been immeasurably enhanced by an amazing community of mentors: Dr. Ken Butler, Dr. Joanne Oakes, Dr. Obi Nnaemeka, Dr. Kevin Klauer, Dr. Angela Siler Fisher, Dr. Andrea Green, Dr. Arlo Weltge, and my sister-mentor, Dr. Trish Stephens.

Needless to say, I have some concrete advice for anyone trying to select a good mentor.

Ask for a Formalized Mentor/Mentee Relationship

I met my first mentor, Dr. Ken Butler, during my first week in medical school. Ken was a seasoned emergency medicine attending who somehow understood how difficult medical school must be for a new mother. From the beginning, I specifically asked for a mentor relationship. In retrospect, perhaps few medical students had asked for such a relationship. Asking for a mentor relationship focuses both the mentor and mentee on a group of objectives and a distinct time framework for achieving them. A formal relationship also provides the matrix for the mentor and mentee to schedule their time commitments around the mentee's goal. I knew I would not have succeeded in medical school had he not guided me through the potential minefields of Step II exams, planning for medical school study, and the residency selection process.

Be Open to Several Types of Mentors

I have learned that successful people need several kinds of mentors. A mentor only has to be someone solidly in your camp. They believe in you, your objectives, your dreams, and yet are not afraid of the occasional redirection. Mentors can have the same life experiences and background as you but may also have vastly different experiences. In fact, you will be pleasantly surprised to find that several mentors who may be completely different from you can provide invaluable insights and life experiences that guide you on your chosen career path. You might be a young male physician from New York City, and your mentor may be an older female physician from the Midwest. The diversity of views all converging to promote your particular agenda can be nothing short of powerful. In fact, mentors with a different background can provide critical perspectives on how the world outside your particular comfort zone intersects with your aspirations.

Choose Mentors Who Believe in Your Brand

We all have a particular brand, a representation of ourselves that is unique. Choosing a mentor is very much like choosing a board member for your cherished startup. It goes without saying that they have to be totally committed to the brand, its success, and its growth trajectory. We are used to family members who believe in our brand, perhaps in an informal way. Mentors have a formalized relationship and belief in your brand. They are willing to advocate for you, guide you through rough times and provide you with constructive feedback because they are a part of your brand and success. They have equity in your brand and will do everything possible to help you avoid failure.

Finally, enjoy the process of creating a community of people who truly become lifelong friends and advocates. Your mentors believe in you, your brand, your dreams, and your aspirations. They are your fellow travelers on medicine's sometimes perilous journey. Choose them wisely.

Nida F. Degesys, MD, is an emergency medicine resident at the University of California, San Francisco–San Francisco General Hospital and the Emergency Medicine Residents' Association (EMRA) immediate past representative to the ACEP Board of Directors. Zach Jarou, MD, is an emergency medicine resident at Denver Health and immediate Past President of EMRA.

NEWS FROM THE COLLEGE

CONTINUED FROM PAGE 6

gency Department Act" and the "Preventing Overdoses While in Emergency Rooms (POWER) Act." ACEP worked closely with the bill sponsors to develop these important pieces of legislation to ensure that emergency physicians are equipped with the tools they need to fight the opioid epidemic from both a prevention and treatment standpoint, and provide patients with the care they need. The legislation is expected to be sent directly to President Donald Trump for signature, which he has agreed to do.

ACEP and ACP

In September, Dr. Kivela led a teleconference discussion with the American College of Physicians (ACP) on ACEP initiatives involving physician wellness, the opioid crisis, end-of-life issues, and how we could potentially work together to create greater cohesion. We will provide more on this as work continues.

ACEP Contributes to Development of Fentanyl Safety Video

The Department of Justice (DOJ) hosted a White House event last month to announce the release of a safety video for first responders called "Fentanyl: The Real Deal." The DOJ worked with nine other federal agencies as well as 24 stakeholder groups, including ACEP, to produce written guidance and this video that enforces that guidance. The guidance and the video include the following science-based recommendations to help first responders protect themselves when the presence of fentanyl is suspected or encountered:

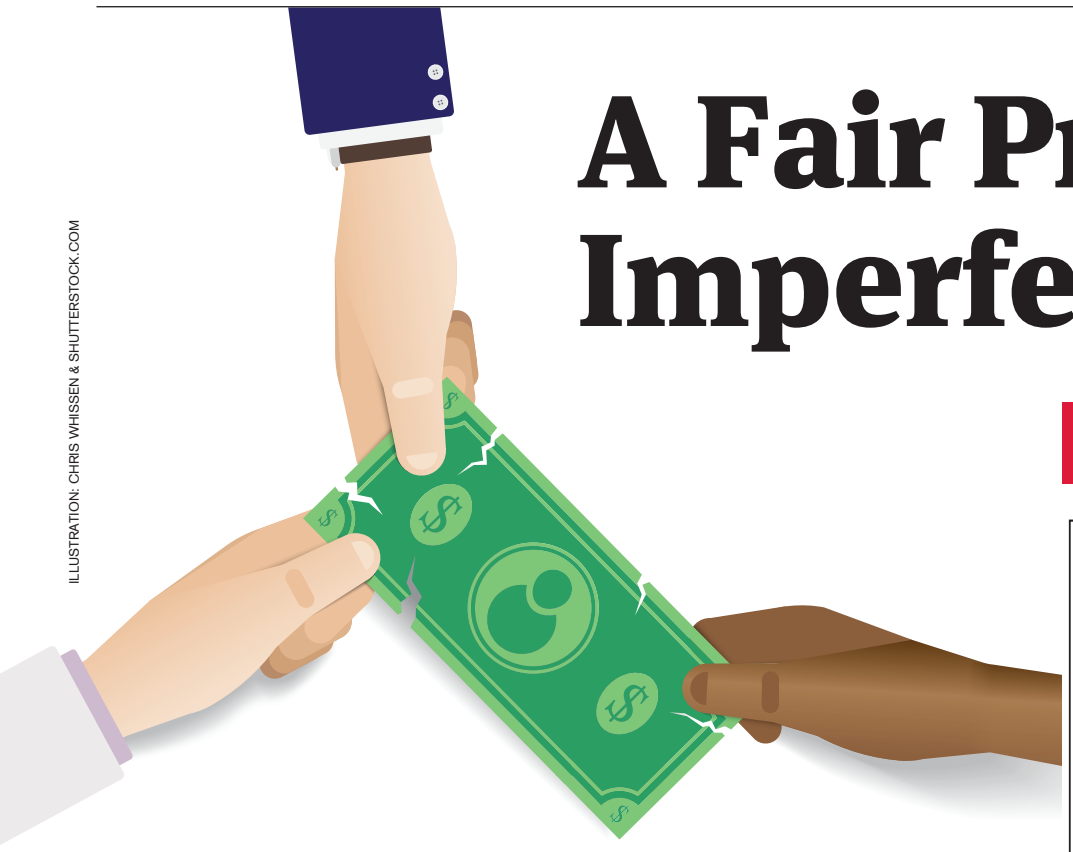
- Actions first responders can take to protect themselves from exposure
- Actions first responders can take when exposure occurs
- Actions first responders can take when they or their coworkers exhibit signs of opioid intoxication

ACEP Participates in Drug Shortage Summit

On Sept. 20, 2018, Dr. Kivela participated in a drug shortage summit hosted by the American Society of Anesthesiologists, the American Hospital Association, and the American Society of Health-System Pharmacists. The summit focused on the national security aspect of drug shortages and ways to improve the resilience of the nation's health care infrastructure. Many of the speakers were federal employees representing HHS, ASPR, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the Defense Logistics Agency who engaged the attendees in discussions on how their programs could work better to facilitate patient care, improve transparency and communications, and more effectively utilize the supply-chain capacity.

DR. DARK is assistant professor of emergency medicine at Baylor College of Medicine in Houston and executive editor of PolicyRx.org.

A Fair Price in an Imperfect Market



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How can health care stakeholders agree on a fair price for health care services?

by CEDRIC DARK, MD, MPH

Emergency medicine, insurance companies, and patients currently exist in what I see as a standoff. The tension between the three parties will remain ever present until an outside force, likely governmental, comes in to resolve the conflict. However, why are each of these parties pointing fingers at one another in the first place? The principle reason is that while we all pretend that American health care functions as a market, like many other goods and services in the United States, emergency care certainly does not conform to market principles like Lasik surgery or joint replacements do.

When someone is having a heart attack, they do not have time to comparison shop. When a patient checks into the emergency department, the clinicians cannot determine in advance if the "customer" is willing and able to pay for the services provided. When you throw third-party payers into the mix, you wind up either with price controls (eg, Medicare and Medicaid) or out-of-network billing (for private insurers) wherever it isn't prohibited. Arguably, the patients are most protected financially in the former situation, least in the latter. Providers, on the other hand, face the opposite financial risks.

Although emergency departments are taking a beating in the media over their billing practices, out-of-network billing is probably less common now than it was just a decade ago.[1,2] For many reasons, including the increasing prevalence of high-deductible coverage, patients are finally becoming cost-conscious. The questions that no one seems to be able to answer: What is a fair price in an imperfect market? Should emergency services be a multiple of the Medicare price? Should it be the usual and customary physician charge or a function of the in-network payment agreed to by providers willing to accept the insurer's reimbursement?

In a marketplace where EMTALA can effectively drive private insurance rates down to zero and where "your money or your life" allows physicians and hospitals to set charges infinitely high, it is imperative that states and/or the federal government establish an actual database where everyone—physicians, insurers, and patients—can see both the charges and the actual reimbursement rates so that a fair price for emergency services can be determined.

Cameron Gettel, MD, in a recent EMRA+PolicyRx Health Policy Journal Club article, articulates why this is high stakes for emergency physicians: "Transparency in how insurance companies provide fair coverage for their beneficiaries and calculate payments to providers is greatly needed as the present one-sided media perspective has misled the public by placing blame solely on physicians."[2] The EMRA+PolicyRx Health Policy Journal Club article on the next page anticipates that without a standard for how much health care services should cost, our work will inevitably be compared to Medicare prices.

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2. Gettel C. Nobody likes surprises. EMRA website. Available at: http://www.emra.org/emresident/article/hpjc-surprise-billing/. Accessed Sept. 28, 2018.

EMRA+POLICYRx HEALTH POLICY JOURNAL CLUB

Determining a Fair Price for Health Care

by ERICA GOLDSTEIN

There is no standard for how much health care services should cost nationally, so it is difficult to determine if and how much hospitals and clinics "overcharge." Insurers do not reimburse the full charges, and health care bills may be inflated to adjust for the reduced reimbursement.

A recent study in *JAMA Internal Medicine* compared Medicare reimbursement to billed services.[1] Medicare provides health insurance for the elderly and reimburses hospitals with predetermined and fixed prices. These reimbursements are called "allowed charges." Allowed charges were used as a proxy for the true price of health care services.

To determine the excess markup of health care services, this retrospective study analyzed Medicare Part B claims submitted in 2013. The study included services provided by 12,337 emergency physicians and 57,607 internal medicine physicians who were affiliated with thousands of hospitals. Markup was defined as the ratio of charges billed to Medicare compared to Medicare allowable charges. The study then compared markup between hospi-

CONTINUED *on page 44*

tals and between specialties.

The study determined that services delivered by emergency physicians were billed at 4.4 times the allowable Medicare payment, while services delivered by internists were billed at 2.1 times the allowable Medicare payment. Hospitals ranged greatly in terms of markup, with emergency services varying from 1 to 12.6 times the allowable amount. For-profit hospitals, hospitals with a high proportion of uninsured patients, and hospitals in the Southeast had greater markups.

The findings of this study must be put into context to understand their implications. This study used Medicare allowed charge as a proxy for health care prices, which represents a significant limitation. Medicare reimbursement has increased less than the inflation rate since the mid 1990s and may significantly undervalue true health care costs.

To understand the findings of the study, we need to make health care costs more transparent. The Fair Health claims database (www.fairhealth.org), for example, is dedicated to gathering independent and unbiased health care cost information. The nation should employ databases like this to advocate for less arbitrary reimbursement by insurance companies and to promote health care billing that is consistent with true cost.

Reference

1. Xu T, Park A, Bai G, et al. Variation in emergency department vs internal medicine excess charges in the United States. *JAMA Intern Med.* 2017;177(8):1139-1145.

MS. GOLDSTEIN is a dual-degree student at NYU School of Medicine and the Wagner School of Public Service in New York City.

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CODING WIZARD

NAVIGATE THE CPT MAZE, OPTIMIZING YOUR REIMBURSEMENT

Editor's Note: *Cutting through the red tape to make certain you get paid for every dollar you earn has become more difficult than ever, particularly in our current climate of health care reform and ICD-10 transition. The ACEP Coding and Nomenclature Committee has partnered with* ACEP Now *to provide you with practical, impactful tips to help you navigate through this coding and reimbursement maze.*

HOW TO CODE NOSEBLEEDS

by **HAMILTON LEMPERT, MD, FACEP, CEDC**

Question: Are there different codes for managing nosebleeds?

Answer: Yes, there are. Epistaxis control is achieved through a variety of modalities. Anterior epistaxis control has two codes: 30901 (simple, 1.62 relative value units [RVU], Medicare $58.32) and 30903 (complex, 2.25 RVU, Medicare $81). These codes are for unilateral procedures.

When a patient has a bilateral nosebleed, some payers require billing the procedure twice (as two units) with a 50 modifier (bilateral procedure) if control procedures are performed on both sides, while other payers will allow it to be billed only once with a 50 modifier.

The difference between "simple" and "complex" is not well-defined. The only description CPT gives to differentiate the two codes is that 30901 is "limited" and 30903 is "extensive."

Posterior epistaxis control only has one code for the initial management (30905, 3.01 RVU, Medicare $108.36) and one for subsequent care (30906, 3.88 RVU, Medicare $139.68) if the bleeding recurs. The 50 modifier is not used for posterior bleeding due to there being only one posterior nasal area.

Brought to you by the ACEP Coding and Nomenclature Committee.

DR. LEMPERT is chief medical officer, coding policy, at TeamHealth, based in Knoxville, Tennessee.

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Susan B. Promes, Professor and Chair, Department of Emergency Medicine c/o Heather Peffley,
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