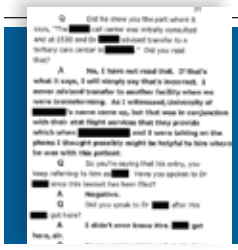

MEDICOLEGAL MIND

A Patient Transfer Leads to a Lawsuit

SEE PAGE 21

EQUITY EQUATION

To All Staying Neutral about Black Lives Matter

SEE PAGE 23

SKEPTICS' GUIDE TO EM

RCTs Show Lack of Efficacy of tPA

SEE PAGE 25

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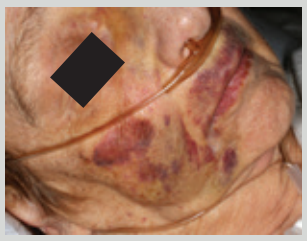
Speaking the Unspeakable

SEE PAGE 4



FORENSICS

Institutional Elder Abuse

SEE PAGE 22

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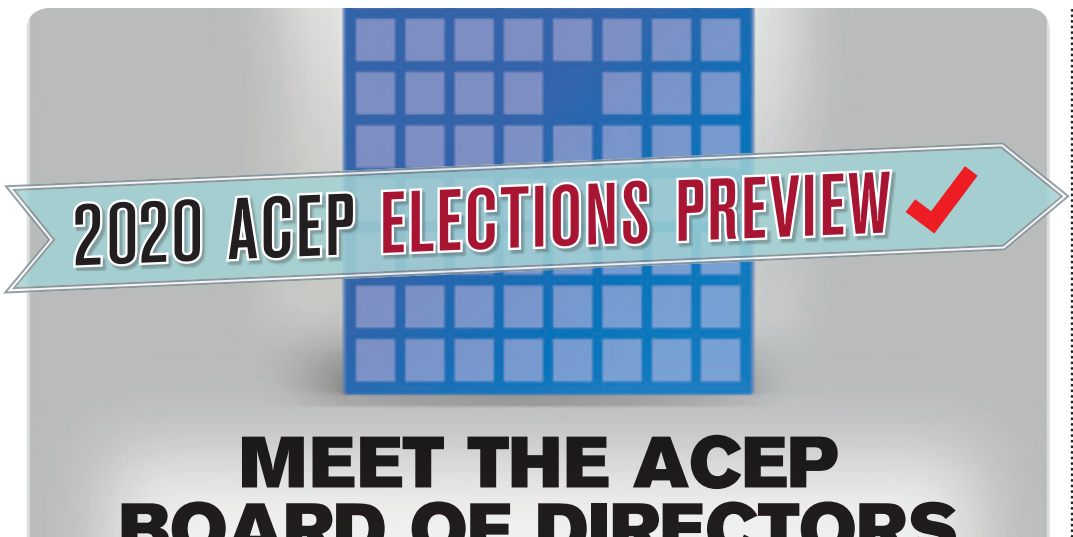

2020 ACEP ELECTIONS PREVIEW

MEET THE ACEP BOARD OF DIRECTORS CANDIDATES

The candidates discuss major issues facing emergency medicine

Each year, ACEP's Council elects new leaders for the College at its meeting. The Council, which represents all 53 chapters, 39 sections of membership, the Association of Academic Chairs of Emergency Medicine (AACEM), the Council of Emergency Medicine Residency Directors, the Emergency Medicine Residents' Association (EMRA), and the Society for Academic Emergency Medicine, will elect the College's President-Elect and four members to the ACEP Board of Directors when it meets in October. This month, we'll meet the Board of Directors candidates.

CONTINUED *on page 8*

One of Us

National Physician Suicide Awareness Day is Sept. 17

by DANIEL LAKOFF, MD, MBA, MS, FACEP; AND LOICE SWISHER, MD, FAAEM

Thursday, Sept. 17, 2020 marks the third annual National Physician Suicide Awareness (NPSA) Day.[1] NPSA Day remains a day of reflection, dedicated to honor the memory of our colleagues who have died by suicide. The day raises awareness about physician suicide and should encourage discussion of how we can prevent it. This year's theme is "One of Us," and is meant to remind us that we, as a community, are at risk. The theme is also meant to remind us that we all have a part to play in preventing suicide among our colleagues. Suicide is preventable if we take the time to care for one another and destigmatize the issues that underlie it by being vulnerable and open to conversations about them.

A Year of Challenges

This year, in the shadow of the COVID-19 pandemic's dramatic arrival in New York, we lost Lorna Breen, MD, FACEP, to suicide. Dr. Breen was *one of us*. She was radiant, charismatic, powerful, interesting, kind, and adored by those around her. She was an adventurer and snowboarder. She was a friend who loved and was loved by so many. She was the director of a major New York City emergency department. She led her department with every fiber of her being. She was an educator and mentor to colleagues, residents, and students. She was also a longtime ACEP and New York ACEP member who participated in committees and Scientific Assemblies. She was optimistic and had even taken on the challenge of starting a new educational path in 2019, studying for an MBA. She had no history of mental health issues and, though she was a colleague and friend, she revealed no signs to suggest she was at risk.[2,3] She was an incredibly strong and effective person. She was the epitome of emergency medicine. She was one of us.

Dr. Breen's death, as well as the deaths of so many others, reminds us that many

CONTINUED *on page 7*

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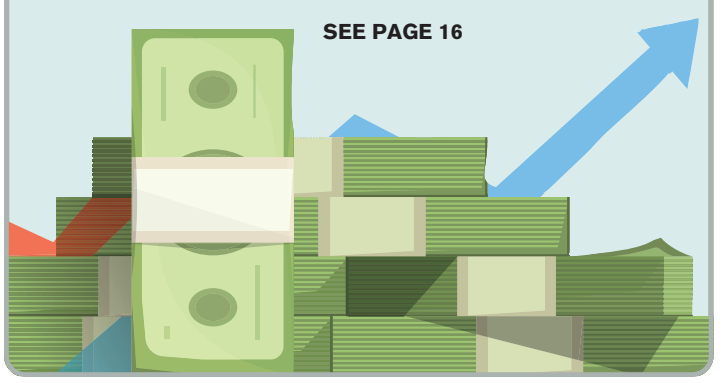
MEDICARE FEE SCHEDULE

Emergency Medicine Gains Ground in 2021

SEE PAGE 16



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NEWS FROM THE COLLEGE

UPDATES AND ALERTS FROM ACEP

COVID-19 Severity Calculation Tool Now Available

ACEP and EvidenceCare created a seven-step triage process for emergency physicians to better classify COVID-19 patients and inform next steps. This new and evolving pathway integrates into many electronic health record systems and also can be downloaded for offline use. Learn more at www.acep.org/covid19-severity-tool.

ACEP20 Announces Dr. Fauci as Special Guest

National Institute of Allergy and Infectious Diseases Director Anthony Fauci, MD, will provide his unique perspective from the epicenter of the pandemic to kick off the ACEP20 opening session. Following Dr. Fauci's remarks, a panel of international emergency physicians will present "Lessons Learned: Global Response to COVID-19." Learn more at www.acep.org/acep20-special-guests.

ACEP20 CME: Gain Access to Hundreds of Courses for Three Years

Have questions about how ACEP20 CME will work? Here's what you need to know.

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- The 26 hours of live CME is available to claim based on what sessions you attend. You'll be able to claim all of these hours at one time at the end of ACEP20. To view a schedule of the live content, visit www.acep.org/sa/education/schedule.
- The 250 on-demand CME hours can be claimed for the next three years. You claim the hours for individual courses after watching on demand. This option is added as courses are finished.
- The ACEP CME Tracker will keep all of these hours documented for members.

Survey Results Show Financial Impact of COVID-19 on Group Practices and Individual Physicians

ACEP has been actively advocating on your behalf to provide the tools and resources you need to safely do your job during the COVID-19 public health emergency. To inform our advocacy strategy, ACEP staff, in conjunction with a subgroup of the ACEP Reimbursement Committee, designed a survey that included 24 questions about the financial impact COVID-19 has had on emergency medicine group practices and individual emergency physicians. We received 197 responses representing all emergency medicine group practice structures, group sizes, and historic volumes from across the country. The data confirmed anecdotal stories of the impacts on emergency medicine group practices, with almost all respondents reporting issues with the lack of or reliable personal protective equipment (PPE) and decreased volume and revenue. View the full article with the survey results and analysis at www.acepnow.com.

Get Your X-Waiver Through Zoom This Fall

ACEP, in partnership with Providers Clinical Support System, is hosting Medications for Addiction Treatment (MAT) X-Waiver (DEA DATA 2000) trainings this fall and in early 2021. These are free virtual live trainings done through the Zoom platform. Attendees who sign up for this training will attend a live four-hour webinar taught by clinical experts. Once completed, participants will receive the second half of the course, a four-hour online self-study portion. Participants are required to pass an exam to complete the training, and the course completion certificate does not expire. Sign up at acep.org/ed-x-waiver.

Virtual Grand Rounds to Continue Through 2021

ACEP's Academic Affairs and Education Committee created the monthly Virtual Grand Rounds program in April as a way to provide free education for emergency physicians and residency programs during this time of social distancing. It allows you to track learner participation while engaging in Q&As with course faculty on different monthly topics. Once the sessions are complete, they are posted in the ACEP eCME catalog for online learning. The following sessions are coming up. Register at www.acep.org/virtualgrandrounds. Past recordings on COVID-19, airway, physician wellness, ultrasound, and pediatrics are free for ACEP members.

- **Sept. 23:** International
- **October:** None—ACEP20 instead
- **Nov. 18:** Neurology
- **Dec. 16:** Cardiology
- **Jan. 27:** Vulnerable Populations/Social Determinants of Health
- **Feb. 24:** Simulation: OB Emergencies with EMRA

Improve Your ED's Pain and Addiction Care

We may be in the midst of a global pandemic, but the opioid epidemic isn't going away. ACEP newest accreditation program, Pain and Addiction Care in the ED (PACED), is the nation's only specialty-specific program that allows emergency departments to improve pain and addiction care. Elevate the quality of patient care with innovative treatments, alternative modalities, and impactful risk reduction strategies in a collaborative team setting, resulting in positive outcomes for your patients, families, and communities. Learn more at www.acep.org/paced.

Exclusive Online-Only Content

Every month, *ACEP Now* publishes additional content online. Here's what we have in store for September:

- Ethics: Research and Information Sharing in a Pandemic
- Ethics: How to Protect Teachers and Learners During the COVID-19 Outbreak
- Survey: How is COVID-19 Affecting EM Reimbursement?
- Clinical: How to Manage Marine Envenomations
- And more!

Speaking the Unspeakable

After Dr. Lorna Breen died by suicide in April, her family took up a cause they never wanted

by JORDAN GRANTHAM

It was less than 24 hours after Lorna Breen, MD, FACEP, died by suicide when *The New York Times* published the news. There it was, a headline the Breen family could have never imagined for their beloved sister, daughter, aunt: "Top ER Doctor Who Treated Virus Patients Dies by Suicide."

Their world had been capsized by shock and grief, and the Breen family was huddled together in Charlottesville, Virginia, holding this horrific, unthinkable news as their own tragic truth. The Breens did not want to tell anyone about Lorna's death, and they certainly did not want to announce it to the *Times'* 47 million Twitter followers. But the news was out there, and there was nothing they could do about it.

As the family cried together, they tried to figure out what to do next. "Jennifer and I had this incredible moment of clarity," said Corey Feist, Lorna's brother-in-law. "We needed to lean into this conversation, and we needed to shine a light on it."

The Breen Bond

Jennifer and Lorna Breen were "soul mates," according to Corey. Jennifer was younger than Lorna by 22 months, and they were inseparable. The sisters developed their own language as children and kept it going into adulthood, often switching into it for secret sister chats. To Corey, a health care executive, Lorna was a "big sister" who shared his passion for running and was his favorite person to talk to about the quirks of working in the medical industry. To the Feist children and her other nieces and nephews, Lorna was "the cool aunt," a status she greatly treasured.

The Feist family had just wrapped up their annual vacation with Lorna when she returned to unfamiliar territory at the emergency department at NewYork-Presbyterian Allen Hospital. COVID-19 had dramatically changed the landscape while she was traveling, and she immediately started sprinting to keep up with the increasing patient loads and rapidly changing protocols. It was March 18—only four days after returning to work—when she experienced her first COVID-19 symptoms.

The Feists spoke with Lorna daily as she tried to manage the illness alone at her home. Feverish and weak, she expressed concern for her colleagues and their safety, worrying about the personal protective equipment shortages and many staffers who had also fallen ill. She tried to help with a group project for the MBA program that she was enrolled in and kept in touch with her Bible study friends. Gifted with an incredible motor and work ethic, resting didn't come naturally for her. The woman who regularly ran marathons was now winded by doing the dishes. Still, she knew she was urgently needed back at work.

She returned to work in the emergency department on April 1. The stress and workload had only mounted while she was sick, but she could

CONTINUED *on page 6*

PHOTOS COURTESY BREEN FAMILY

TOP: Corey and Jennifer Feist speaking about the Lorna Breen Heroes' Foundation at a charity event.

LEFT: Dr. Lorna Breen (left) with sister Jennifer.

ABOVE: Dr. Lorna Breen running the New York City Marathon.

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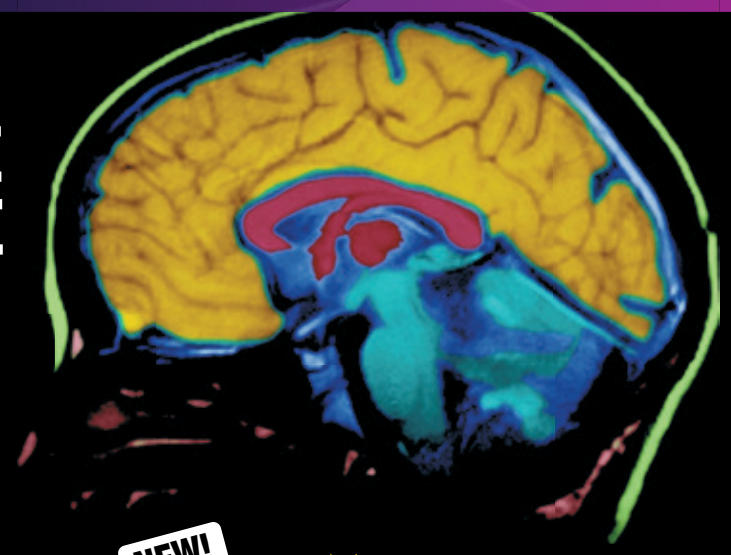

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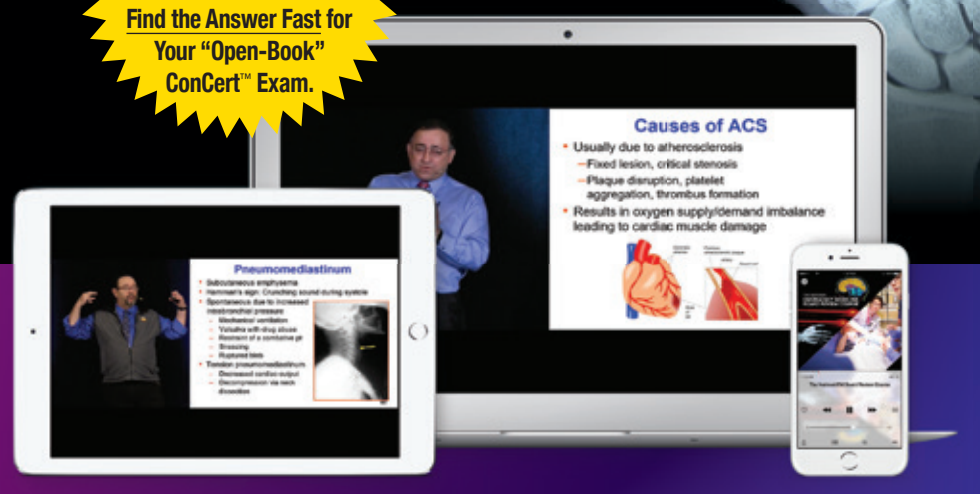

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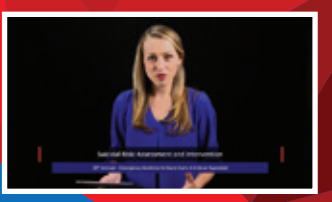
*Topics listed with an asterisk (*) are 90-minute faculty panel discussions; all other topics are 30 minutes.





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no longer pull from her legendary energy reserves. Lorna was scheduled to work nine 12-hour shifts in a row, and she stayed late every day. A relentless stream of flashing ambulances delivered COVID-19 patients to the hospital. Sleep eluded her. Jennifer and Corey were very worried about Lorna—they could hear the deepening distress in her voice.

The Stigma Trap

Months after Lorna's suicide, Corey reflected on the cascading events that led to the Breens deciding to shine a light on one of the darkest topics during their family's darkest hours. He explained that they initially fell into the same trap as most families who lose a loved one to suicide—they wanted to stay silent to avoid the stigma associated with it.

They may have remained silent, but the *Times* article put them on the spot. The Breens were caught in a stigma standoff. On the one hand, suicide stigma implores you to stay quiet about your tragedy. Keeping your secret means you don't have to answer unwanted questions and relive your tragedy over and over again. The unbearable grief and pain? Stigma says keep it to yourself.

On the other hand, what about the stigma Lorna faced as a health care hero on the front lines of COVID-19? She witnessed unimaginable suffering as the COVID-19 losses piled up, but she was trained to never show weakness. And what about the stigma that persists in medicine that says it isn't OK to sit down and take a break? The stigma that prevents health care workers from seeking crisis support because they're worried it will affect their licensure and career prospects?

In the blink of an eye, they had to make a decision about how to move forward and honor Lorna's legacy. Once the family decided to share their story, they set a movement in motion.

The Cause

The first thing the Breen family did was set up the Lorna Breen Heroes' Fund to provide mental health support to health care professionals. Soon that grew into a foundation dedicated to protecting and preserving the wellbeing of health care workers while destigmatizing mental health support for clinicians. The Lorna Breen Heroes' Foundation has told her story to many audiences over the last three months, furthering its mission to prioritize the protection and well-being of health care workers while breaking down barriers that prevent clinicians from seeking mental health support.

In June, Jennifer and Corey submitted written testimony to a Congressional hearing examining the pandemic's toll on the mental well being of clinicians. The Feists included multiple calls to action imploring the various entities involved in the clinician wellness crisis—the health care industry, federal and state governments, health care rating agencies, and the clinicians themselves—to each do their part to chip away at the harmful stigmas that keep clinicians from seeking support.

In late July, Sen. Tim Kaine (D-VA), Sen. Todd Young (R-IA), Sen. Jack Reed (D-RI), and Sen. Bill Cassidy, MD (R-LA), introduced S. 4349: The Dr. Lorna Breen Health Care Provider Protection Act to honor Dr. Breen and prevent suicide and mental health issues among health care professionals amid the COVID-19 pandemic and beyond. The movement was gaining momentum.

For the Breens, the cause is equal parts uplifting and heart-wrenching. The hardest part, Corey said, has been reliving their loss over and over again. "When we've wanted to advance the conversation to how we can help others, what we keep getting pulled back to is, 'Tell me the story again—we want to hear the gory details.'" As the Breen family grieves, each media interview and article published resurfaces painful feelings that leave them emotionally drained.

Lorna was a natural problem solver, a woman of action. At the time of her passing, she had recently co-authored a paper on physician burnout and was almost done chairing the work group that created ACEP's point-of-care tool for managing patients with autism in the emergency department. (Her nephew has autism, Corey explained, so she was particularly passionate about that project.)

Powered by the same problem-solving instincts that fed Lorna's drive, the Breens are dedicated to shifting the focus off Lorna's personal story and on to the solutions needed to protect and prioritize the emotional well being of health care workers. "That's the way [Lorna] would have operated," Corey explained.

As the public and medical community mark Suicide Prevention Week (Sept. 6–12) and National Physician Suicide Awareness Day (Sept. 17) during this pandemic that has only compounded the nation's mental health crisis, the Breen family said they will continue to speak to the unspeakable in Lorna's honor.

"She cared so deeply about her colleagues. ...We feel like this work is spreading *her*," Corey explained. "It's the hardest thing I've ever done in my life. And it's the most rewarding."

MS. GRANTHAM is ACEP's communications manager.

PEER SUPPORT PROJECT

Physician wellness is a complicated concept. Emergency medicine comes with unique challenges, and all emergency physicians cope in their own ways. There is one thing most ACEP members agree on, though: It helps to talk to someone who "gets it."

If you'd like to be that peer who gets it and recognizes when a colleague is needs extra support, we encourage you to check out **ACEP's new Peer Support Project**. You'll receive peer support resources and tips, plus monthly prompts that encourage you to check on your colleagues—and yourself. Sign up at **acep.org/peer-support-project**.

By the Numbers

PHYSICIAN SUICIDE

U.S. SUICIDE RATE INCREASED

35%

from 1999 to 2018

RELATIVE RISK OF SUICIDE FOR PHYSICIANS VS. GENERAL POPULATION

2.27x FEMALE

1.41x MALE

50%

of suicide decedents did not have a known mental health condition

30%

of resident physicians experience depression or depressive symptoms

SUICIDE: 2ND MOST COMMON CAUSE OF DEATH IN RESIDENTS

U.K. PHYSICIANS

50%

would not seek professional outpatient help for mental illness

ESSENTIAL WORKERS

21.7%

have seriously considered suicide in the past 30 days

Compiled by **Daniel Lakoff, MD, MBA, MS, FACEP,** clinical assistant professor of emergency medicine at Weill Cornell Medical College and associate director of emergency medicine at NYC Health + Hospitals | Harlem in New York City.

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SUICIDE AWARENESS

CONTINUED FROM PAGE 1

among us are at risk and struggle to process and vocalize our own emotions. Though each story varies, we physicians tend to have a problem acknowledging our own mental health struggles and we need to make concerted efforts to change that. While we have always been the safety net for our communities, we lack our own safety net to effectively deal with the barrage of psychological injuries that our jobs confer.

2020 has given emergency physicians front-row seats to one of the most tumultuous periods in generations. The COVID-19 pandemic has put the spotlight squarely on the health care system, medicine, and, in particular, on us as the front lines for our communities. The record number of unemployed due to furloughs and layoffs has given way to social and economic strife, even affecting emergency physicians. Our communities have also seen increasing numbers of opioid-related deaths, domestic violence, and gun violence. It would be ignorant to assume that we are all somehow psychologically insulated from our environments.

How We Can Help Prevent Suicide

Though there is a need for broader systemic change to improve the physician experience, changes are occurring. For example, as a result of Dr. Breen's suicide, her family helped push the State of Virginia to make changes to several laws to better protect physicians seeking mental health care.[4] (See page 4 to read about how Dr. Breen's family is honoring her legacy.) Similarly, on July 29, 2020, the U.S. Senate introduced bipartisan legislation, the Dr. Lorna Breen Health Care Provider Protection Act, that aims to reduce and prevent suicide, burnout, and mental and behavioral health conditions among health care professionals.[5] Recognizing the need to minimize barriers to obtaining help, the Federal Communications Commission (FCC) unanimously voted to create a national three-digit suicide prevention hotline, 988, which will be implemented on July 16, 2022.6 Organizations like The Joint Commission, the Federation of State Medical Boards, and the American Medical Association have released statements to aimed at making it easier for physicians to access mental health services without deleterious effects on their own ability to practice medicine."[7] ACEP has expanded its offerings for mental health and well-being support by compiling wellness resources and even offering three free confidential counseling or wellness coaching sessions.[8]

Locally, there are actions within our grasp that can help create the safety net we need. Starting with empathy and kindness, we can create supportive workplace environments that promote a willingness to share experiences and permit both cognitive and emotional unloading. Just as we rally when critical patients arrive and support one another with treatment recommendations and procedural support, we must do the same when we are ourselves at risk. Over time, once momentum and buy-in from leadership is assured, operational changes can be implemented to better safeguard physicians.

We urge emergency physicians across the country and around the globe to mark Sept. 17 on your calendars as NPSA Day and to take the following steps at your home institutions:

1) Create a safe space by dedicating time to talk about mental health and suicide. Set aside time at your morning report, morning huddle, or faculty meeting to discuss physician mental health, depression, and suicide. More participation will allow individuals in your group to speak freely about these issues without creating a spotlight on any one person.

2) Speak the names of your colleagues who have died by suicide. Remember them, honor their memory, and share stories and lessons learned.

3) Be vulnerable and be a role model for your colleagues and trainees. Physicians are notoriously constricted in sharing their own emotions and experiences, which may contribute to higher rates of burnout, depression, and suicide. We need courageous individuals to start the conversation and break the ice. By modeling vulnerability, you are helping to change the culture in medicine.

4) Support access to mental health. This may take a little preparation, but review and share how mental health care and resources are accessed locally. As you are doing the research, look for the barriers to access care: How easy is it to access care? How long does it take to get an appointment? Is confidentiality protected? Does your employer-provided insurance plan have adequate mental health options?

If you would like to donate to Dr. Lorna Breen's Heroes Foundation, visit www.drlornabreen.com.

If you would like to purchase National Physician Suicide Awareness Day pins, visit www.cordem.org/npsa.

If you are having thoughts of suicide or self-harm, please call a friend or a loved one or the National Suicide Prevention Lifeline at 1-800-273-8255 (TALK).

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DR. SWISHER is co-creator of National Physician Suicide Awareness Day and associate professor of emergency medicine at Mercy Catholic Medical Center in Philadelphia.

CONTINUED FROM PAGE 1

MEET THE ACEP BOARD OF DIRECTORS CANDIDATES

PLATFORM STATEMENTS

The candidates for the Board responded to the following question:

What are the two greatest opportunities and threats to ACEP?

Michael J. Baker, MD, FACEP (Michigan)

Current Professional Positions: director of telehealth, EPMG/Envision; medical director, Munson Healthcare Cadillac Hospital, Cadillac, Michigan; clinical assistant professor, Michigan State University College of Osteopathic Medicine, East Lansing; ED informatics representative on the clinical excellence committee and chairperson for optimizing information technology, Trinity-Health; adjunct clinical instructor, University of Michigan College of Medicine, Ann Arbor; core faculty, University of Michigan/St. Joseph Mercy Hospital emergency medicine residency; attending physician, member of the telemedicine clinical quality committee, and Cerner physician liaison, St. Joseph Mercy Hospital, Ann Arbor

Internships and Residency: emergency medicine residency, University of Michigan

Medical Degree: MD, Ohio State University, Columbus (1993)

Response

ACEP's strategic plans revolve around both threats and opportunities. The unpredictability of the COVID-19 health emergency represents a threat to ACEP. ACEP risks losing members to furloughs and burnout. Lower volumes and reimbursement will drive a reduction in the cost of care. Some emergency physicians have experienced a 20 percent wage drop. Cutting CME benefits will drive our members to low-cost options for education. As hospitals cut positions to save money, more work will fall on the physician. Emergency physician positions might be filled with nurse practitioners or physician assistants who must be adequately supervised and trained. ACEP must connect with members and support them in the workplace during this challenging time.

The second threat is the consolidation of insurers, health systems, and physician groups. Although ACEP has faced consolidation in the past, the level experienced today could restrict competition. As insurance carriers face reduced competition, they will force new ways to lower payments to physicians. One example is the ongoing attempts to pass unfair "surprise billing" legislation. Reduced competition among employers raises physician concerns with ensuring fair compensation, quality patient care, due process, and a safe working environment. ACEP's vision statement declares, "Emergency physicians practice in an environment in which their rights, safety, and wellness are assured." ACEP leaders can work with payers, health systems, and physician groups to establish fair workplace policies, promote appropriate reimbursement, and encourage competition.

One of ACEP's most significant opportunities is to create and analyze big data through CEDR, E-QUAL, and EMF-sponsored research. Reliable data can support the adoption of new concepts, such as telemedicine and electronic records improvements. The consolidation of health systems provides opportunities to collect data in a standardized way. For example, I worked to convince a 93-hospital health system to support CEDR reporting for any participating emergency center. Lastly, EMF must be strongly supported in its vital support of independent research efforts and developing future researchers.

ACEP's other opportunity is to push for insurance reforms. The COVID-19 pandemic demonstrated the value of emergency medicine to the health care system. Our work with disaster preparedness and ACEP's quick development of COVID resources such as the ACEP *COVID-19 Field Guide* (acep.org/corona/covid-19-field-guide) stunned many outsiders who portrayed the emergency center as a high-priced place to receive medical care. ACEP can use that realization to push for fair payment, end narrow networks and surprise billing, and identify mechanisms to ensure adequate health care coverage. ACEP continues to push for a fair resolution to the surprise billing issue and advocates alongside state chapters advocacy, emergency physician groups, and other medical organizations. ACEP can re-affirm its commitment to its vision that "All patients have health care coverage that ensures access to emergency services. Legally mandated health care services are fully funded." ACEP needs Board members who can quickly recognize and respond to new threats and opportunities

Allison Haddock, MD, FACEP (incumbent, Texas)

Current Professional Positions: assistant professor of emergency medicine, director of health policy: advocacy, assistant director of faculty development, department of emergency medicine, Baylor College of Medicine, Houston

Internships and Residency: emergency medicine residency, University of Michigan, Ann Arbor

Medical Degree: MD, Cornell Medical College (2007)

Response

ACEP has 41,435 members, and while our membership is growing, our rate of growth is declining. The growing number of EM residencies in the United States has brought an increase in our candidate membership, but we are seeing a drop in the percentage of graduating residents who retain their membership. ACEP must ensure that we are the premier source of opportunities—for networking, education, and personal development—for emergency physicians. We must demonstrate that we share our members' values and are advocates for them and their most vulnerable patients. While some will dedicate the time and effort required to be councillors and committee members, we must also offer smaller innovative opportunities

for members to get involved with issues that are critical to them personally to support their growth as educators and advocates. As a Board member, I have been involved in our efforts to trial new membership models that meet member needs at every career stage. The picture isn't grim—our overall membership is still up 5 percent this year—but we should embrace this opportunity to ensure that residency-trained emergency physicians look to ACEP first as an advocate for them on the front lines. We must show our members that we are not afraid to put the needs of the individual emergency physician first—advocating for physician-led teams with no absentee chart signing when working with NPs and PAs, and paid parental leave for EPs—while maintaining a viable emergency medicine practice and fighting external threats to our livelihood like "surprise billing" legislation that allows insurers to set arbitrary and unviable reimbursement levels and persistent insurer downcoding while we provide critical services.

As we lead the front lines in the fight against COVID-19, the eyes of the country have been drawn to emergency physicians. For ACEP, this has presented an opportunity for us to serve as a critical clearinghouse of information, including the *COVID-19 Field Guide* and the EngagED coronavirus community. Our staff has done an incredible job of finding and sharing resources, like free hotel nights and meals, as we have balanced our dedication to our patients with the threat to our families. However, some of ACEP's core activities have been put at risk by COVID. We offer robust online educational offerings, but our premier educational and social event has always been an in-person annual meeting. As the Board Liaison to the Education Committee, I have helped convert our annual meeting into an "UnConventional" experience that will offer unique educational and networking moments. To protect us from the threat of COVID in our EM practice, the College has advocated tirelessly for more resources for us—for more PPE, liability protections, hazard pay, and adequate insurance coverage for patients seeking COVID-related care. COVID has brought an immediacy to our advocacy efforts and reminded legislators of the critical role that we play in the health care system.

Aimee Moulin, MD, FACEP (California)

Current Professional Positions: associate professor, department of emergency medicine, department of psychiatry, University of California at Davis Medical Center
Internships and Residency: emergency medicine residency, LAC+USC Medical Center, Los Angeles
Medical Degree: MD, University of Southern California Keck School of Medicine, Los Angeles (2003)

Response

The greatest threats to ACEP are health care consolidation and disenfranchisement of frontline emergency physicians. We are in a time of stress. The forces that have led to consolidation will accelerate. As groups, health systems and insurance companies become larger while the relative power of an individual emergency physician shrinks. The ability of a single emergency physician to speak freely and to control their own practice is threatened, and ACEP must be the solution.

This past year, the systems we have relied on to protect us failed. Our health and safety were not prioritized. ACEP was there to lead the grassroots fight for PPE and protections for emergency physicians. We must protect our communities. We must protect ourselves. We must speak up when there is inadequate PPE or when the health care infrastructure crumbles. We need ACEP to support and protect our rights. I will do everything possible to ensure that it does.

We must acknowledge the tension between frontline emergency physicians and their employers. Their goals are not always aligned. In times of financial stress, it takes courage to challenge the status quo. As emergency physicians and as ONE organization, we need to address this inherent tension openly. It doesn't matter if you are working for a large group or small group, a hospital, a university, or a government or employer-owned entity, emergency physicians have a unique skill set and a vital role in the health care system that must be valued and protected. Just as emergency physicians have unflinchingly risen to daily challenges and shown value to our patients and our communities, so must ACEP rise to the challenge and unflinchingly support and defend its members.

It is clear that we will continue to see increased productivity demands, increased responsibilities to manage the ills of society with decreased financial, administrative, and material support. These are threats we all face, and this situation provides a unique opportunity for us to come together like never before. Now is not the time to narrowly defend our past but instead to look to the future, to take the broadest view of our specialty and what we can become. From our vantage point, we have the clearest view of our health care system and what is needed to deliver high-value, quality care to all who seek it. Now is the moment to fill the void. Now is the moment to expand and innovate and lead the way to meaningful, sustainable, and equitable health reform.

As emergency physicians, we will not agree on every issue. We need ACEP to provide the forum to discuss complex issues in a meaningful, collegial way. We are made for these unprecedented times. Emergency physicians excel at rapidly making critical decisions with limited time and limited information. There is no one better. The challenge before us is to do it together. I have been proud to build consensus around potentially controversial topics. I hope to bring my skills to the ACEP Board to continue this effort and look to our future.

Aisha T. Terry (formerly Liferidge) MD, MPH, FACEP (incumbent, Washington, D.C.)

Current Professional Positions: associate professor, emergency medicine and health policy, and senior advisor, emergency medicine health policy fellowship, George Washington University School of Medicine and Health Sciences, Washington, D.C.
Internships and Residency: emergency medicine residency, University of Maryland Medical System department of emergency medicine, Baltimore
Medical Degree: MD, University of North Carolina School of Medicine, Chapel Hill (2003)
Response

ACEP's greatest opportunity lies in boldly embracing the enormous opportunity to capitalize upon innovative technical advancement and data analytics in order to solidify emergency medicine as a premier leader of health care transformation, ensure the long-term solvency of College operations through non-dues revenue, and create sustainability of emergency medicine practice relative to quality standards and physician payment. ACEP's clinical registry—CEDR—offers the perfect opportunity by which to accomplish these goals.

CEDR is currently used to collect and submit quality data to the federal government to evaluate emergency physicians' provision of care. Since its inception in 2015, CEDR has collected data on over 50 million emergency department visits and saved emergency physicians over $300 million in avoided penalties. CEDR has even greater functional capacity, however. If fully optimized, CEDR could also serve as a vehicle for curating robust data, facilitating transformative research, and informing innovation around health care delivery. Strengthening CEDR's technical infrastructure and diversifying its capacity would also provide the College with the ability to perform data analytics and pursue non-dues revenue by offering highly sought-after, real-time, robust emergency care data. A more widely adopted CEDR would additionally continue to foster high emergency medicine quality standards while protecting emergency physicians from penalties and creating eligibility for bonuses.

ACEP's biggest threat is passivity as related to firmly defining the identity of our specialty and the roles of emergency physicians. This is necessary to ensure the longevity, growth, and integrity of our specialty. Emergency medicine must be identified as an essential safety-net health care service. Emergency physicians must be clearly named as the lead clinician in the ED and the primary stakeholder in EM practice models. The coronavirus pandemic has magnified for the world what emergency physicians have always known—that is, that EM is absolutely essential and of tremendous value to the entire health care system. As such, emergency care should be compensated accordingly, regardless of patient volumes, and viewed as a prized resource. ACEP now has an unprecedented opportunity to capitalize upon the momentum of the pandemic by insisting that policies and fiscal support structures fairly and durably recognize EM as vital and essential.

As a champion of quality care, ACEP must also be intentional about clarifying the identity of the emergency physician in the clinical setting. While advance practice providers are welcome and indispensable members of the ED team, their intended skill set does not equate to that of a physician, and patients deserve to have their care led and supervised by the clinician with the highest level of competency—an emergency physician. Finally, the role of the emergency physician relative to the management of their practice should be addressed. EM practice models have evolved such that physician autonomy in the decision-making process for the practice has declined. In some instances, this has resulted in a shift away from patient-centered approaches to care. ACEP should study this phenomenon and model options that promote physician-led practice management, without creating excessive burden or risk.

Arvind Venkat, MD, FACEP (Pennsylvania)

Current Professional Positions: vice chair for research and faculty academic affairs, department of emergency medicine, Allegheny Health Network, Pittsburgh, Pennsylvania; ethics committee chair and ethics consultant, Allegheny General Hospital, Pittsburgh; national director of research, US Acute Care Solutions, Canton, Ohio
Internships and Residency: emergency medicine residency, University of Cincinnati College of Medicine/University Hospital
Medical Degree: MD, Yale University School of Medicine, New Haven, Connecticut (2000)

Response

ACEP and our members are at a crossroads. The COVID-19 pandemic accelerated our challenges but also provided ACEP with a window to ensure emergency physicians and our patients have a better future, one where the emergency care system is properly resourced for all who need it.

Our greatest opportunity as a College and as emergency physicians is to capitalize on the public stature earned through the current crisis in order to advocate for a reimbursement system that recognizes our frontline public health role. This is a role we have always fulfilled but now is the focus of public, governmental, and media admiration. We must seize this opportunity to push for direct funding of capacity and readiness at the emergency physician level. We deserve reimbursement for the expertise and preparation we deliver to our patients and our communities when crisis strikes. Having worked in reimbursement advocacy throughout my career and having witnessed how we are often placed on the defensive in debates over balance billing and insurance downcoding, our opportunity is to take our enhanced reputation from the current crisis to advocate proactively for reimbursement for our public health role. To prepare for the next crisis, whether it is the next wave of COVID-19, mass casualty events, or other societal ills that inevitably will present to the ED, we need all payers to compensate us for the patients we are rightly expected to be prepared to care for, not just those who seek our care. The specific ask may take the form of pushing for enhanced RVU attribution for our CPT codes to spread increased reimbursement across all payers or direct federal funding of emergency physicians and their practices, among other strategies. The opportunity to make the ask successfully will never be higher or more appropriate.

Our greatest threat as a College and as emergency physicians is that we will simply return to a reimbursement system nearly entirely based on volume of patients seen. It is unconscionable that, as we are called heroes by the public, our compensation is threatened. This results from a volume-based reimbursement system adversely driving the levels of emergency physician staffing, the role of mid-level providers in our practice, the divisions in our specialty on the scale and types of our practice organizations and their relationship with their constituent emergency physicians, and the personal well-being of our members when forced to work clinically on the thinnest of margins. We must use our enhanced stature from the current crisis to advocate successfully that emergency physicians, as the front line against this pandemic and future public health crises, must be compensated as highly skilled and essential public health professionals. The current reimbursement system based on volume alone divides us, leads to burnout, and jeopardizes the future of our profession and ACEP. This must change.

EMF GRANT HELPED PHYSICIAN STUDY BYSTANDER CPR DISPARITIES

For Dr. Comilla Sasson, early career research funding helped launch a career investigating health disparities

When Comilla Sasson, MD, PhD, FACEP, was an emergency medicine resident, she couldn't understand why so many cardiac arrest patients were coming into her emergency department without having had any CPR performed. The issue occupied her mind so much that she decided to apply for a grant with the Emergency Medicine Foundation (EMF) to study it.

EMF is a nonprofit organization whose mission is to fund research that "develops career emergency medicine researchers, improves patient care, and provides the basis for effective health policy." Since its founding in 1972, EMF has awarded more than $17 million in research grants.

Today, Dr. Sasson is associate clinical professor of emergency medicine at the University of Colorado Denver and author of more than 90 research papers. Dr. Sasson recently spoke with EMF about how the grant she received more than a decade ago propelled her career.

EMF: Tell us about your EMF grant project.

CS: I got an EMF grant to look at racial and health disparities and who is getting bystander CPR. This involves looking at data to actually figure out where in neighborhoods people are getting CPR done or not getting it done. We looked at Denver data, and were able to see that if your heart stopped on one side of the street, your chances of getting CPR were 40 percent less than on the other side of the street. This actually changed the entire trajectory of my career.

EMF: Why did you choose this topic?

CS: I've always had an interest in looking at why there are differences in how people do in the emergency department. I did my training at Grady Hospital, which is a Level 1 trauma center in Atlanta, and saw that time and time again, patients primarily who were African American were not having CPR done before they got to the hospital or to the emergency department. We know that time is essential for the brain and heart muscle. For every one minute that you don't have CPR performed, your chances of surviving go down by about 10 percent. You only have this 10-minute window.

EMF: How did this grant changed the trajectory of your career?

CS: I work for the American Heart Association where every day we think about how can we reduce racial and health disparities in CPR and cardiac arrest survival. Everything that I did from the EMF grant has translated to what I'm making my life's work and my passion.

EMF: What was the most significant impact of your EMF research grant?

CS: We've been able to work with community groups, police, fire, EMS, hospital systems, nonprofit organizations, community-based organizations. We've been able to take that data that I got from the EMF grant and do actionable change. We're making improvements in neighborhoods because of the work that I did through the EMF grant, and now we're taking that research, turning it into real-world outcomes, and saving more lives by teaching people CPR and then, more importantly, when to call 911.

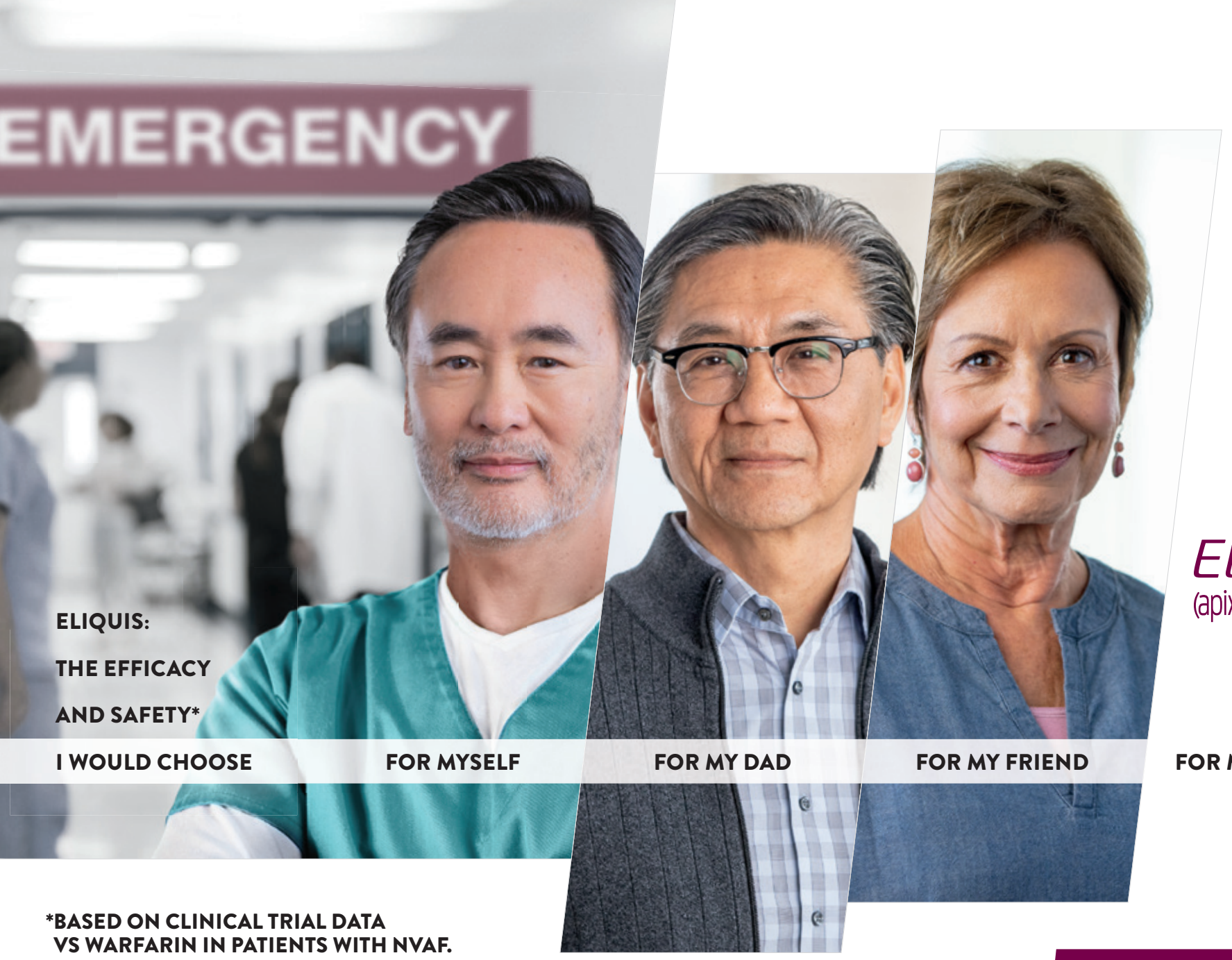
COMILLA SASSON

EMF: Since receiving your EMF grant, what other research awards and achievements have you received?

CS: I've gotten a career development award and have an additional $1.5 million of funding to work on opioids, overdose deaths, and how that relates to cardiac arrest. You need somebody to believe in you, and then I think that sets you up to make a huge impact.

EMF: What breakthrough treatments or protocols resulted from your research?

CS: We've been able to completely change the way in which we were looking at how to go into communities and do targeted training. It sounds like a really simple concept. We were the first ones that really launched this idea, and since that time, we've been going out to more than 10 major urban cities to do the same type of program and we're working on scaling up to a national program as well. ✪.



Eliquis® (apixaban) tablets 5mg 2.5mg

*BASED ON CLINICAL TRIAL DATA VS WARFARIN IN PATIENTS WITH NVAF.

Visit EliquisData.com

INDICATION

ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).

SELECTED IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

CONTRAINDICATIONS

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

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

ARISTOTLE study design[1,2]

A phase III, double-blind, randomized trial designed to compare the effects of ELIQUIS 5 mg twice daily* (n=9120) and warfarin (n=9081) (target INR range: 2.0-3.0) in reducing the risk of stroke and systemic embolism in 18,201 patients with NVAF and ≥1 additional risk factor for stroke: prior stroke or transient ischemic attack (TIA); prior systemic embolism; age ≥75 years; arterial hypertension requiring treatment; diabetes mellitus; heart failure ≥New York Heart Association (NYHA) Class 2; or left ventricular ejection fraction (LVEF) ≤40%. Patients were followed for a median of ≈1.7 years. The 2 treatment groups were well balanced with respect to baseline characteristics, including age, stroke risk at entry as measured by $CHADS_2$ score,† and prior vitamin K antagonist (VKA) experience. The primary efficacy endpoint was stroke/systemic embolism, and the primary safety endpoint was major bleeding. Patients who needed aspirin >165 mg/day or needed aspirin plus a thienopyridine (eg, clopidogrel) were excluded from ARISTOTLE.

AVERROES study design[1,3]

AVERROES was a phase III, double-blind, randomized trial designed to compare the effects of ELIQUIS 5 mg twice daily* (n=2807) and aspirin (81 mg–324 mg once daily) (n=2791) in reducing the risk of stroke and systemic embolism in 5598 patients with NVAF thought not to be candidates for warfarin therapy, and with ≥1 additional risk factor for stroke: prior stroke or TIA; age ≥75 years of age; arterial hypertension (receiving treatment); diabetes mellitus (receiving treatment); heart failure (≥NYHA Class 2 at the time of enrollment); LVEF ≤35%, or documented peripheral artery disease. Patients could not be receiving VKA therapy (eg, warfarin), either because it had already been demonstrated to be or was expected to be unsuitable for them. The 2 treatment groups were well balanced with respect to baseline characteristics, including age, stroke risk at entry as measured by $CHADS_2$ score,† and prior use of a VKA within 30 days before screening. The mean follow-up period was approximately 1.1 years. The primary efficacy endpoint was stroke/systemic embolism, and the primary safety endpoint was major bleeding.

*A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.[1]
†Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.[1]

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

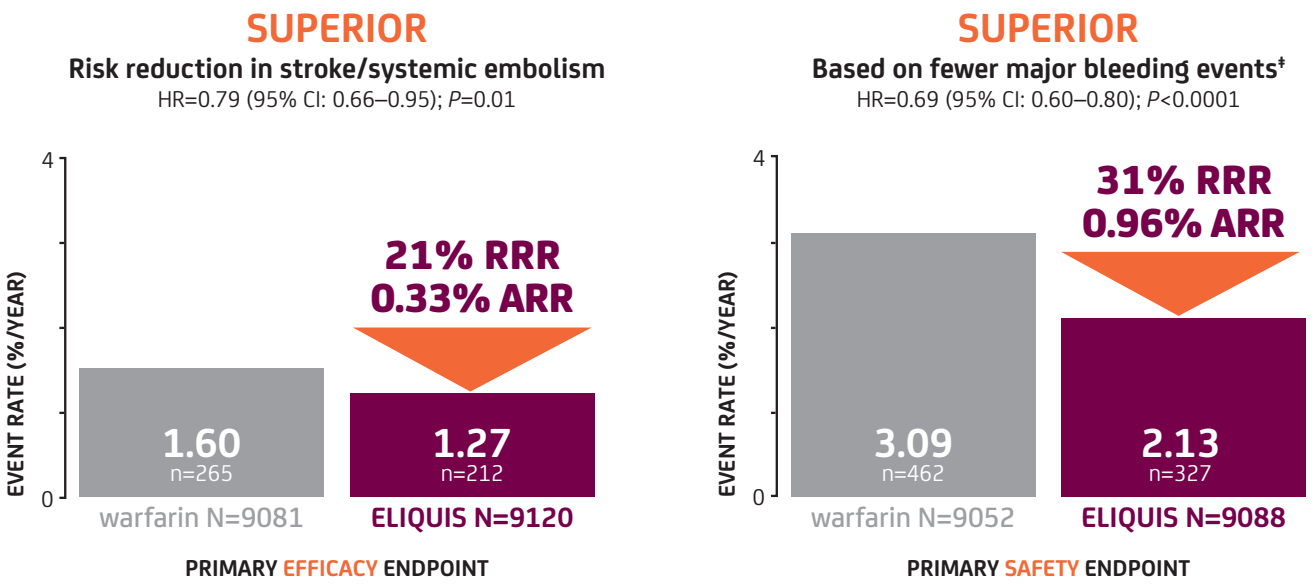
- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is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

  Clarithromycin

  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

FOR PATIENTS WITH NVAF

ARISTOTLE: ONLY ELIQUIS demonstrated superiority in BOTH stroke/systemic embolism and major bleeding vs warfarin[1]



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

- Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs[1]
- In another clinical trial (AVERROES), ELIQUIS was associated with an increase in major bleeding compared with aspirin that was not statistically significant (1.41%/yr vs 0.92%/yr, HR=1.54 [95% CI: 0.96–2.45]; *P*=0.07)[1]
- The most common reason for treatment discontinuation in both ARISTOTLE and AVERROES was 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[1]

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

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

‡Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period). Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints.[1]

§In AVERROES, a decrease in hemoglobin of 2 g/dL or more over a 24-hour period.[3]

¶In ARISTOTLE, intracranial bleeding included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as intracranial major bleeding.[1]

ARR=absolute risk reduction; Cl=confidence interval; HR=hazard ratio; INR=international normalized ratio; RRR=relative risk reduction.

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (cont'd)

- **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

- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes.

  Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
  - *Labor or delivery*: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

References: 1. Eliquis [package insert]. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY. **2.** Granger CB, Alexander JH, McMurray JJV, et al; for ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. **3.** Connolly SJ, Eikelboom J, Joyner C, et al; for AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364(9):806-817.

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

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y of Prescribing Information. For complete prescribing information consult e insert.

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

(B) SPINAL/EPIDURAL HEMATOMA

JRE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC

liscontinuation of any oral anticoagulant, including ELIQUIS, increases hrombotic events. If anticoagulation with ELIQUIS is discontinued for a than pathological bleeding or completion of a course of therapy, consider th another anticoagulant *[see Dosage and Administration, Warnings and and Clinical Studies (14.1) in full Prescribing Information]*.

EPIDURAL HEMATOMA

spinal hematomas may occur in patients treated with ELIQUIS who are uraxial anesthesia or undergoing spinal puncture. These hematomas may g-term or permanent paralysis. Consider these risks when scheduling spinal procedures. Factors that can increase the risk of developing pinal hematomas in these patients include:

dwelling epidural catheters

tant use of other drugs that affect hemostasis, such as nonsteroidal mmatory drugs (NSAIDs), platelet inhibitors, other anticoagulants

of traumatic or repeated epidural or spinal punctures

of spinal deformity or spinal surgery

iming between the administration of ELIQUIS and neuraxial procedures is m

gs and Precautions]

ients frequently for signs and symptoms of neurological impairment. al compromise is noted, urgent treatment is necessary *[see Warnings and *.

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

ND USAGE

tisk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— cated to reduce the risk of stroke and systemic embolism in patients with al fibrillation.

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

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

ulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

e Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of nd PE following initial therapy.

ADMINISTRATION (Selected information)

erruption for Surgery and Other Interventions

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

TIONS

aindicated in patients with the following conditions:

ological bleeding *[see Warnings and Precautions and Adverse Reactions]*

ersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse*

D PRECAUTIONS

of Thrombotic Events after Premature Discontinuation

ontinuation of any oral anticoagulant, including ELIQUIS, in the absence of ative anticoagulation increases the risk of thrombotic events. An increased rate bserved during the transition from ELIQUIS to warfarin in clinical trials in atrial nts. If ELIQUIS is discontinued for a reason other than pathological bleeding or course of therapy, consider coverage with another anticoagulant *[see Dosage and 2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

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

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

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

icoagulant Effect

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

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

l Anesthesia or Puncture

anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, with antithrombotic agents for prevention of thromboembolic complications are ping an epidural or spinal hematoma which can result in long-term or permanent

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

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

rosthetic Heart Valves

efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. f ELIQUIS is not recommended in these patients.

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

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

Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

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

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)
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 subje contributed events to multiple endpoints.

Other Adverse Reactions

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surger

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

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

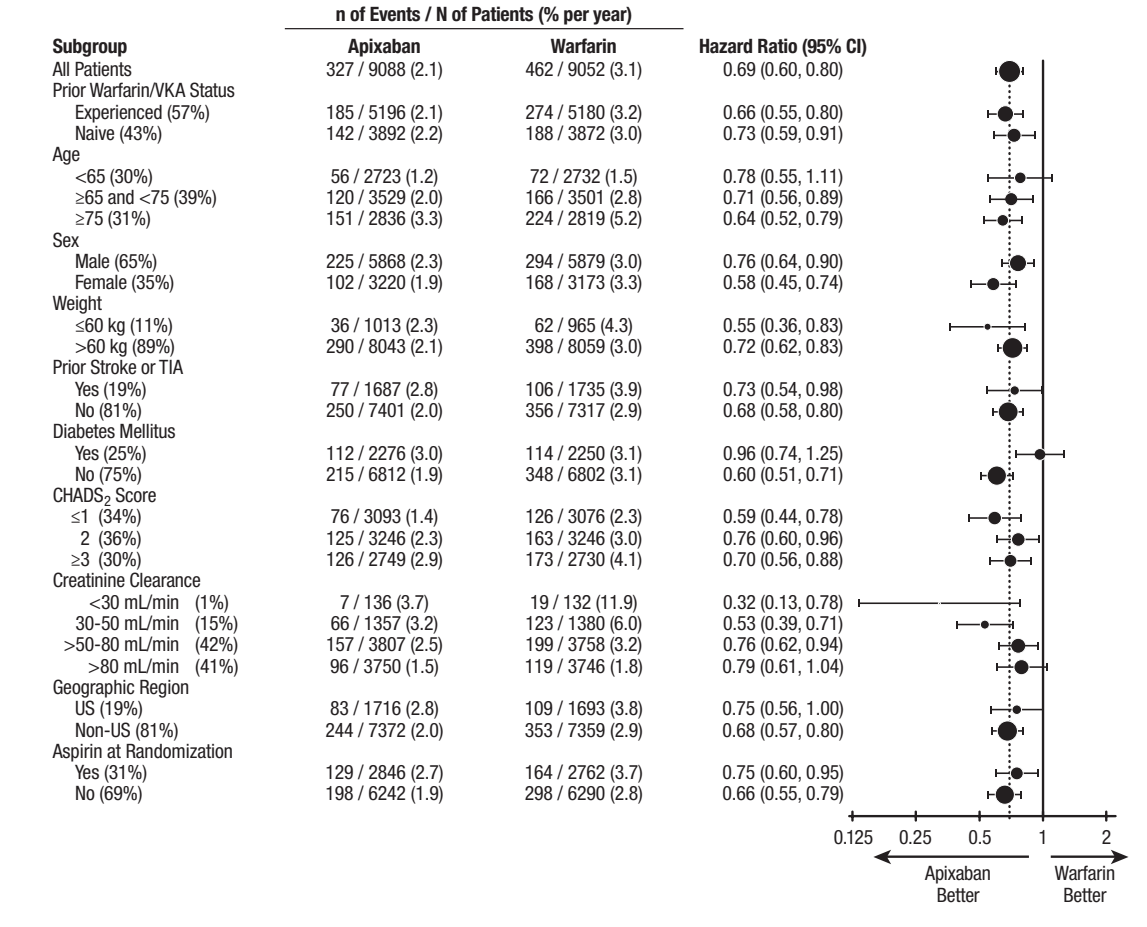
Bleeding results during the treatment period in the Phase III studies are shown in Tal was assessed in each study beginning with the first dose of double-blind study drug

Table 3: Bleeding During the Treatment Period in Patients Undergoing E Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADV Knee Re Su
	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
	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
All treated	N=2673	N=2659	N=1501	N=1508	N=1596
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)
Fatal	0	0	0	0	0
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)

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

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



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits t 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 heterog groups should not be over-interpreted.

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

dverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing ip 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
	153 (2.6)	159 (2.7)
ng postoperative and hemorrhagic spective laboratory parameters)	153 (2.6)	178 (3.0)
	83 (1.4)	115 (1.9)
cluding hematoma, and vaginal morrhage)	67 (1.1)	81 (1.4)
hemorrhage (including hematoma, wound hemorrhage, e-site hematoma and catheter-site	54 (0.9)	60 (1.0)
increased (including alanine se increased and alanine se abnormal)	50 (0.8)	71 (1.2)
otransferase increased	47 (0.8)	69 (1.2)
yltransferase increased	38 (0.6)	65 (1.1)

dverse reactions in ELIQUIS-treated patients undergoing hip or knee replacement ng at a frequency of ≥0.1% to <1%:

hatic system disorders: thrombocytopenia (including platelet count decreases)

ers: hypotension (including procedural hypotension)

racic, and mediastinal disorders: epistaxis

l disorders: gastrointestinal hemorrhage (including hematemesis and melena),

sorders: liver function test abnormal, blood alkaline phosphatase increased, blood ed

ry disorders: hematuria (including respective laboratory parameters)

g, and procedural complications: wound secretion, incision-site hemorrhage on-site hematoma), operative hemorrhage

dverse reactions in ELIQUIS-treated patients undergoing hip or knee replacement ng at a frequency of <0.1%:

g, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including norrhage), rectal hemorrhage

/T and PE and Reduction in the Risk of Recurrence of DVT or PE

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

rse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, ge, hematoma, menorrhagia, and hemoptysis.

ation of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) d patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. ation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients 7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

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

from the AMPLIFY study are summarized in Table 5.

leeding Results in the AMPLIFY Study

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

cally relevant nonmajor bleeding.
ted with each endpoint were counted once per subject, but subjects may have nts to multiple endpoints.

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

dverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the MPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
	77 (2.9)	146 (5.4)
	49 (1.8)	97 (3.6)
	46 (1.7)	102 (3.8)
	38 (1.4)	30 (1.1)
	35 (1.3)	76 (2.8)
	32 (1.2)	31 (1.2)
age	26 (1.0)	39 (1.5)
ng	26 (1.0)	50 (1.9)

tudy

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

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

leeding Results in the AMPLIFY-EXT Study

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

cally relevant nonmajor bleeding.
ted with each endpoint were counted once per subject, but subjects may have nts to multiple endpoints.

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Combined P-gp and Strong CYP3A4 Inhibitors

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

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

Clarithromycin

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

Combined P-gp and Strong CYP3A4 Inducers

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal adverse reactions

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

Labor or delivery

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

Data

Animal Data

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

Lactation

Risk Summary

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

Data

Animal Data

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% we age and older, and >31% were 75 years of age and older. In the ADVANCE-1, AD ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, wh 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32 were 65 years of age and older and >13% were 75 years of age and older significant differences in safety or effectiveness were observed when compari different age groups.

Renal Impairment

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

The recommended dose is 2.5 mg twice daily in patients with at least two of 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 w renal disease (ESRD) on dialysis. In patients with ESRD maintained on hemodialysis, administration of ELIQUIS at the usually recommended dose *[se Administration (2.1) in full Prescribing Information]* will result in concentration and pharmacodynamic activity similar to those observed in the ARISTOTLE stud *Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these will lead to similar stroke reduction and bleeding risk in patients with ESRD on d seen in ARISTOTLE.

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

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

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Chi A). Because patients with moderate hepatic impairment (Child-Pugh class intrinsic coagulation abnormalities and there is limited clinical experience with EL patients, dosing recommendations cannot be provided *[see Clinical Pharmaco*

OVERDOSAGE

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

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

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

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 b more easily when treated with ELIQUIS. Advise patients about how to reco or symptoms of hypovolemia and of the urgent need to report any unusu their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other to affect bleeding (including nonprescription products, such as aspirin or NSAI surgery or medical or dental procedure is scheduled and before any new drug
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patie signs and symptoms of spinal or epidural hematomas *[see Warnings and Prec* of these symptoms occur, advise the patient to seek emergent medical attentio
- To tell their physicians if they are pregnant or plan to become pregnant or are or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Popu*
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[s Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in f Information]*.

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Emergency Medicine Gains Ground in 2021

2021 CMS PROPOSED RULES WILL INCREASE RVUS AND RELAX MIPS REQUIREMENTS

by MICHAEL GRANOVSKY, MD, FACEP; DAVID MCKENZIE, CAE

The Centers for Medicare & Medicaid Services (CMS) has released the 2021 Physician Fee Schedule (PFS) proposed rule, which will affect emergency medicine reimbursement significantly. Following a commentary period lasting until Oct. 5, 2020, CMS is expected to issue its final PFS rule, which will impact services beginning Jan. 1, 2021.

Here are some highlights from this year's PFS rule. A longer summary is available at www.acep.org/globalassets/new-pdfs/advocacy/summary-of-the-cy-2021-pfs-and-qpp-proposed-rule.pdf.

2021 RVUs Increase for ED E/M Services

Acting to protect the safety net, ACEP asked CMS to recognize the intensity of ED services and maintain the relativity between the ED evaluation and management (E/M) codes and the new patient office codes. Even though the ED codes received increases of about 5 percent for code levels 1–4 in 2020, CMS has accepted our arguments and agreed to increase the ED relative value units (RVUs) for 99283–99285 again in 2021 (see Table 1).

2021 Conversion Factor Decrease

For 2021, CMS proposes a Medicare PFS conversion factor of $32.26, a 10.6 percent decrease from the 2020 conversion factor of $36.09. This historic decrease was due to the CMS decision to increase reimbursement for the office visit codes, a boon for urgent care (which reports using office codes). However, this increased spending triggered a significant "budget neutrality adjustment," as required by law. However, in light of the COVID-19 pandemic and the stresses placed on the whole house of medicine, Congress may waive the budget neutrality requirements, which could shield us from this significant potential decrease.

Due to the budget neutrality adjustment in the conversion factor for the whole house of medicine, emergency medicine could see as much as a 6 percent net decrease. ACEP has mounted a vigorous campaign to protect the safety net and is urging Congress to support the conversion factor at current levels (see "Advocate to Waive Budget Neutrality" for more on this effort).

ED Continued Traction with Telehealth Services

CMS is examining which of the codes that are temporarily on the list of approved Medicare telehealth services during the COVID-19 public health emergency will remain on the list permanently. CMS is proposing to keep ED E/M code levels 1–3 (CPT codes 99281–99283) on the approved telehealth list for the remainder of the year after the public health emergency expires. However, CMS is *not* proposing to include ED E/M code levels 4 and 5 (CPT codes 99284 and 99285) on the list of approved Medicare services past the duration of the public health emergency, citing these services as too intense to be routinely performed via telehealth.

Table 1: 2021 Proposed Increases to ED Work RVUs

CODE/ED VISIT LEVEL	2020 WORK RVUS	2021 PROPOSED WORK RVUS	% INCREASE IN WORK RVUS IN 2020
99281/Level I	0.48	0.48	0%
99282/Level 2	0.93	0.93	0%
99283/Level 3	1.42	1.60	12.68%
99284/Level 4	2.60	2.74	5.38%
99285/Level 5	3.80	4.00	5.26%

Table 2: MIPS Performance Category Weighting in Final Score

CATEGORY	2020	2021
Quality	45%	40%
Cost	15%	20%
Improvement Activities	15%	15%
Promoting Interoperability	25%	25%

Merit-Based Incentive Payment System

- **2020 Reporting Exemptions Due to COVID-19:** CMS is granting hardship exemptions to Merit-Based Incentive Payment System (MIPS) reporting requirements on a case-by-case basis due to COVID-19. It is therefore possible for a clinician or group to request exemption from all four performance categories in 2020 (see Table 2). If clinicians submit a hardship exception application for all four MIPS performance categories and their application is approved, they will be held harmless from a payment adjustment in 2022—meaning they will not be eligible for a bonus and not face potential penalties based on their MIPS performance in 2020.
- **Performance Threshold:** CMS proposes to set the performance threshold that clinicians need to achieve to avoid a penalty in 2021 at 50 points, down from 60 points, which had been floated previously.
- **MIPS Value Pathways (MVPs):** CMS is committed to developing MVPs, which would combine all four categories of MIPS reporting into a single, more harmonized process. However, due to COVID-19, the implementation of MVPS is being delayed until 2022. ACEP is working with CMS on developing an MVP for emergency medicine and is examining how ACEP's qualified clinical data registry, the Clinical Emergency Data Registry (CEDR), can help emergency physicians participate in an MVP.

Additional information on MIPS is available at https://qpp.cms.gov/mips/overview.

Other Resources

Resources for these and other topics can be found on the reimbursement section of the ACEP website. ACEP Director of Reimbursement David McKenzie, CAE, is also available to field your questions at 800-708-1822, ext. 3233. Finally, ACEP offers well-attended and highly recommended coding and reimbursement educational conferences annually. Visit www.acep.org/rc for more information.

DR. GRANOVSKY is president of LogixHealth, an ED coding and billing company, and currently serves as the course director of ACEP's Coding and Reimbursement courses. He may be reached at mgranovsky@logixhealth.com.

MR. MCKENZIE is ACEP director of reimbursement.

Advocate to Waive Budget Neutrality

Efforts are under way to ask Congress to waive budget neutrality for 2021 and maintain the Medicare payment per RVU close to current levels.

A more detailed fact sheet on the 2021 PFS payment proposals can be found at www.acep.org/corona/COVID-19-alert/covid-19-articles/2021-medicare-physician-fee-schedule-pfs-and-macra-quality-payment-program-qpp-proposed-rule-aceps-first-take-/.

Also, check out a blog from Jeff Davis, ACEP's director of regulatory affairs, that highlights key proposals in the rule at www.acep.org/2021-pfs-info.

Less than 20 hours after CMS released the proposed rule, ACEP sent a letter to Congress expressing our strong concerns on this proposed cut, noting the unprecedented strain emergency physician practices already are facing due to the ongoing COVID-19 pandemic.

Congress has the power to fix this by waiving the budget neutrality requirement. If Congress acts, emergency medicine reimbursement could actually increase by about 3 percent instead of decreasing by 6 percent.

WHAT CAN YOU DO?

Urge your member of Congress to waive the budget neutrality requirement for calendar years 2021 and 2022 at https://p2a.co/SeZSlvU.

Congress is already juggling many other priorities as a result of the pandemic and pressure from the upcoming November elections. **It is essential that they hear directly from emergency physicians in their district just how devastating these cuts could be for access to emergency care for patients across the country.**

BRIEF19 RESEARCH UPDATES

COVID-19 and Children

New research is broadening our understanding of the virus in kids

by JOSHUA NIFORATOS, MD, MTS

With thousands of articles published weekly on COVID-19, navigating the literature on this emerging infectious disease can be daunting. To help health care professionals and the general public keep up and to fight medical misinformation, a group of emergency physicians started the website Brief19.com, which publishes analysis of COVID-19 research and policy five days a week, all for free. Here are highlights from recent Briefs. (Note: ACEP Now*'s medical Editor in Chief, Jeremy Samuel Faust, MD, MS, MA, FACEP, is also Editor in Chief of Brief19.)*

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For the first few months of the COVID-19 pandemic, it was thought that children were not important vectors of transmission of the SARS-CoV-2 virus. Early data reported from the Centers for Disease Control and Prevention (CDC) in April found that children only accounted for 1.7 percent of positive tests in the United States.[1] By the middle of August, we now know that children account for approximately 7.3 percent of all positive cases in the United States.[2]

ACE2 Gene and Viral RNA

Biological hypotheses have emerged to account for these trends in transmission as it varies by age group. A paper published in late May in the *JAMA* was among the first to show that levels of *ACE2* gene expression of cells lining the airway of humans differ by age.[3] ACE2 is one of the receptors that SARS-CoV-2 binds to enter cells of the upper and lower airways. In that study, *ACE2* gene expression was lowest in younger children with levels of gene expression and it rose with increasing age. A few months later, research published in *JAMA Pediatrics* found quantitative differences of viral genetic material among different age groups.[4] In young children (under age 5), older children (age 5–17), and adults who had mild or moderate COVID-19 illnesses, young children had between 10 and 100 times the amount of SARS-CoV-2 RNA in their upper airways as compared to older children and adults. However, those studies do not directly report on replication-competent virus, so it is not necessarily the case that contagiousness correlates with these figures.

This research suggests that children may have fewer receptors for SARS-CoV-2 to bind, but when a child does become infected, the amount of viral RNA in the upper airways appears to be significantly greater than in adults, which further suggests that children may, in fact, play a role as important vectors of transmission. However, these are still hypotheses that have yet to be demonstrated causally.

Severity and Disparities

What about asymptomatic infection in children? The epidemiology of COVID-19 among children suggests, at least in the United States, that the rate of asymptomatic carriers is relatively low. A robust study in *JAMA Pediatrics* revealed that asymptomatic children presenting for elective medical and surgical care had a pooled prevalence of 0.65 percent out of 33,041 children in tests conducted across 28 children's hospitals.[5] That said, the incidence of SARS-CoV-2 is not random and this may not be an accurate reflection of the entire country.

Recent data published in *Pediatrics* reveals racial/ethnic and socioeconomic disparities of COVID-19 among children.[6] Among 1,000 children tested at a drive-through/walk-up testing site within one mile of Children's National Hospital in Washington D.C., the demographic breakdown of children who tested positive was 46 percent Latinx, 30 percent Black, and 7 percent white. Of the children who tested positive, 9 percent were children from families in the highest income quartile and 38 percent were in the lowest income quartile. These results corroborate findings published in *JAMA* from the Johns Hopkins Health System, which found that of 37,727 patients tested for COVID-19, the positivity rate was 42.6 percent for Latinx patients and 17.6 percent for Black patients.[7] To date, no data suggest that presenting symptoms of COVID-19 among children differ by race/ethnicity or socioeconomic status.

Children tend to have less severe disease compared to

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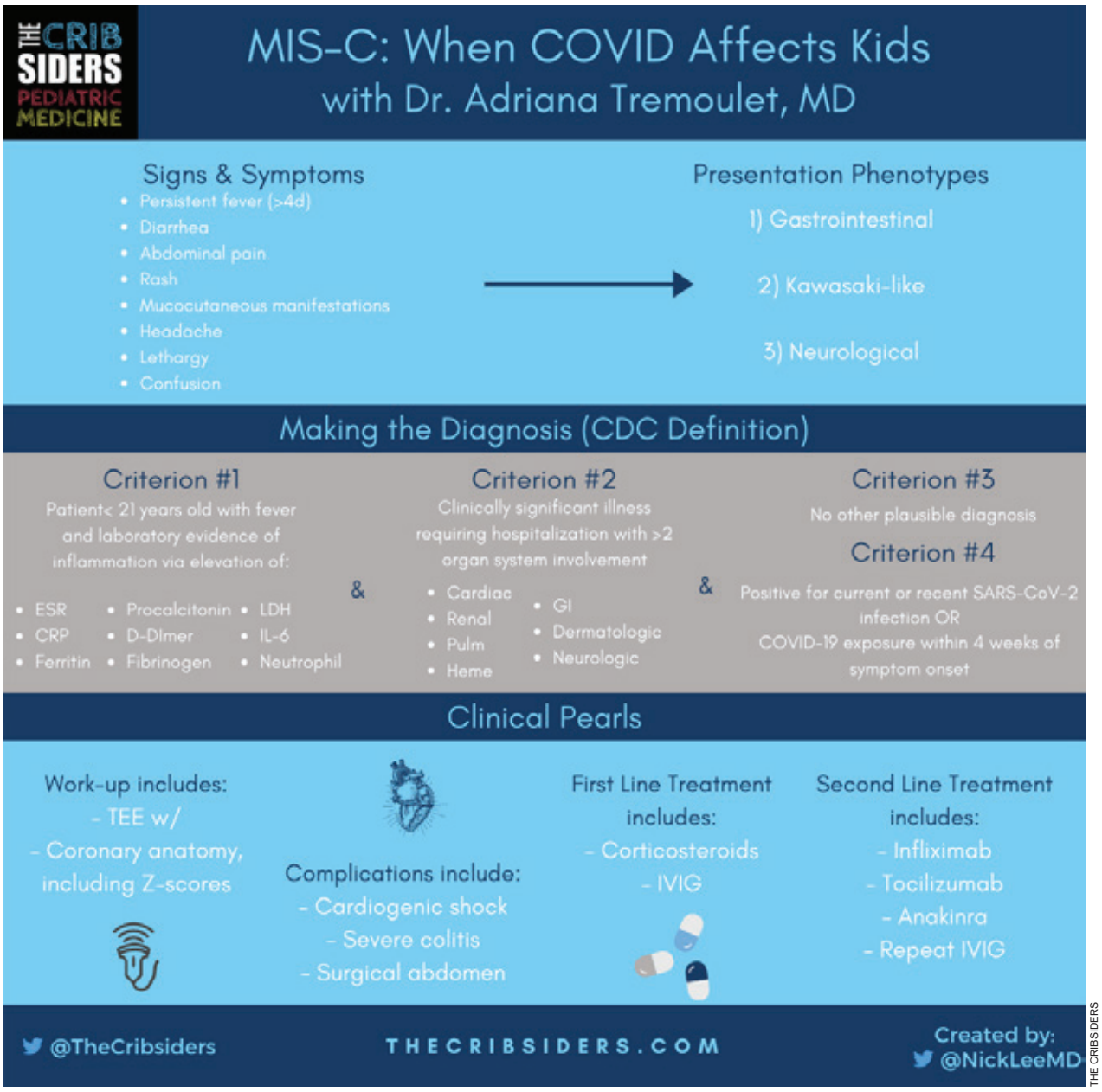

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adults. The CDC estimates the rate of hospitalization among children at 8.0 per 100,000 compared to adults at 164.5 per 100,000 population, with similar lower rates of mechanical ventilation and death.[2] Children with symptomatic COVID-19 often have nonspecific symptoms, including vague respiratory or only gastrointestinal symptoms. The most common presenting symptoms are cough and/or fever.[2] However, almost one-third of children admitted to the hospital are admitted to intensive care units.[8]

Multisystem Inflammatory Syndrome

A new complication of COVID-19 that is particularly devastating is the multisystem inflammatory syndrome in children (MIS-C).[9] While rare, it has received attention. The American College of Rheumatology defines MIS-C as an postinfectious inflammatory syndrome characterized by fever, inflammation, and multiorgan dysfunction that occurs late in the course of COVID-19 in children.[10] The new FOAMed website and podcast The Cribsiders (https://thecurbsiders.com/thecribsiders), led by internists and pediatricians from 15 different institutions across the country, recently published an episode dedicated to MIS-C.[11] In brief, the presentation of MIS-C seems to have three common phenotypes: Kawasaki-like, gastrointestinal, and neurologic. In Figure 1, the signs and symptoms, evaluation, and management of MIS-C are summarized. Interestingly, data from the CDC reveals that MIS-C is more prevalent among Latinx (38 percent) and Black (33 percent) children compared to white (15 percent) children.[12]

Finally, with respect to COVID-19 treatment, the evidence for children in the United States (and elsewhere) is an evolving area of research. Treatments for moderate-to-severe COVID-19, such as remdesivir and dexamethasone, have not been fully evaluated in children of different age groups. What is clear, however, is that children are vectors of the SARS-CoV-2 virus. They may be asymptomatic or have nonspecific symptoms, and a smaller subset can become quite ill from the acute illness or later as a result of MIS-C.

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EM LITERATURE OF NOTE

PEARLS FROM THE MEDICAL LITERATURE

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Updates from the Gut

Latest research on when to do an endoscopy and administer tranexamic acid

by RYAN PATRICK RADECKI, MD, MS

When COVID-19 reached the United States, emergency departments had one of two experiences. In places with large outbreaks, every ounce of energy went into taking care of critically ill patients. Everywhere else, emergency visits plummeted by 42 percent.[1] It was actually a quiet time.

Now, patient volumes are starting to return to normal in many areas. That means that the usual culprits are back in steady force. Depending on whether your emergency department is in a COVID-19 hotspot, you may feel the need either to rush patients to endoscopy (ie, keeping the emergency department and observation units as empty as possible) or delay the procedures out of a concern for the safety of everyone involved. Regardless of COVID-19, where do we stand on the question of how quickly patients with suspected upper gastrointestinal bleeding (UGIB) must have an endoscopy?

Best Timing for Endoscopy

The first of two important related articles released during the COVID-19 pandemic (and perhaps flying under the radar) looks at this.[2] Do GI consultants really need to answer our 2 a.m. pages and rally the team of nurses and equipment for endoscopy immediately?

CONTINUED *on page 20*

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The answer is surprising, especially considering how ill the patients enrolled in the first trial we'll discuss were. The authors recruited and enrolled patients with Glasgow-Blatchford Bleeding Scores (GBS) of 12 or above, which is considered "high risk" for an UGIB likely to require a medical intervention (transfusion, endoscopy, or surgery).

The median enrolled hemoglobin level was 7.4 g/dL, a third had tachycardia, and about a sixth were already hypotensive. Virtually all (90 percent) received a transfusion of packed red blood cells, with a mean requirement of 2.4 units. Patients were excluded if they were in hypotensive shock and unstable despite initial resuscitation (ie, the need for a procedure meant that waiting was not an option). In short, these were genuinely the sort of patients who are worrying to emergency physicians but not clearly in extremis.

The 516 patients randomized in this trial were sorted to either an "urgent endoscopy," endoscopy within six hours, or "early endoscopy," an endoscopy within 24 hours. All patients were treated with continuous infusion of high-dose proton-pump inhibitors, while those suspected of having variceal bleeding received vasoactive agents and antibiotics. The primary outcome of the study was mortality at 30 days following enrollment, with secondary measures of clinical progression, recurrence, and resource utilization.

The quick answer: Mortality was not significantly different between groups. The difference favored waiting for endoscopy, but the trial was not large enough to claim any sort of hidden trend. As might be expected, delaying endoscopy meant fewer patients with active bleeding identified and subsequently fewer interventions. Neither transfusion requirements nor occurrences of rebleeding were different, and there were no signs of potential hazard associated with waiting.

It should be noted there were 20 patients in the "early" endoscopy cohort who converted to "urgent" as a result of new hypotension, hematemesis, melena, or otherwise failing to respond to initial resuscitation. While these data indicate it is clearly safe to delay endoscopic evaluation, vigilance regarding possible deterioration is required. A little fewer than one in 10 patients may necessitate a change in plans.

When to Give Tranexamic Acid

The second new article on this topic represents a possible change in practice many of us have likely adopted or considered adopting already: Should emergency physicians be giving tranexamic acid (TXA) to patients with acute gastrointestinal bleeding?[3] After all, we've been giving it to patients with major bleeding in trauma, as well as considering it to be likely beneficial for those with severe head injuries and postpartum hemorrhage.[4–6]

Like other TXA trials, this latest trial was a massive undertaking, enrolling nearly 12,000 patients over six years across 164 hospitals. Patients were eligible for inclusion based on pragmatic, subjective clinical assessment. To be included, patients simply needed to be judged likely to have a significant or life-threatening gastrointestinal bleed. Disease severity was assessed using the Rockall Score, which differs from the GBS as it incorporates findings identified at endoscopy as well as clinical presentation. Overall, however, patients appeared similarly ill as the endoscopy study above when accounting for tachycardia, melena, and signs of shock.

In contrast to the other TXA trials, unfortunately, there is simply no way to parse these results in a fashion favoring the intervention. Whether measured in deaths due to bleeding, recurrent bleeding, or all-cause mortality, outcomes were virtually identical. A majority of patients required transfusion, and these transfusion requirements were not altered by whether TXA was given. Adverse events were rare, but a small excess of venous thromboembolic events was seen in the cohort receiving TXA. The absolute difference, even in this study of 12,000 patients, was just a handful but likely does reflect an increased risk for venous thromboembolism in those receiving TXA.

Considering neither the CRASH-2 nor WOMAN trial detected an increase in thromboembolic events, the risk seen with TXA here is likely related to this specific population enrolled with gastrointestinal bleeding. Conceptually, this makes sense. Nearly half the patients enrolled were described as having liver disease severe enough to be judged to potentially result in variceal bleeding. Patients with advanced liver disease maintain a balance of deranged hemostasis, with relative excess and absence of coagulation factors and components. It is likely that hypofibrinolytic underlying states tipped off-balance by TXA resulted in the observed increases in venous thromboembolism. Regardless of liver functional status, however, absent a detectable benefit for TXA in gastrointestinal bleeding, this trial reveals that this medication has no apparent role in the treatment of GIB.

Conclusions

In sum, we have two potentially practice-changing conclusions. First, even a very ill patient with UGIB undergoing transfusion may be managed medically for an extended period of time prior to a decision to perform an endoscopy, rather than requiring urgent intervention, provided they are hemodynamically stable. Second, if you've been extrapolating the potential advantage of TXA from other clinical applications to your gastrointestinal bleeding patients, it seems clear this is unlikely to help and may even result in a small amount of harm in a subset of patients.

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

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A Patient Transfer Leads to a Lawsuit

This case reminds us we can be sued for anything

by ERIC FUNK, MD

A difficult airway is every emergency physician's worst nightmare. The decision to intubate a patient needs to be coupled with adequate preparation, good communication with nurses and other team members, and a backup plan for possible complications.

These situations require rapid decision making under stress. The case below depicts a real-life situation that resulted in a medical malpractice lawsuit. The descriptions and figures shown are the actual evidence used in the lawsuit.

The Case

A 52-year-old woman presented to the emergency department with shortness of breath. She was brought to the emergency department in a wheelchair by her husband. The triage nurse immediately recognized that she was in severe respiratory distress. Her respirations were noted to be rapid and labored, and she had an audible gurgle. She was assigned a triage Level 1.

There were no available rooms, so she was put in a hallway bed. The physician was immediately at the bedside. He noted that she was cool, clammy, and grossly cyanotic. The patient was able to state that she did not have asthma or chronic obstructive pulmonary disease but did note a history of congestive heart failure. After a very limited history, the patient's respiratory status declined into complete apnea. The physician made an initial attempt at blind nasal intubation while the nurses started an IV, but he was unsuccessful. A second attempt was made, also with no success. By that time, the nurses had cleared a room and she was brought into the resuscitation bay. The patient's heart rate declined to 40 bpm on the monitor, a pulse could not be palpated, and chest compressions were started. One milligram of epinephrine was given.

By then, the nurses had established an IV, and 5 mg midazolam (Versed) was given. An oral intubation was attempted without any success. The doctor then elected to place a King Airway device. The patient was ventilated through the King Airway, return of spontaneous circulation was obtained, and her oxygen saturation increased to 97 percent.

A portion of the doctor's note describing the events is shown in Figure 1.

Over the next 10 minutes, the patient's oxygen saturation declined to the mid-80s. She was given lorazepam (Ativan) for sedation and furosemide (Lasix), as the physician suspected fluid overload. The physician also prescribed dexamethasone (Decadron) and diphenhydramine (Benadryl) to reduce airway swelling as well as metoprolol due to the fact that she was hypertensive. Outside medical records were obtained showing that she had a coronary artery bypass graft approximately 18 months earlier.

Figure 1

Nasal intubation was initially attempted due to her placement in a bed in the hall way rather than in an emergency bay. The attempt was unsuccessful due to lack of patient cooperation. Efforts were discontinued when the patient became apneic and she was expeditiously transferred to an emergency bay that had been cleared for her. Subsequent oral intubation was complicated by anatomy and a King esophageal obturator airway was placed. The patient had become bradycardic, initial hyperventilation by bag valve mask restored a normal heart rate. She did become bradycardic again and required intravenous epinephrine. After her airway was established a pulse and pressure returned.

Figure 2

FINAL DISCHARGE DIAGNOSES
1. Acute respiratory failure.
2. Status post cardiopulmonary arrest.
3. Anoxic brain injury.

Obtaining a Transfer

With her oxygen saturation holding in the 80s, the physician began the process to transfer her to a hospital with ICU capabilities. This process was unfortunately fraught with unnecessary delays. An emergency physician (Dr. H) at a regional medical center recommended that she be transferred to an academic center. The academic center was called, took down the patient's information, and said they would call back, but 30 minutes later there was still no response. The doctor then tried a third hospital, and the cardiologist on-call declined the admission until the emergency physician consulted the patient's outpatient cardiologist. The outpatient cardiologist worked at the first hospital that had been called, and he ultimately accepted the patient.

The patient departed the emergency department via helicopter with an oxygen saturation of approximately 80 percent. On arrival to the receiving hospital, her oxygen saturation was noted to be 40 percent. The anesthesia team was waiting for the patient at the bedside in the ICU, removed the King airway, and intubated the patient.

The patient's status continued to decline. She sadly passed away five days after going into the emergency department, with the final diagnoses shown in Figure 2.

The Lawsuit

The patient's family was understandably upset and contacted an attorney. The subsequent lawsuit is unusual and demonstrates an interesting legal twist emergency physicians should be aware of and understand. The lawsuit alleged an EMTALA violation by Dr. H, the emergency physician at the receiving hospital. He had originally recommended that the patient be transferred to a nearby academic medical center instead, but she ultimately was transferred to his facility after numerous phone calls. In addition to an alleged EMTALA violation, the lawsuit also alleged that he was negligent in his responsibility to the patient.

Dr. H was deposed (see Figure 3). He stated that he did not explicitly decline the transfer but that he was helping the sending physician brainstorm the best arrangement for the transfer.

Ultimately, Dr. H's attorneys filed for summary judgment. The lawsuit was dismissed because EMTALA allows for legal action against hospitals but not against individual physicians. Further, the defense asserted that Dr. H could not be personally liable for negligence because he did not establish a relationship with the patient solely on the basis of taking a phone call about her possible transfer.

Learning Points

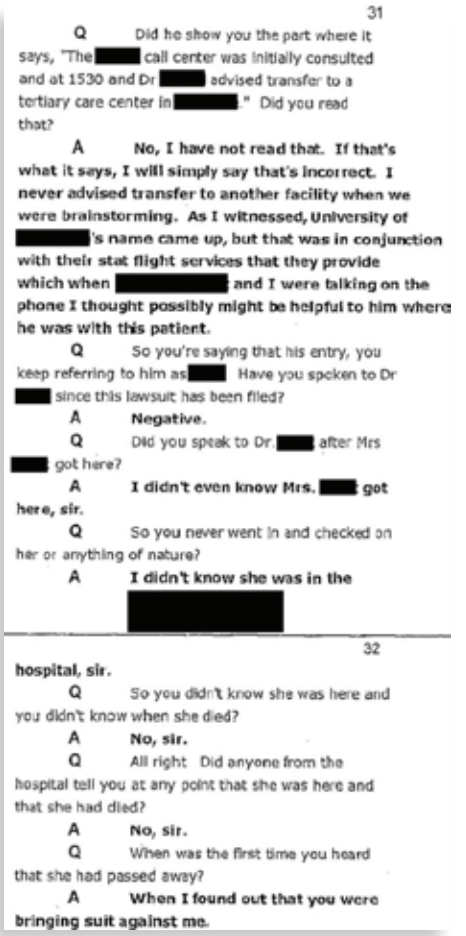
The initial approach to intubation was challenging due to a precipitous arrival to the emergency department and the fact that there were no appropriate rooms available. Without the correct setting and tools, no physician can be successful. Administrators and directors are responsible for putting physicians in a position to succeed. The decision to rapidly proceed with nasal intubation and without rapid sequence intubation (RSI) medications is suspect. Instead, giving bag-valve mask-assisted ventilations while IV access was established and RSI medications were prepared may have temporized the situation and permitted the possibility of a better outcome. That said, moving to a King Airway or supraglottic device shows the physician had a backup plan, which should always be in the forefront of the mind when performing an intubation.

The patient's transfer proved challenging for the emergency physician. He made numerous calls to several institutions before eventually sending the patient to the first hospital he had called. This prolonged delay did the patient no favors. Physicians working in large medical centers sometimes have difficulty understanding the situation in rural emergency departments. They should keep in mind the challenges of working in a small hospital with limited resources. There have been numerous lawsuits that involved determining precisely when a consulting or receiving physician establishes a patient-doctor relationship. The issue is murky and can vary in different states and by the facts of the case.

Finally, this case involved an alleged EMTALA violation as opposed to standard medical negligence. As demonstrated in this instance, an EMTALA lawsuit brought by a patient against an individual physician is unlikely to succeed. However, this does not mean that doctors are free from punishment for EMTALA violations. The Centers for Medicare and Medicaid Services and the Office of the Inspector General have enforcement powers that include fines up to $50,000 for physicians.

This case also illustrates the false security of the idea that "you can't be sued for that." You can be sued for *anything*, and even if you are correct, the process is unpleasant. Despite Dr. H's ultimate vindication, he undoubtedly had numerous meetings with attorneys, spent hours in depositions, and felt a lot of stress over the multiyear course of the lawsuit—and his attorneys certainly did not work for free.

Figure 3



31

Q Did he show you the part where it says, "The [redacted] call center was initially consulted and at 1530 and Dr [redacted] advised transfer to a tertiary care center in [redacted]." Did you read that?

A **No, I have not read that. If that's what it says, I will simply say that's incorrect. I never advised transfer to another facility when we were brainstorming. As I witnessed, University of [redacted]'s name came up, but that was in conjunction with their stat flight services that they provide which when [redacted] and I were talking on the phone I thought possibly might be helpful to him where he was with this patient.**

Q So you're saying that his entry, you keep referring to him as [redacted] Have you spoken to Dr [redacted] since this lawsuit has been filed?

A **Negative.**

Q Did you speak to Dr. [redacted] after Mrs [redacted] got here?

A **I didn't even know Mrs. [redacted] got here, sir.**

Q So you never went in and checked on her or anything of nature?

A **I didn't know she was in the [redacted]**

32

hospital, sir.

Q So you didn't know she was here and you didn't know when she died?

A **No, sir.**

Q All right Did anyone from the hospital tell you at any point that she was here and that she had died?

A **No, sir.**

Q When was the first time you heard that she had passed away?

A **When I found out that you were bringing suit against me.**

SEE THE RECORDS

To read the entire medical record from this case, depositions of the staff involved, and more details about the lawsuit, visit www.medmalreviewer.com/case-6-respiratory-arrest.

BE A MEDICAL DETECTIVE—BONE UP ON YOUR FORENSIC SKILLS

FORENSIC FACTS

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DR. RIVIELLO is chair and professor of emergency medicine at the University of Texas Health Science Center at San Antonio.

Institutional Elder Abuse

Early recognition in the ED is a key factor in stopping abuse

by HEATHER ROZZI, MD, FACEP; AND RALPH RIVIELLO, MD, FACEP

The Case

A 74-year-old female nursing home resident with moderate dementia presents with her daughter for evaluation of rash to the mother's face and arms (see Figure 1). The daughter has not seen her mother for several weeks due to COVID-19 visitation restrictions. The nursing home cannot explain how the resident got the bruises. There were no reports of a fall. The last time the daughter video-chatted with her mom was about two weeks ago. The daughter also says her mom seems quieter and more withdrawn than usual. Her mother seemed fearful of the male medics who transported her to the emergency department.

Discussion

The Centers for Disease Control and Prevention defines elder abuse as "an intentional act or failure to act that causes or creates a risk of harm to an older adult. An older adult is someone age 60 or older. The abuse often occurs at the hands of a caregiver or a person the elder trusts."[1] Legal definitions vary from state to state. Elder abuse can be further divided into neglect (the most common form of abuse), physical abuse, sexual abuse, financial abuse, and emotional/psychological abuse.

Elder abuse is a serious problem and a public health emergency. It is estimated that one in 10 people older than 60 who live at home are abused.[2,3] This is likely a substantial underestimate as studies often only look at ED visits and not other sites of care like primary care offices and clinics. A high number of cases are thought to go unreported because patients do not have someone who can advocate on their behalf.

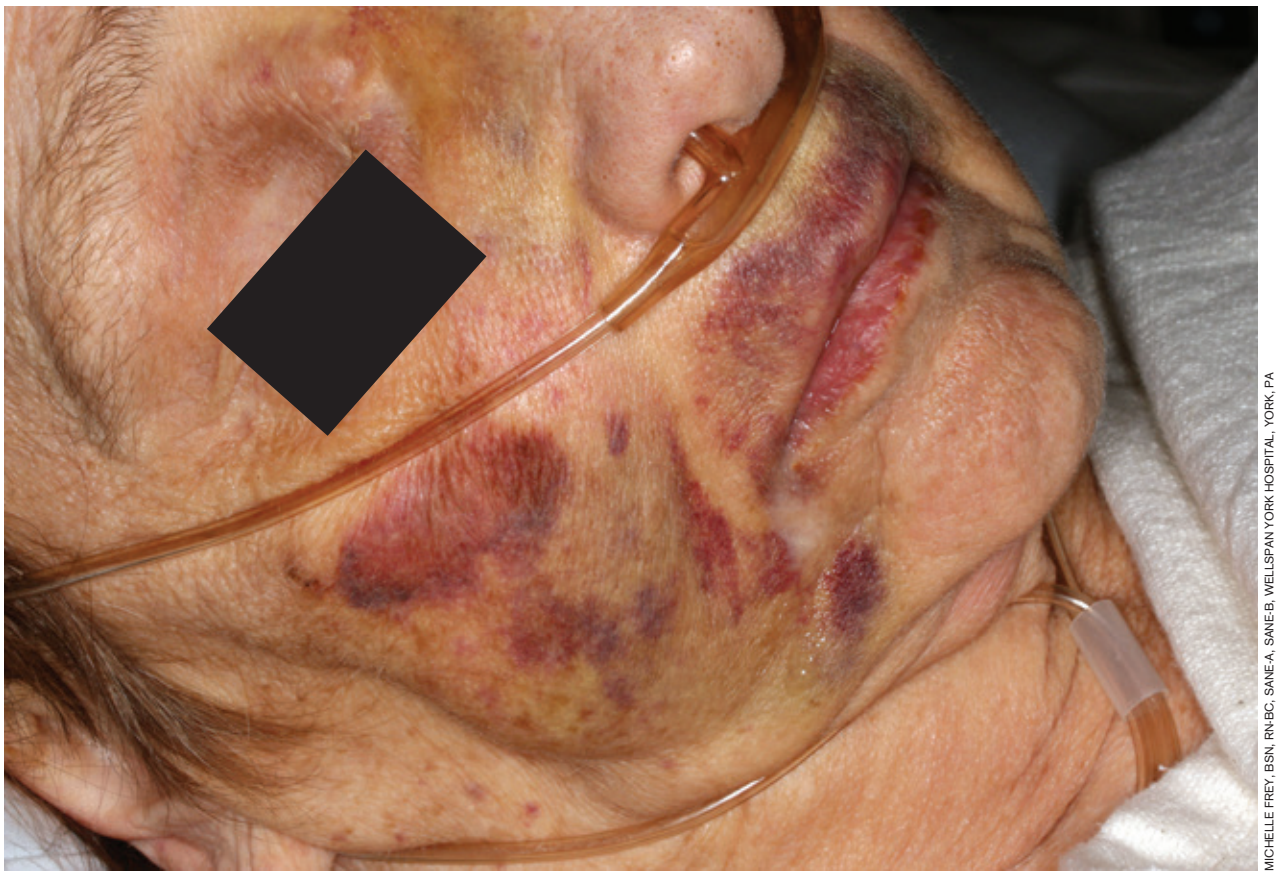
There are numerous physical and emotional effects of elder abuse. Physical injuries can be minor or severe and can cause lasting or permanent disabilities. These injuries can lead to premature death and worsen existing health problems. There are also immediate and long-term emotional effects. Victims are often fearful and anxious. They may have problems trusting others and are wary around them.

There are several identified risk and protective factors for elder abuse perpetration. Risk factors can be divided as individual, relationship, institutional, and societal. Individual factors include: current diagnosis of mental illness, alcohol or drug abuse, high levels of hostility, poor or inadequate preparation or training for caregiving responsibilities, early age assumption of caregiving responsibilities, inadequate coping skills, and exposure to abuse as a child. Relationship factors include: high financial and emotional dependence upon a vulnerable elder, past experience of disruptive behavior, lack of social support, and lack of formal support. Institutional factors include: unsympathetic or negative attitudes toward residents, chronic staffing problems, and lack of administrative oversight, staff burnout, and stressful working conditions. Societal factors include a culture where there is high tolerance and acceptance of aggressive behavior; health care personnel, guardians, and other agents are given greater freedom in routine care and decision making; family members are expected to care for elders without seeking help from others; persons are encouraged to endure suffering or remain silent regarding any pain and suffering; and negative beliefs about aging and elders exist.[4,5] It should be noted, however, that the presence of risk factors does not necessarily mean an elder will be abused.

Protective factors against elder abuse have not been as extensively studied as risk factors. Institutional protective factors include effective monitoring systems, solid institutional policies and procedures regarding patient care regular training on elder abuse and neglect for employees; education and clear guidance on durable power of attorney and how it is to be used; and regular visits by family members, volunteers, and social workers. The other factors are based on strong sense of community; respect for elders; and healthy, strong relationships.

In additional to the protective factors and elder abuse prevention strategies, one of the key factors in stopping abuse is early recognition by health care workers. Elders should be screened for abuse using any of several validated tools. In the emergency department, there are several red flags that should alert the care team to the possibility that an elder is being abused. These include a lack of basic hygiene, food, medical aids, and clean and appropriate clothing; a person with dementia left unsupervised; a bed-bound person left without care; untreated or unusual pressure sores/ulcers; a caregiver who isolates the elder; a caregiver who is verbally aggressive or demeaning to the elder; inadequately explained fractures, bruises, welts, cuts, sores, or burns; a delay in seeking care for obvious injuries or conditions; unexplained sexually transmitted infections; and behavioral changes.[6]

Health care workers in most states are mandated reporters of elder abuse and should alert the proper authorities and adult protective services when abuse or neglect is suspected. Patients may require additional workup to determine abuse from progression of chronic diseases, as well as admission to the hospital for the patient's protection.



A 74-year-old woman with a rash on her face and arms.

MICHELLE FREY, BSN, RN-BC, SANE-A, SANE-B, WELLSPAN YORK HOSPITAL, YORK, PA

KEY POINTS

- Elder abuse is a serious health problem.
- Any elder is potentially at risk.
- Elder abuse may not always be readily evident.
- The risk factors for elder abuse are contributing factors, not direct causes.
- Health care workers should screen elders and have a high index of suspicion when red flags are present.
- Treatment includes a multidisciplinary approach including geriatric medicine, social services, law enforcement, and adult protective services.

Case Outcome

The emergency physician was concerned that the rash was actually bruising and suspected elder abuse. Labs, X-rays, and CT scans were negative. A forensic nurse examiner was consulted. On exam, in addition to the bruises, there was evidence of genital injury and vaginal discharge, which subsequently tested positive for chlamydia. Based on the concern for abuse, police and adult protective services were consulted. An investigation identified a dietary worker at the nursing home as the perpetrator.

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DOING THE MATH TO BENEFIT OUR SPECIALTY

THE EQUITY EQUATION

DR. GIWA is associate professor of emergency medicine at the Icahn School of Medicine at Mount Sinai Hospital in New York City. He is the founding Chair of the American Academy of Emergency Medicine's Ethics Committee, and a former member of the ACEP Ethics Committee.

To All People Staying Neutral About Black Lives Matter

An eight-minute video caused me to question my neutrality

by AL GIWA, LLB, MD, MBA, MBE

Physicians from the University of Pennsylvania participate in a protest on June 7, 2020.

FELIPE TERAN, MD, FACEP (@FTERANMD)

Just when we thought life in 2020 couldn't get any worse after the COVID-19 pandemic began to wreak havoc, social unrest broke out all over country. Some saw yet another a series of lynchings. Others saw just another round of uprising. And some just didn't want to be bothered, did not want to take a stand, let alone voice an opinion. It is you, my fellow "stay out of it" colleagues, whom I'd like to address.

At first, I was like so many of you when it came to people crying injustice at the hands of the police. I refused to fall prey to the cop bashing or twisting the narrative from an unarmed person being shot to it being justice for a "bad hombre." Personally, I think I was in denial because, in my mind, that was "their" problem. But in reality, I am one of them.

These last few years (and months) have revealed the continued racial disharmony that exists in America, most pronounced between Blacks and whites. (Many briefly focused their hate on Asians during the initial outbreak of the COVID-19 pandemic, but that seems to have faded now.)

When the Black Lives Matter movement emerged after the killing of unarmed Black people, I must confess that I was initially conflicted about it. After all, I had drunk the Kool-Aid; I was "a good Negro." I moved to the suburbs and did all the necessary things to be accepted by white America. Most important, I never brought attention to my Blackness, nor involved myself in anything that could be considered divisive or offensive, lest I offended anyone's sensibilities. I supported arguments that seemed, on the surface, to make sense, and even echoed that "all lives matter." Why were those Black "troublemakers" being so divisive and running counter to becoming a more united people?

So when reports of unarmed Black men and women dying at the hands of police officers started appearing in the media again and again, I largely avoided discussing it. I listened to the narrative that discouraged second-guessing police officers who must make life-or-death decisions in a split second, which is hard for the media to capture.

However, I began to ruminate out loud about my own—and most especially my kids'—safety at the hands of a police officer. I reassured myself that *those* Black people were *different*. After all, why were they struggling with an officer to begin with? Why were they running away if they were innocent? Why were they speaking back to the officers so rudely? Innocent people don't do that. Or do they?

Then George Floyd was killed. And it was there on tape. Almost eight minutes of it. And it became painfully clear. *I am one of them.*

Despite my being part of a respected profession, when I enter a convenience store, no one seems to recognize my education or multiple advanced degrees. Instead, I become just another Black man. Apparently, that means I require additional scrutiny afforded only to people of color in the United States and many other places. Once you have been profiled and assumed to be a criminal just because of the color of your skin, it is very hard to say things are "fair" or that one should be "grateful" for the opportunities and "privilege" to be in this country. One thing that white privilege has made painfully obvious is a lack of awareness of racial injustices that are everyday realities for people of color. So despite my upbringing, education, and current living circumstances, *I am one of them.*

One of my proudest accomplishments was becoming an officer in the U.S. Armed Forces. I work alongside courageous men and women from all socioeconomic, racial, and national origins. My desire to serve was born out of an upbringing that prioritized hard work, dedication, and responsibility, as well as a belief in the duty to serve to one's nation. I accepted the calling and now proud-

CONTINUED *on page 24*

EQUITY EQUATION

CONTINUED FROM PAGE 23

ly take care of the men and women of the Armed Forces, who ensure the liberties for each and every one of us in this country. My military service has taken me to many parts of the country where race relations are not always the best. But wearing this uniform has given me access and exposure to people I would normally never be able to speak to personally. I am happy that I have been able to be a real-life person who shatters negative preconceptions of Black people to those willing to listen. But at the end of the day, *I am still one of them*.

As a soldier and officer in the U.S. Army, I am aware and appreciate the daily sacrifices of the women and men who serve and protect the public in this country. The job is unenviable and often thankless, and I truly salute their service. However, just like there are bad apples in the U.S. military (eg, some of those who served at Abu Ghraib), we, as a people, should demand accountability from our police and military service members. Law enforcement agencies need to institute protective measures for the public through better and accountable reporting mechanisms, ensuring leaders have zero tolerance for the "fraternity of silence" that keeps the actions of bad cops hidden. We need to improve neighborhood outreach through education and immersion. We need to evaluate the processes and procedures that lead to the clear racial disparities around when force is used disproportionately on people of color. I am a Black man who supports accountable policing and Black lives, *as I am one of them*.

For me, it took accidentally stumbling across comedian Trevor Noah's poignant discussions on what the Black Lives Matter movement truly meant for me to finally understand that unless Black lives matter, "all lives matter" carries no meaning. Until then, I missed that in the screaming and protesting by angry Black people was not just their anger but my suppressed anger, too. Their screams were my screams. Their sense of betrayal and injustice were the same as mine even in the ivory towers of academic medicine. I could have been George Floyd; in fact, I was George Floyd. Each and every person of color in America is George Floyd; all of us are just an incident away from having our breath permanently taken away for doing nothing except living Black in America.

So, yes, all lives matter—but only when every life is respected or cared for like every other life. For too long, we've ignored that the most urgent work in this area, the opportunity for the most improvement, is to first insist that Black lives matter.

Let's start to fix it. Let's ensure that Black lives, brown lives, and all other lives really do matter the same. Let's stop just watching others' lives being subjugated to unfair treatment, hoping to avoid controversy. Let's stop pretending that a good education and a house in the suburbs are the cure. They aren't. That realization finally hit home for Americans of all colors this summer. Continuing to ignore it is not much better than someone kneeling on a Black man's neck for eight minutes. It is time we realize *WE are all one of them*.

As Desmond Tutu said, "If you are neutral in situations of injustice, you have chosen the side of the oppressor."

DOGMA FEELS RIGHT UNTIL YOU STEP IN IT

SKEPTICS' GUIDE TO EMERGENCY MEDICINE

Dr. Milne is chief of emergency medicine and chief of staff at South Huron Hospital, Ontario, Canada. He is on the Best Evidence in Emergency Medicine faculty and is creator of the knowledge translation project the Skeptics' Guide to Emergency Medicine (www.TheSGEM.com).

And Then There Were None

Randomized controlled trials show lack of efficacy of tPA in acute ischemic stroke

by KEN MILNE, MD

The Case

A 71-year-old woman arrives to the ED by EMS with right-sided weakness beginning 3 hours prior. Immediate neuroimaging demonstrates she does not qualify for endovascular clot retrieval. She has a National Institutes of Health Stroke Scale (NIHSS) score of 12 and no contraindications for systemic thrombolysis.

Clinical Question

Is tissue plasminogen activator (tPA) safe and effective 3–4.5 hours after onset of symptoms in patients with acute ischemic stroke (AIS)?

Background

One of the most debated subjects in EM over the years is the use of thrombolytics in AIS. The controversy goes back to 1995 when the National Institute of Neurological Disorders and Stroke (NINDS) trial was published.[1] This was the first randomized controlled trial (RCT) to claim efficacy for tPA in patients presenting with stroke symptoms of less than 3 hours. The authors of NINDS reported a 12 percent absolute benefit (good neurological outcome on the modified Rankin Scale [mRS]) at 90 days, with a 6 percent absolute increase in harm (bleeding).

A reanalysis of the NINDS data published in 2009 revealed that a baseline imbalance in stroke severity at presentation likely led to the difference in outcomes.[2] After controlling for these baseline differences, the claimed efficacy of tPA was no longer statistically significant.

There's only one other RCT claiming benefit for the primary outcome of thrombolytics in AIS—the ECASS-III trial that gave tPA 3–4.5 hours after stroke symptom onset.[3] ECASS-I and -II did not show a benefit with thrombolysis but did find an increase in harm (7 percent increase in mortality and 7 percent increase in intracranial hemorrhage, respectively).

The ECASS-III trial reported a 7 percent absolute benefit of improved mRS at 90 days compared to placebo, 9 percent increase in intracranial hemorrhage, 2 percent increase in symptomatic intracranial hemorrhage, and no significant difference in mortality.

NINDS and ECASS-III informed the ACEP clinical policy statement on the issue.[4] The policy looked at the less than 3-hour time frame and the 3–4.5-hour time frame and made no level A recommendations, but it did make level B and C recommendations:

- Is IV tPA safe and effective for patients with AIS if given within 3 hours of symptom onset?
  - » **Level B Recommendations:** With a goal to improve functional outcomes, IV tPA should be offered and may be given to selected patients with AIS within 3 hours after symptom onset at institutions where systems are in place to safely administer the medication. The increased risk of symptomatic intracerebral hemorrhage (sICH) should be considered when deciding whether to administer IV tPA to patients with AIS.
  - » **Level C Recommendations:** When feasible, shared decision-making between the patient (and/or their surrogate) and a member of the health care team should include a discussion of potential benefits and harms prior to deciding whether to administer IV tPA for AIS. (Consensus recommendation.)
- Is IV tPA safe and effective for patients with AIS treated between 3–4.5 hours after symptom onset?
  - » **Level B Recommendations:** Despite the known risk of sICH and the variability in the degree of benefit in functional outcomes, IV tPA may be offered and may be given to carefully selected patients with AIS within 3–4.5 hours after symptom onset at institutions where systems are in place to safely administer the medication.
  - » **Level C Recommendations:** When feasible, shared decision-making between the patient (and/or their surrogate) and a member of the care team should include a discussion of potential benefits and harms prior to the decision whether to administer IV tPA for AIS. (Consensus recommendation.)

Now, 12 years after the publication of ECASS-III, a reanalysis of the RCT—similar to the reanalysis of the NINDS trial 14 years after it was published—has been published.

Reference: Alper BS, Foster G, Thabane L, et al. Thrombolysis with alteplase 3–4.5 hours after acute ischemic stroke: trial reanalysis adjusted for baseline imbalances [published online ahead of print May 19, 2020]. *BMJ Evid Based Med*.

- **Population:** Adult patients age 18–80 years with at least 30 minutes of AIS symptoms presenting between 3–4.5 hours after onset of symptoms with no significant improvement.
  - » **Main Exclusion:** Multiple exclusions were listed in the manuscript.
- **Intervention:** tPA 0.9 mg/kg;initial 10 percent bolus, remainder given over 60 min.
- **Comparison:** Placebo.
- **Outcomes:**
  - » **Primary:** mRS score 0–1 (favorable) versus 2–6 (unfavorable) at 90 days.
  - » **Secondary:** Global outcome measure

CONTINUED *on page 26*

Table 1: Trials Involving Thrombolytics for Acute Ischemic Stroke

TRIAL	NUMBER OF PATIENTS	REFERENCE	TIME TO TREATMENT	THROMBOLYTICS	RESULTS
MAST-Italy	622	*Lancet.* 1995;3461509-1514.	<6 hours	Streptokinase	No difference in primary benefit, increased chance of early death.
ECASS-I	620	*JAMA* 1995;274:1017-1025.	<6 hours	tPA	No difference on disability scores and 7% increase in mortality.
NINDS-I	291	*N Engl J Med.* 1995;333:1581-1588.	<3 hours	tPA	No difference in symptoms or 3-month outcomes.
NINDS-II*	333	*Ann Emerg Med.* 2009;54:329-336	<3 hours	tPA	No difference in favorable mRS at 90 days, 6% absolute increase in brain bleeds, and no mortality difference.
MAST- Europe	310	*N Engl J Med.* 1996;335:145-150.	<6 hours	Streptokinase	No difference in death or disability at 3–6 months, 18% increase in brain bleed, and stopped early due to harm.
ASK	340	*JAMA.* 1996; 276:961-966.	<4 hours	Streptokinase	No difference in death or disability at 3 months, 10% increase in brain bleeds, and stopped early due to harm.
ECASS-II	800	*Lancet.* 1998;352:1245-1251.	<6 hours	tPA	No difference in outcomes on the mRS or mortality, and 7% increase in brain bleeds.
ATLANTIS-B	613	*JAMA.* 1999; 282:2019-2026.	3–5 hours	tPA	No difference in neurologic recovery and stopped early because "unlikely to prove beneficial."
ATLANTIS-A	142	*Stroke.* 2000; 31:811-816.	<6 hours	tPA	No benefit in NIH stroke scale at 30 days, 18% greater risk of mortality, and stopped early due to harm.
ECASS-III **	821	*BMJ Evid Based Med.* 2020. doi: 10.1136/bmjebm-2020-111386.	3–4.5 hours	tPA	No difference in favorable mRS score after 90 days, and 9% increased rate of brain bleed.
DIAS-2	193	*Lancet Neuro.* 2009;8:141-150.	3–9 hours	Desmoteplase	No difference in clinical response, and increased rate of brain bleed.
IST-3	3035	*Lancet.* 2012; 379:2352-2363.	<6 hours	tPA	No difference in mortality or independence after 6 months, 4% increase in death at 1 week, and 6% increase in fatal or non-fatal brain bleeding.
DIAS-3	492	*Lancet Neuro.* 2015;14:575-584.	3–9 hours	Desmoteplase	No difference in favorable mRS at 90 days, and no difference in major adverse events.

* Reanalysis of NINDS-2 ** Reanalysis of ECASS-III Red indicates trials that were stopped before completion.

combining 90-day outcomes of mRS 0–1, ≥95 Barthel Index, NIHSS score 0–1, score of 1 Glasgow Outcome Scale; mortality at 90 days; any ICH, sICH, symptomatic edema, and other serious adverse events.

Authors' Conclusions

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

Key Results

ECASS-III included 821 patients with a mean age of 65 years and 60 percent male. After adjusting for baseline imbalances, multiple methods failed to find statistically significant benefits with thrombolysis given 3–4.5 hours after stroke onset and confirmed the significant increase in harm.

Evidence-Based Medicine Commentary

1. Inter-rater reliability (IRR): The outcome assessment used mRS. The IRR for mRS is moderate at best.[5,6] A clinical trial has internal validity only if imbalances between groups and bias in the assessment of outcome and chance have been excluded as possible explanations for the observed difference in outcomes.

2. Fragility index (FI): The FI is another way to represent the data, and it's statistically reproducible.[7] FI is the minimum number of patients who would need to have a different outcome to change the *P* value from <0.05 to >0.05, although the 0.05 threshold as a measure of statistical significance has its own problems.[8] A low FI means only a small number of patients would need to have their outcome change for the trial to lose statistical significance. The FI of the original ECASS-III data is 1, meaning only one patient would need to have a different outcome to change the result. This is consistent with the reanalysis study by Alper et al, which found no significant benefit for tPA.

Other data for this time window support the fragility of ECASS-III data. IST-3 was the largest RCT investigating tPA for AIS in treated patients up to 6 hours.[9] It didn't show a benefit for its primary outcome. The pre-specified 3–4.5-hour subgroup was around double that of ECASS-III (n=1,177 versus n=821). IST-3 had a significant decrease in good neurologic outcome in patients randomized to tPA (32 percent) versus placebo (38 percent).

3. Baseline imbalances: A strong predictor of stroke outcome is severity of symptoms at presentation. There was an important baseline imbalance in stroke between the two groups in the ECASS-III trial. Those randomized to placebo had a worse median and mean baseline NIHSS score.

Another difference between the two groups was that double the number of patients with a history of a previous stroke (7.7 percent tPA versus 14.1 percent placebo; $P = 0.003$) appeared in the placebo arm. Recurrent strokes have a worse outcome than first strokes. The statistical difference in outcome favoring tPA over placebo could be explained by the baseline imbalance.

Bottom Line

Reanalysis of the original ECASS-III data does not support a patient-oriented benefit of tPA given 3–4.5 hours after onset of stroke symptoms and confirms the known potential harm.

Summary of Thrombolytics for AIS

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

The table does not include two newer RCTs looking at extending the therapeutic window to 4.5–9 hours. These newer trials were done with more advanced brain imaging, selecting patients with a perfusion mismatch. Both RCTs were stopped early, which can introduce bias toward efficacy. In addition, the majority of patients included in these trials would now qualify for endovascular therapy (EVT) clot retrieval. EVT has more evidence for efficacy than systemic thrombolysis and a recent RCT has shown that EVT alone is noninferior to EVT plus tPA.

Case Resolution

You provide the patient with the latest information on thrombolytics for stroke. Her mental status is intact and she clearly understands the information as presented. She elects not to move forward with systemic tPA administration.

Thank you to Prof. Daniel Fatovich, an emergency physician at Royal Perth Hospital in western Australia and the head of the Centre for Clinical Research in EM, for his help with this review.

Remember to be skeptical of anything you learn, even if you heard it on the Skeptics' Guide to Emergency Medicine.

Visit ACEPNow.com for references and additional reading recommendations for this article.

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