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Racism in medicine: Implicit and explicit

By Sarah Ludwig Rausch
MDedge News

With the violent deaths of Breonna Taylor, George Floyd, and other Black citizens setting off protests and unrest, race was at the forefront of national conversation in the United States – along with COVID-19 – over the past year.

"We've heard things like, 'We're in a post-racial society,' but I think 2020 in particular has emphasized that we're not," said Gregory Johnson, MD, SFHM, chief medical officer of hospital medicine at Sound Physicians, a national physician practice. "Racism is very present in our lives, it's very present in our world, and it is absolutely present in medicine."

Yes, race is still an issue in the United States as we head into 2021, though this may have come as something of a surprise to people who do not live with racism daily.

Continued on page 14

Dr. Ndidi Unaka, hospitalist and associate program director of the pediatric residency training program at Cincinnati Children's Hospital

Michael Wilson/Cincinnati Children's Hospital

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Hospitalist movers and shakers

By Matt Pesyna

Daniel Steinberg, MD, SFHM, recently was among 10 medical educators across the country to receive the Accreditation Council for Graduate Medical Education 2021 Parker J. Palmer Courage to Teach Award. Considered the most prestigious award given to graduate medical education program directors, it "recognizes program directors who have fostered innovation and improvement in their residency/fellowship program and served as exemplary role models for residents and fellows."


Dr. Steinberg

Dr. Steinberg was program director for internal medicine residency at Mount Sinai Beth Israel, New York, for 11 years (2009-2020) before becoming associate dean for quality and patient safety in graduate medical education in September. He is a professor of medicine and medical education at Icahn School of Medicine at Mount Sinai, New York.

Dr. Steinberg also is a leader within SHM, serving on the education, physicians-in-training, and annual conference committees. He is the course director for SHM Converge 2021.

Ann Sheehy, MD, SFHM, was honored in a virtual ceremony in December 2020 by the University of Wisconsin celebrating Physician Excellence Award winners. She was presented with the Physician Excellence Leadership Award.


Dr. Sheehy

Dr. Sheehy is division chief of the division of hospital medicine at the University of Wisconsin–Madison, and chair of the SHM Public Policy Committee.

Donald Schmidt, MD, has been named chief medical officer and vice president of medical affairs at Madonna Rehabilitation Hospitals in Omaha and Lincoln, Neb. He will replace Thomas Stalder, MD, who is retiring. Dr. Schmidt brings 20 years of experience to Madonna Rehabilitation Hospitals, including his most recent post as a hospitalist and medical director of the hospitalist program at Catholic Health Initiatives Health St. Elizabeth in Lincoln.

Dr. Schmidt currently serves on the board of directors for OneHealth Nebraska, an independent physicians association.

Ezinne Nwude, MD, recently was presented with the SCP Health Excellence in Leadership Award during the organization's Medical Leadership Conference. Dr. Nwude is chief of staff and hospitalist at the Medical Center of South Arkansas, El Dorado.

SCP Health coordinates staffing for more than 7,500 providers covering 30 states and is one of the nation's largest clinical practice management companies. More than 420 medical leaders nationwide were eligible for the award. Dr. Nwude has focused on positive culture and health education since her start at MSCA in 2014. She has been chief of staff since October 2018.

RWJ Barnabas Health (West Orange, N.J.) recently named two new health system leaders from among its hospital medicine ranks, as **Christopher Freer, MD,** was selected as senior vice president for emergency and hospital medicine, and **Maninder "Dolly" Abraham, MD,** was picked as chief of hospital medicine. The moves were made as RWJBH takes over as the direct employer for Envision Physician Services in Nashville, Tenn.

Dr. Freer was elevated to her new role after spending the past 5 years as RWJBH's system director for emergency services. He has nearly 3 decades of experience in hospital medicine.

Dr. Abraham comes to his new position after directing the hospitalist program at Saint Barnabas and serving as regional medical director with Envision.

Newman Regional Health (Emporia, Kan.) recently established a partnership with **FreeState Healthcare** (Wichita, Kan.). FreeState will be responsible for providing hospitalist services to adult inpatients and observation patients at Newman Regional Health during overnights.

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

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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

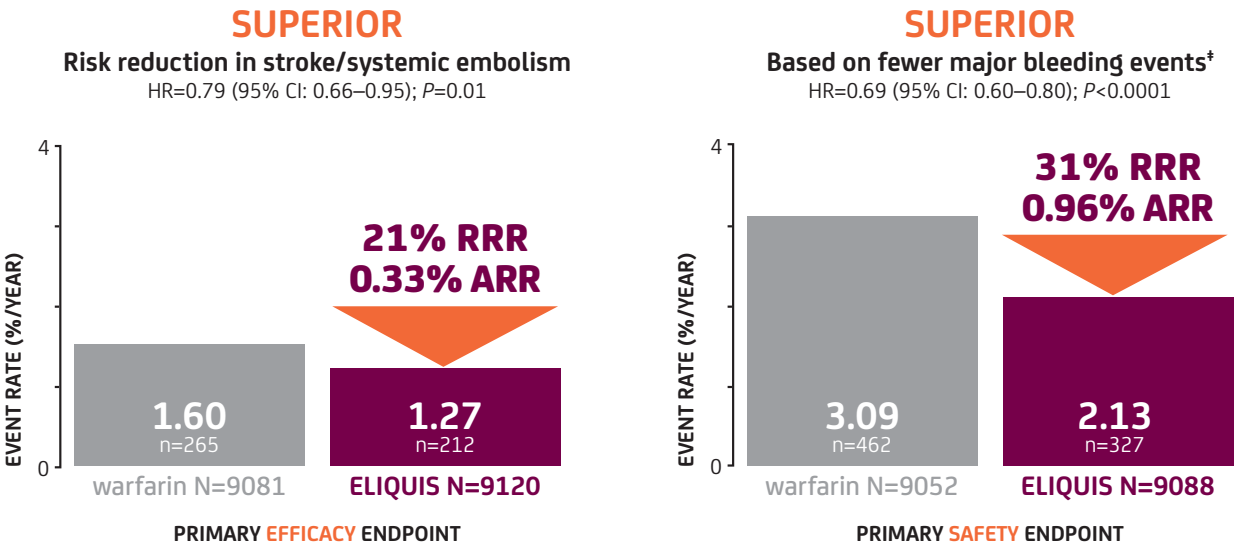
- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is 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; CI=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.

Eliquis® (apixaban) tablets 5mg 2.5mg

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ELIQUIS® (apixaban) tablets, for oral use

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

Reversal of Anticoagulant Effect

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

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

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

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

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

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

Other Adverse Reactions

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

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

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

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

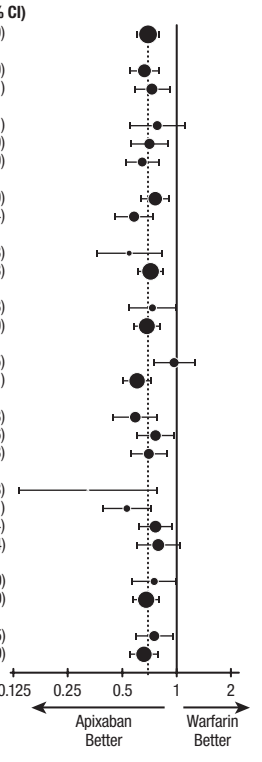
Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

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

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

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

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



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

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

* CRNM = clinically relevant nonmajor bleeding.

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

* CRNM = clinically relevant nonmajor bleeding.

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Combined P-gp and Strong CYP3A4 Inhibitors

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

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

Clarithromycin

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

Combined P-gp and Strong CYP3A4 Inducers

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Fetal/Neonatal adverse reactions

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

Labor or delivery

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

Data

Animal Data

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

Lactation

Risk Summary

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

Data

Animal Data

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

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

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

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

Patients with End-Stage Renal Disease on Dialysis

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

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

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

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

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

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‘Hospital at home’ increases COVID capacity in large study

By Ken Terry

2K Studio/Getty Images

A “hospital at home” (HaH) program at Atrium Health, a large integrated delivery system in the Southeast, expanded its hospital capacity during the early phase of the COVID-19 pandemic by providing hospital-level acute care to COVID-19 patients at home, according to a new study in Annals of Internal Medicine.

“Virtual hospital programs have the potential to provide health systems with additional inpatient capacity during the COVID-19 pandemic and beyond,” wrote Kranthi Sitammagari, MD, from the Atrium Health Hospitalist Group, Monroe, N.C., and colleagues.

Whereas most previous HaH programs have relied on visiting nurses and physicians, the new study uses telemedicine to connect with patients. Advocate Health Care researchers published the only other study using the telemedicine-powered model in 2015.

The new Atrium Health study evaluated 1,477 patients who received care in the HaH program between March 23 and May 7 of this year after having been diagnosed with COVID-19. The program provided home monitoring and hospital-level care in a home-based virtual observation unit (VOU) and a virtual acute care unit (VACU).

Dr. Sitammagari

Patients were tested for the virus in Atrium emergency departments, primary care clinics, urgent care centers, and external testing sites. Those who tested positive were invited to be cared for either in the VOU, if they had mild to moderate symptoms, or in the VACU, if they were sick enough to be admitted to the hospital.

Patients hop onboard

Nearly all COVID-positive patients tested in these sites agreed to be admitted to the hospital at home, coauthor Stephanie Murphy, DO, medical director of the Atrium Health HaH program, said in an interview.

Patients with moderate symptoms were glad to be monitored at home, she said. When they got to the point where the nurse supervising their care felt they needed escalation to acute care, they were asked whether they wanted to continue to be cared for at home. Most opted to stay home rather than be admitted to the hospital, where their loved ones couldn’t visit them.

Low-acuity patients in the VOU received daily telemonitoring by a nurse to identify disease progression and escalate care as needed. For those who required more care and were admitted to the VACU, a team of paramedics and registered nurses (RNs; mobile clinicians) visited the patient’s home within 24 hours, setting up a hospital bed, other necessary medical equipment, videoconferencing gear, and a remote-monitoring kit that included a blood pressure cuff, a pulse oximeter, and a thermometer.

> *“Virtual hospital programs have the potential to provide health systems with additional inpatient capacity during the COVID-19 pandemic and beyond.”*

Dedicated hospitalists and nurses managed patients with 24/7 coverage and monitoring, bringing in other specialties as needed for virtual consults. Mobile clinician and virtual provider visits continued daily until a patient’s condition improved to the point where they could be deescalated back to the VOU. After that, patients received mobile app–driven symptom monitoring and telephone follow-up with a nurse until they got better.

Few patients go to hospital

Overall, patients had a median length of stay of 11 days in the VOU or the VACU or both. The vast majority, 1,293 patients (88%), received care in the VOU only. In that cohort, just 40 patients (3%) required hospitalization in an Atrium facility. Sixteen of those patients spent time in an ICU, seven required ventilator support, and two died in the hospital.

A total of 184 patients (12%) were admitted to the VACU. Twenty-one (11%) required intravenous fluids, 16 (9%) received antibiotics, 40 (22%) required inhaler or nebulizer treatments, 41 (22%) used supplemental oxygen, and 24 (13%) were admitted to a conventional hospital. Of the latter patients, 10 were admitted to an ICU, 1 required a ventilator, and none died in the hospital.

Dr. Sitammagari, a hospitalist and co–medical director for quality at Atrium Health, said that, overall, the outcomes for patients in the system’s HaH were comparable to those seen in the literature among other COVID-19 cohorts.

Hospital capacity augmented

The authors note that treating the 160 VACU patients within the HaH saved hospital beds for other patients. The HaH maintained a consistent census of between 20 and 30 patients for the first 6 weeks as COVID-19 cases spread.

Since last spring, Dr. Murphy said, the Atrium HaH’s daily census has grown to between 30 and 45 patients. “We could absorb 50 patients if our hospitals required it.”

How much capacity does that add to Atrium Health? While there are 50 hospitals in the health system, the HaH was set up mainly to care for COVID-19 patients who would otherwise have been admitted to the 10 acute-care hospitals in the Charlotte, N.C., area.

In the 4 weeks ending Nov. 16, these facilities carried an average daily census of around 160 COVID-19 patients, Dr. Murphy noted. “During that time, the Atrium Health HaH has carried, on average, about 20%-25% of that census.”

If the pandemic were to overwhelm area hospitals, she added, “the structure would support flexing up our staffing and supplies to expand to crisis capacity,” which could be up to 200 patients a day.

For the nurses who make most of the phone calls to patients, patients average about 12-15 per RN, Dr. Murphy said, and there’s one mobile clinician for every 6-9 patients. That’s pretty consistent with the staffing on med-surg floors in hospitals, she said.

The physicians in the program include hospitalists dedicated to telemedicine and some doctors

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CMS launches 'hospital at home' program to free up hospital capacity

By Ken Terry

As an increasing number of health systems implement "hospital at home" (HaH) programs to increase their traditional hospital capacity, the Centers for Medicare & Medicaid Services has given the movement a boost by changing its regulations to allow acute care to be provided in a patient's home under certain conditions.

The CMS announced last November that it was launching its Acute Hospital Care at Home program "to increase the capacity of the American health care system" during the COVID-19 pandemic.

At the same time, the agency announced it was giving more flexibility to ambulatory surgery centers (ASCs) to provide hospital-level care.

The CMS said its new HaH program is an expansion of the Hospitals Without Walls initiative that was unveiled last March. Hospitals Without Walls is a set of "temporary new rules" that provide flexibility for hospitals to provide acute care outside of inpatient settings. Under those rules, hospitals are able to transfer patients to outside facilities, such as ASCs, inpatient rehabilitation hospitals, hotels, and dormitories, while still receiving Medicare hospital payments.

Under CMS's new Acute Hospital Care at Home, which is not described as temporary, patients can be transferred from emergency departments or inpatient wards to hospital-level care at home. The CMS said the HaH program is designed for people with conditions such as the acute phases of asthma, heart failure, pneumonia, and chronic obstructive pulmonary disease. Altogether, the agency said, more than 60 acute conditions can be treated safely at home.

However, the agency didn't say that facilities can't admit COVID-19 patients to the hospital at home. Rami Karjian, MBA, cofounder and CEO of Medically Home, a firm that supplies health systems with technical services and software for HaH programs, said in an interview that several Medically Home clients plan to treat both COVID-19 and non–COVID-19 patients at home when they begin to participate in the CMS program in the near future.

The CMS said it consulted extensively with academic and private industry leaders in building its HaH program. Before rolling out the initiative, the agency noted, it conducted successful pilot programs in leading hospitals and health systems.

Participating hospitals will be required to have specified screening protocols in place before beginning acute care at home. An in-person physician evaluation will be required before starting care at home. A nurse will evaluate each patient once daily in person or remotely, and either nurses or paramedics will visit the patient in person twice a day.

In contrast, Medicare regulations require nursing staff to be available around the clock in traditional hospitals. So the CMS has to grant waivers to hospitals for HaH programs.

While not going into detail on the telemonitoring capabilities that will be required in the acute hospital care at home, the release said, "Today's announcement builds upon the critical work by CMS to expand telehealth coverage to keep beneficiaries safe and prevent the spread of COVID-19."

More flexibility for ASCs

The agency is also giving ASCs the flexibility to provide 24-hour nursing services only when one or more patients are receiving care on site. This flexibility will be available to any of the 5,700 ASCs that wish to participate, and will be immediately effective for the 85 ASCs currently participating in the Hospital Without Walls initiative, the CMS said.

The new ASC regulations, the CMS said, are aimed at allowing communities "to maintain surgical capacity and other life-saving non–COVID-19 [care], like cancer surgeries." Patients who need such procedures will be able to receive them in ASCs without being exposed to known COVID-19 cases.

Similarly, the CMS said patients and families not diagnosed with COVID-19 may prefer to receive acute care at home if local hospitals are full of COVID-19 patients. In addition, the CMS said it anticipates patients may value the ability to be treated at home without the visitation restrictions of hospitals.

Early HaH participants

Six health systems with extensive experience in providing acute hospital care at home have been approved for the new HaH waivers from Medicare rules. They include Brigham and Women's Hospital (Mass.); Huntsman Cancer Institute (Utah); Massachu-

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who can't work in the regular hospital because they're immunocompromised. The physicians round virtually, covering 12-17 HaH patients per day, according to Dr. Murphy.

Prior planning paid off

Unlike some other health care systems that have launched HaH programs with the aid of outside vendors, Atrium Health developed its own HaH and brought it online just 2 weeks after deciding to launch the program. Atrium was able to do this, Dr. Sitammagari explained, because before the pandemic its hospitalist program was already developing an HaH model to improve the care of high-risk patients after hospital discharge to prevent readmission.

While Atrium's electronic health record system wasn't designed for hospital at home, its health information technology department and clinicians collaborated in rewriting some of the workflows and order sets in the EHR. For example, they set up a nursing questionnaire to administer after VACU admission, and they created another form for automatic admission to the HaH after a patient tested positive for COVID-19. Atrium staff also modified a patient-doctor communications app to help clinicians monitor HaH patients, Dr. Murphy noted.

Other hospital systems have gotten up to speed on HaH pretty quickly by using platforms supplied by outside vendors. Adventist Health in Los Angeles, for example, started admitting patients to its hospital at home just a month after approaching a vendor called Medically Home.

COVID and non-COVID patients considered

Atrium's decision to focus its HaH effort on COVID-19 patients is unusual among the small but growing number of health systems that have adopted the HaH model to increase their capacity. (Atrium is now transferring some hospitalized patients with other conditions to its HaH, but is still focusing mainly on COVID-19.)

Bruce Leff, MD, a professor of health policy and management at Johns Hopkins Bloomberg School of Public Health, Baltimore, a leading expert on the HaH model, agrees that it can increase hospital capacity significantly.

Dr. Leff praised the Atrium Health study. "It proves that within an integrated delivery system you can quickly deploy and implement a virtual hospital in the specific-use case of COVID, and help patients and help the system at scale," he said. "They took a bunch of people into the virtual observation unit and thereby kept people from overwhelming their [emergency department] and treated those people safely at home."

Dr. Leff had no problem with Atrium's focus on patients with COVID-19 rather than other conditions. "My guess is that they have the ability to take what they developed and apply it to other conditions. Once you have the ability to do acute care at home, you can do a lot at home."

The biggest barrier to the spread of hospital at home remains the lack of insurer coverage. Dr. Murphy said that health plans are covering virtual physician consultations with patients in the HaH, as well as some other bits and pieces, but not the entire episode of acute care.

Dr. Leff believes that this will start changing soon. COVID-19 has altered the attitudes of physicians and hospitals toward telehealth, he noted, "and it has moved policy makers and payers to start thinking about the new models – home-based care in general and hospital at home in particular. For the first time in 25 years, payers are starting to get interested."

Most of the authors are employees of Atrium Health. In addition, one coauthor reports being the cofounder of a digital health company, iEnroll, and receiving grants from The Heineman Foundation. Dr. Leff is an adviser to Medically Home, which provides support to hospital at home programs.

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Leading in crisis

Lessons from the trail

By Danielle Scheurer, MD, MSCR, SFHM

I have learned a lot about crisis management and leadership in the rapidly changing COVID health care environment. I have learned how to make quick and imperfect decisions with limited information, and how to move on swiftly. I have learned how to quickly fade out memories of how we used to run our business, and pivot to unknown and untested delivery modalities. I have learned how to take regulatory standards as guidance, not doctrine. And I have learned how tell longstanding loyal colleagues that they are being laid off.

Many of these leadership challenges are not new, but the rapidity of change and the weight and magnitude of decision-making is unparalleled in my relatively short career. In some ways, it reminds me of some solid lessons I have learned over time as a lifetime runner, with many analogies and applications to leadership.

Some people ask me why I run. "You must get a runner's high." The truth is, I have never had a runner's high. I feel every step. In fact, the very nature of running makes a person feel like they are being pulled under water. Runners are typically tachycardic and short of breath the whole time they are running. But running allows you to ignore some of the signals your body is sending, and completely focus on other things. I often have my most creative and innovative thoughts while running. Here are a few things that running and leadership have in common – and how lessons learned can translate between the two:

They are both really hard. As I mentioned above, running literally makes you feel like you are drowning. But when you finish running, it is amazing how easy everything else feels! Similar to leadership, it should feel hard, but not too hard. I have seen firsthand the effects of under- and over-delegating, and both are dysfunctional. Good leadership is a blend of being humble and servant, but also ensuring self-care and endurance. The other aspect of leadership that I find really hard is that often, people's anger is misdirected at leaders as a natural outlet for that anger. Part of being a leader is enduring such anger, gaining an understanding for it, and doing what you can to help people through it.

They both work better when you are restored. It sounds generic and cliché, but you can't be a good runner or a good leader when you are totally depleted.

They both require efficiency. When I was running my first marathon, a complete stranger ran up beside me and told me I should run in as straight of a line as possible, regardless of the road, to preserve energy and save steps. He recommended picking a point on the horizon and running toward that point. As he sped off ahead of me, his parting words were, "You'll thank me at mile 24." The same can be said for leadership; as you pick a point on the horizon, keep yourself and your team heading toward that point with intense focus, and before you realize it, you've reached your destination.

They both require having a goal. That same stranger who gave me advice on running efficiently also asked what my goal was. It caught me off guard a bit, as I realized my only goal was to finish. He encouraged me to make a goal for the run, which could serve as a motivator when the going got tough.

They both can be endured by committing to continuous forward motion. Running and leadership both become psychologically much easier when you realize all you really have to do is maintain continuous forward motion.

They both are easier if you don't overthink things. When I first started in a leadership position, I would have moments of anxiety if I thought too hard about what I was responsible for. Similar to running, it works best if you don't overthink what difficulties it may bring; rather, just put on your shoes and get going.

Dr. Scheurer is chief quality officer and professor of medicine at the Medical University of South Carolina, Charleston. She is president of SHM.

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setts General Hospital; Mount Sinai Health System (N.Y.); Presbyterian Healthcare Services (N.M.); and UnityPoint Health (Iowa).

The CMS said that it's in discussions with other health care systems and expects new applications to be submitted soon.

To support these efforts, the CMS has launched an online portal to streamline the waiver request process. The agency said it will closely monitor the program to safeguard beneficiaries and will require participating hospitals to report quality and safety data on a regular basis.

Support from hospitals

The first health systems participating in the CMS HaH appear to be supportive of the program, with some hospital leaders submitting comments to the CMS about their view of the initiative.

"The CMS has taken an extraordinary step today, facilitating the rapid expansion of Hospitalization at Home, an innovative care model with proven results," said Kenneth L. Davis, MD, president and CEO of the Mount Sinai Health System in New York City. "This important and timely move will enable hospitals across the country to use effective tools to safely care for patients during this pandemic."

David Levine, MD, assistant professor of medicine and medical director of strategy and innovation for Brigham Health Home Hospital in Boston, was similarly laudatory: "Our research at Brigham Health Home has shown that we can deliver hospital-level care in our patients' homes with lower readmission rates, more physical mobility, and a positive patient experience," he said. "We are so encouraged that CMS is taking this important step, which will allow hospitals across the country to increase their capacity while delivering the care all patients deserve."

Quick scale up

If other hospitals and health systems recognize the value of HaH, how long might it take them to develop and implement these programs in the midst of a pandemic?

Atrium Health, a large health system in the Southeast, ramped up a hospital at home initiative last spring for its 10 hospitals in the Charlotte, N.C., area, in just 2 weeks. However, it had been working on the project for some time before the pandemic struck. Focusing mostly on COVID-19 patients, the initiative reduced the COVID-19 patient load by 20%-25% in Atrium's hospitals.

Medically Home, the HaH infrastructure company, said in a news release that it "enables health systems to establish new hospital-at-home services in as little as 30 days." Medically Home has partnered in this venture with Huron Consulting Group, which has about 200 HaH-trained consultants, and Cardinal Health, a large global medical supplies distributor.

Mr. Karjian said in an interview that he expects private insurers to follow CMS's example, as they often do. "We think this decision will cause not only CMS but private insurers to cover hospital at home after the pandemic, if it becomes the standard of care, because patients have better outcomes when treated at home," he said.

Asked for his view on why the CMS specified that patients could be admitted to an HaH only from emergency departments or inpatient settings, Mr. Karjian said that the CMS wants to make sure that patients have access to brick-and-mortar hospital care if that's what they need. Also, he noted, this model is new to most hospitals, so the CMS wants to make sure it starts "with all the safety guardrails" in place.

Overall, Mr. Karjian said, "What CMS has done is terrific in terms of letting patients get the care they want, where they want it, and get the benefit of better outcomes while the nation is going through this capacity crunch for hospital beds."

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Finding meaning in 'Lean'?

Using systems improvement strategies to support the Quadruple Aim

By Pallabi Sanyal-Dey, MD, FHM; Larissa Thomas, MD, MPH; and David Chia, MD, MSc

Background on well-being and burnout

With burnout increasingly recognized as a shared responsibility that requires addressing organizational drivers while supporting individuals to be well,[1-4] practical strategies and examples of successful implementation of systems interventions to address burnout will be helpful for service directors to support their staff. The Charter on Physician Well-Being, developed through collaborative input from multiple organizations, defines guiding principles and key commitments at the societal, organizational, and interpersonal and individual levels and may be a useful framework for organizations developing well-being initiatives.[5]

The charter advocates including physician well-being as a quality improvement metric for health systems, aligned with the concept of the Quadruple Aim of optimizing patient care by enhancing provider experience, promoting high-value care, and improving population health.[6] Identifying areas of alignment between the charter's recommendations and systems improvement strategies that seek to optimize efficiency and reduce waste, such as Lean Management, may help physician leaders to contextualize well-being initiatives more easily within ongoing systems improvement efforts. In this perspective, we provide one division's experience using the Charter to assess successes and identify additional areas of improvement for well-being initiatives developed using Lean Management methodology.

The state of affairs

In 2011, the division of hospital medicine at Zuckerberg San Francisco General Hospital was established and has seen continual expansion in terms of direct patient care, medical education, and hospital leadership.

In 2015, the division of hospital medicine experienced leadership transitions, faculty attrition, and insufficient recruitment resulting in staffing shortages, service line closure, schedule instability, and low morale. A baseline survey was conducted using the 2-Item Maslach Burnout Inventory. This survey, which uses one item in the domain of emotional exhaustion and one item in the domain of depersonalization, has shown good correlation with the full Maslach Burnout Inventory.[7] At baseline, approximately one-third of the division's physicians experienced burnout.

In response, a subsequent retreat focused on the three greatest areas of concern identified by the survey: scheduling, faculty development, and well-being.

Like many health systems, the hospital has adopted Lean as its preferred systems improvement framework. The retreat was structured around the principles of Lean philosophy, and was designed to emulate that of a consolidated Kaizen workshop.

"Kaizen" in Japanese means "change for the better." A typical Kaizen workshop revolves around rapid problem-solving over the course of 3-5 days, in which a team of people come together to identify and implement significant improvements for a selected process. To this end, the retreat was divided into subgroups for each area of concern. In turn, each subgroup mapped out existing workflows ("value stream"), identified areas of waste and non–value added time, and generated ideas of what an idealized process would be. Next, a root-cause analysis was performed and subsequent interventions ("countermeasures") developed to address each problem. At the conclusion of the retreat, each subgroup shared a summary of their findings with the larger group.

Next, this information served as a guiding framework for service and division leadership to run small tests of change. We enacted a series of countermeasures over several years, and multiple cycles of improvement work addressed the three areas of concern. We developed an A3 report (a Lean project management tool that incorporates the plan-do-study-act cycle, organizes strategic efforts, and tracks progress on a single page) to summarize and present these initiatives to the Performance Improvement and Patient Safety Committee of the hospital executive leadership team. This structure illustrated alignment with the hospital's core values ("true north") of "developing people" and "care experience."

In 2018, interval surveys demonstrated a gradual reduction of burnout to approximately one-fifth of division physicians as measured by the 2-item Maslach Burnout Inventory.

Initiatives in faculty well-being

The Charter of Physician Well-Heing outlines a framework to promote well-being among doctors by maximizing a sense of fulfillment and minimizing the harms of burnout. It shares this responsibility among societal, organizational, and interpersonal and individual commitments.[5]

As illustrated here, we used principles of Lean Management to prospectively create initiatives to improve well-being in our division. Lean in health care is designed to optimize primarily the patient experience; its implementation has subsequently demonstrated mixed provider and staff experiences,[8,9] and many providers are skeptical of Lean's potential to improve their own well-being. If, however, Lean is aligned with best practice frameworks for well-being such as those outline in the charter, it may also help to meet the Quadruple Aim of optimizing both provider well-being and patient experience. To further test this hypothesis, we retrospectively categorized our Lean-based interventions into the commitments described by the charter to identify areas of alignment and gaps that were not initially addressed using Lean Management (Table).

Organizational commitments[5]

We optimized scheduling and enhanced physician staffing by budgeting for a physician staffing buffer each academic year in order to minimize mandatory moonlighting and jeopardy pool activations that result from operating on a

Mapping the charter of well-being to Lean Management[5]

Charter principle	Lean philosophy	Division goal and intervention
Societal commitments		
Supportive culture and policies	"Kaizen," "Going to the Gemba"	Use Lean as a tool to optimize well-being in the division of hospital medicine
Organizational commitments		
Supportive systems	Sort, Set in order, Shine, Standardize, Sustain ("5S")	Optimize workspace using 5S with new workstations and power standing desks Improve communication and access to policies through mobile and cloud-based platforms
	Automated method to prevent any possible errors ("Mistake Proofing")	Optimize schedule to improve balance of predictability and flexibility Eliminate mandatory moonlighting and reduce clinical back-up pool activations through increased physician staffing
	Identifying areas of value-added time and waste, designing future state ("Value Stream")	Optimize workflow of clinical shifts to eliminate waste (waiting, minimizing nonclinical tasks, etc.)
	Standard work	Create a template for safe and efficient patient handoffs
Develop leadership engagement	Root-cause analysis and solutions ("A3 Thinking," "PDSA")	Create a transparent forum to discuss challenges and brainstorm solutions Guide academic growth of faculty by promoting faculty development
Optimizing highly functional interprofessional teams	Identifying value added time and waste, designing future state	Maximize efficiency and streamline communication in multidisciplinary rounds
Interpersonal and individual commitments		
Anticipate and respond to inherent challenges	No direct parallel	Provide a forum to discuss clinical and emotional aspects of caring for patients through case conferences, Schwartz rounds
Practice and promote self care	No direct parallel	Incorporate well-being topics into divisional meetings
Prioritize mental health	No direct parallel	Educate faculty about existing resources (Faculty and staff assistance program)

Source: Dr. Sanyal-Dey, Dr. Thomas, Dr. Chia

thin staffing margin when expected personal leave and reductions in clinical effort occur. Furthermore, we revised scheduling principles to balance patient continuity and individual time-off requests while setting limits on the maximum duration of clinical stretches and instituting mandatory minimum time off between them.

We initiated monthly operations meetings as a forum to discuss challenges, brainstorm solutions, and message new initiatives with group input. For example, as a result of these meetings, we designed and implemented an additional service line to address the high census, revised the distribution of new patient admissions to level-load clinical shifts, and established a maximum number of weekends worked per month and year.

This approach aligns with recommendations to use participatory leadership strategies to enhance physician well-being.[10] Engaging both executive level and service level management to focus on burnout and other related well-being metrics is necessary for sustaining such work.

We revised multidisciplinary rounds with social work, utilization management, and physical therapy to maximize efficiency and streamline communication by developing standard approaches for each patient presentation.

Interpersonal, individual commitments[5]

Emotional challenges of physician work

Although these commitments did not have a direct corollary with Lean philosophy, some of these needs were identified by our physician group at our annual retreats. As a result, we initiated a monthly faculty-led noon conference series focused on the clinical challenges of caring for vulnerable populations, a particular source of distress in our practice setting, and revised the division schedule to encourage attendance at the hospital's Schwartz rounds.

Mental health and self-care

We organized focus groups and faculty development sessions on provider well-being and burnout and dealing with challenging patients and invited the Faculty and Staff Assistance Program, our institution's mental health service provider, to our weekly division meeting.

Future directions

After using Lean Management as an approach to prospectively improve physician well-being, we were able to use the Charter on Physician Well-Being retrospectively as a "checklist" to identify additional gaps for targeted intervention to ensure all commitments are sufficiently addressed.

Overall, we found that, not surprisingly, Lean Management aligned best with the organizational commitments in the charter. Reviewing the organizational commitments, we found our biggest remaining challenges are in building supportive systems, namely ensuring sustainable workloads, offloading and delegating non-physician tasks, and minimizing the burden of documentation and administration.

Reviewing the societal commitments helped us to identify opportunities for future directions that we may not have otherwise considered. As a safety-net institution, we benefit from a strong sense of mission and shared values within our hospital and division. However, we recognize the need to continue to be vigilant to ensure that our physicians perceive that their own values are aligned with the division's stated mission. Devoting a Kaizen-style retreat to well-being likely helped, and allocating divisional resources

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Dr. Thomas


Dr. Chia

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Racism in medicine

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"If you have a brain, you have bias, and that bias will likely apply to race as well," Dr. Johnson said. "When we're talking about institutional racism, the educational system and the media have led us to create presumptions and prejudices that we don't necessarily recognize off the top because they've just been a part of the fabric of who we are as we've grown up."


Dr. Johnson

The term "racism" has extremely negative connotations because there's character judgment attached to it, but to say someone is racist or racially insensitive does not equate them with being a Klansman, said Dr. Johnson. "I think we as people have to acknowledge that, yes, it's possible for me to be racist and I might not be 100% aware of it. It's being open to the possibility – or rather probability – that you are and then taking steps to figure out how you can address that, so you can limit it. And that requires constant self-evaluation and work," he said.

Racism in the medical environment

Institutional racism is evident before students are even accepted into medical school, said Areeba Kara, MD, SFHM, associate professor of clinical medicine at Indiana University School of Medicine and a hospitalist at IU Health Physicians.

Mean MCAT scores are lower for applicants traditionally underrepresented in medicine (UIM) compared to the scores of well-represented groups.[1] "Lower scores are associated with lower acceptance rates into medical school," Dr. Kara said. "These differences reflect unequal educational opportunities rooted in centuries of legal discrimination."

Racism is apparent in both the hidden medical education curriculum and in lessons implicitly taught to students, said Ndidi Unaka, MD, MEd, associate program director of the pediatric residency training program at Cincinnati Children's Hospital. "These lessons inform the way in which we as physicians see our patients, each other, and how we practice," she said. "We reinforce race-based medicine and shape clinical decision-making through flawed guidelines and practices, which exacerbates health inequities. We teach that race – rather than racism – is a risk factor for poor health outcomes. Our students and trainees watch as we assume the worst of our patients from marginalized communities of color."


Dr. Kara

Terms describing patients of color, such as "difficult," "noncompliant," or "frequent flyer" are thrown around and sometimes, instead of finding out why, "we view these states of being as static, root causes for poor outcomes rather than symptoms of social conditions and obstacles that impact overall health and well-being," Dr. Unaka said.

Leadership opportunities

Though hospital medicine is a growing field, Dr. Kara noted that the 2020 *State of Hospital Medicine* Report found that only 5.5% of hospital medical group leaders were Black, and just 2.2% were Hispanic/Latino.[2] "I think these numbers speak for themselves," she said.

Dr. Unaka said that the lack of UIM hospitalists and physician leaders creates fewer opportunities for "race-concordant mentorship relationships." It also forces UIM physicians to shoulder more responsibilities – often obligations that do little to help them move forward in their careers – all in the name of diversity. And when UIM physicians are given leadership opportunities, Dr. Unaka said they are often unsure as to whether their appointments are genuine or just a hollow gesture made for the sake of diversity.

Dr. Johnson pointed out that Black and Latinx populations primarily get their care from hospital-based specialties, yet this is not reflected in the number of UIM prac-

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to a well-being committee indirectly helped, to foster a culture of well-being; however, we could more deliberately identify local policies that may benefit from advocacy or revision. Although our faculty identified interventions to improve interpersonal and individual drivers of well-being, these charter commitments did not have direct parallels in Lean philosophy, and organizations may need to deliberately seek to address these commitments outside of a Lean approach. Specifically, by reviewing the charter, we identified opportunities to provide additional resources for peer support and protected time for mental health care and self-care.

Conclusion

Lean Management can be an effective strategy to address many of the organizational commitments outlined in the Charter on Physician Well-Being. This approach may be particularly effective for solving local challenges with systems and workflows. Those who use Lean as a primary method to approach systems improvement in support of the Quadruple Aim may need to use additional strategies to address societal and interpersonal and individual commitments outlined in the charter.

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titioners in leadership roles. He said race and ethnicity, as well as gender, need to be factors when individuals are evaluated for leadership opportunities – for the individual's sake, as well as for the community he or she is serving.

"When we can evaluate for unconscious bias and factor in that diverse groups tend to have better outcomes, whether it's business or clinical outcomes, it's one of the opportunities that we collectively have in the specialty to improve what we're delivering for hospitals and, more importantly, for patients," he said.

Relationships with colleagues and patients

Racism creeps into interactions and relationships with others as well, whether it's between clinicians, clinician to patient, or patient to clinician. Sometimes it's blatant; often it's subtle.

A common, recurring example Dr. Unaka has experienced in the clinician to clinician relationship is being confused with other Black physicians, making her feel invisible. "The everyday verbal, nonverbal, and environmental slights, snubs, or insults from colleagues are frequent and contribute to feelings of exclusion, isolation, and exhaustion," she said. Despite this, she is still expected to "address microaggressions and other forms of interpersonal racism and find ways to move through professional spaces in spite of the trauma, fear, and stress associated with my reality and lived experiences." She said that clinicians who remain silent on the topic of racism participate in the violence and contribute to the disillusionment of UIM physicians.

Dr. Kara said that the discrimination from the health care team is the hardest to deal with. In the clinician to clinician relationship, there is a sense among UIM physicians that they're being watched more closely and "have to prove themselves at every single turn." Unfortunately, this comes from the environment, which tends to be adversarial rather than supportive and nurturing, she said.

"There are lots of opportunities for racism or racial insensitivity to crop up from clinician to clinician," said Dr. Johnson. When he started his career as a physician after his training, Dr. Johnson was informed that his colleagues were watching him because they were not sure about his clinical skills. The fact that he was a former chief resident and board certified in two specialties did not seem to make any difference.

Patients refusing care from UIM physicians or expressing disapproval – both verbal and nonverbal – of such care, happens all too often. "It's easier for me to excuse patients and their families as we often meet them on their worst days," said Dr. Kara. Still, "understanding my oath to care for people and do no harm, but at the same time, recognizing that this is an individual that is rejecting my care without having any idea of who I am as a physician is frustrating," Dr. Johnson acknowledged.

Then there's the complex clinician to patient relationship, which research clearly shows contributes to health disparities.[3] For one thing, the physician workforce does not reflect the patient population, Dr. Unaka said. "We cannot ignore the lack of race concordance between patients and clinicians, nor can the continued misplacement of blame for medical mistrust be at the feet of our patients," she said.

Dr. Unaka feels that clinicians need to accept both that health inequities exist and that frontline physicians themselves contribute to the inequities. "Our diagnostic and therapeutic decisions are not immune to bias and are influenced by our deeply held beliefs about specific populations," she said. "And the health care system that our patients navigate is no different than other systems, settings, and environments that are marred by racism in all its forms."

Systemic racism greatly impacts patient care, said Dr. Kara. She pointed to several examples: research showing that race concordance between patients and providers in an emergency department setting led to better pain control with fewer analgesics;[4] the high maternal and infant mortality rates amongst Black women and children;[5] evidence of poorer outcomes in sepsis patients with limited English proficiency.[6] "There are plenty more," she said. "We need to be asking ourselves what we are going to do about it."

Work in progress

That racial biases are steeped so thoroughly into our culture and consciousness means that moving beyond them is a continual, purposeful work in progress. But it is work that is critical for everyone, and certainly necessary for those who care for their fellow human beings when they are in a vulnerable state.

Health care systems need to move toward *equity* – giving everyone what they need to thrive – rather than focusing on *equality* – giving everyone the same thing, said Jenny Baenzinger, MD, assistant professor of clinical medicine and pediatrics at Indiana University School of Medicine and associate director of education at IU Center for Global Health. "We know that minoritized patients are going to need more attention, more advocacy, more sensitivity, and more creative solutions in order to help them achieve health in a world that is often stacked against them," she said.

Dr. Baenzinger

"The unique needs of each patient, family unit, and/or population must be taken into consideration," said Dr. Unaka. She said hospitalists need to embrace creative approaches that can better serve the specific needs of patients. Equitable practices should be the default, which means data transparency, thoroughly dissecting hospital processes to find existing inequities, giving stakeholders – especially patients and families of color – a voice, and tearing down oppressive systems that contribute to poor health outcomes and oppression, she said.

"It's time for us to talk about racism openly," said Dr. Kara. "Believe your colleagues when they share their fears and treat each other with respect. We should be actively learning about and celebrating our diversity." She encourages finding out what your institution is doing on this front and getting involved.

Dr. Johnson believes that first and foremost, hospitalists need to be exposed to the data on health care disparities. "The next step is asking what we as hospitalists, or any other specialty, can do to intervene and improve in those areas," he said. Focusing on unconscious bias training is important, he said, so clinicians can see what biases they might be bringing into the hospital and to the bedside. Maintaining a diverse workforce and bringing UIM physicians into leadership roles to encourage diversity of ideas and approaches are also critical to promoting equity, he said.

"You cannot fix what you cannot face," said Dr. Unaka. Education on how racism impacts patients and colleagues is essential, she believes, as is advocacy for changing inequitable health system policies. She recommends expanding social and professional circles. "Diverse social groups allow us to consider the perspectives of others; diverse professional groups allow us to ask better research questions and practice better medicine."

Start by developing the ability to question personal assumptions and pinpoint implicit biases, suggested Dr. Baenzinger. "Asking for feedback can be scary and difficult, but we should take a deep breath and do it anyway," she said. "Simply ask your team, 'I've been thinking a lot about racial equity and disparities. How can I do better at my interactions with people of color? What are my blind spots?'" Dr. Baenzinger said that "to help us remember how beautifully complicated and diverse people are," all health care professionals need to watch Nigerian novelist Chimamanda Adichie's TED talk "The Danger of a Single Story."

Dr. Baenzinger also stressed the importance of conversations about "places where race is built into our clinical assessments, like eGFR," as well as being aware that many of the research studies that are used to support everyday clinical decisions didn't include people of color. She also encouraged clinicians to consider how and when they include race in their notes.[7] "Is it really helpful to make sure people know right away that you are treating a '46-year-old Hispanic male' or can the fact that he is Hispanic be saved for the social history section with other important details of his life such as being a father, veteran, and mechanic?" she asked.

"Racism is real and very much a part of our history. We can no longer be in denial regarding the racism that exists in medicine and the impact it has on our patients," Dr. Unaka said. "As a profession, we cannot hide behind our espoused core values. We must live up to them."

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Social isolation at the time of social distancing

Implications of loneliness and suggested management strategies in hospitalized patients with COVID-19

By Yelena Burklin, MD, FHM, FACP, and Zanthia Wiley, MD

During a busy morning of rounds, our patient, Mrs. M., appeared distraught. She was diagnosed with COVID-19 2 weeks prior and remained inpatient because of medicosocial reasons. Since admission she remained on the same ward, in the same room, cared for by the same group of providers donned in masks, gowns, gloves, and face shields. The personal protective equipment helped to shield us from the virus, but it also shielded Mrs. M. from us.

During initial interaction, Mrs. M. appeared anxious, tearful, and detached. It seemed that she recognized a new voice; however, she did not express much interest in engaging during the visit. When she realized that she was not being discharged, Mrs. M. appeared to lose further interest. She wanted to go home. Her outpatient dialysis arrangements were not complete, and that precluded hospital discharge. Prescribed anxiolytics were doing little to relieve her symptoms.

The next day, Mrs. M. continued to ask if she could go home. She stated that there was nothing for her to do while in the hospital. She was tired of watching TV, she was unable to call her friends, and was not able to see her family. Because of COVID-19 status, Mrs. M. was not permitted to leave her hospital room, and she was transported to the dialysis unit via stretcher, being unable to walk. The more we talked, the more engaged Mrs. M. had become. When it was time to complete the encounter, Mrs. M. started pleading with us to "stay a little longer, please don't leave."

Throughout her hospitalization, Mrs. M. had an extremely limited number of human encounters. Those encounters were fragmented and brief, centered on the infection mitigation. The chaplain was not permitted to enter her room, and she was unwilling to use the phone. The subspecialty consultants utilized telemedicine visits. As a result, Mrs. M. felt isolated and lonely. Social distancing in the hospital makes human interactions particularly challenging and contributes to the development of isolation, loneliness, and fear.

Reality of loneliness

Loneliness is the "subjective experience of involuntary social isolation." As the COVID-19 pandemic began to entrap the world in early 2020, many people have faced new challenges – loneliness and its impact on physical and mental health. The prevalence of loneliness nearly tripled in the early months of the pandemic, leading to psychological distress and reopening conversations on ethical issues.

Ethical implications of loneliness

Social distancing challenges all four main ethical principles: autonomy, beneficence, nonmaleficence, and justice. How do we reconcile these principles from the standpoint of each affected individual, their caregivers, health care providers, and public health at large? How can we continue to mitigate the spread of COVID-19, but also remain attentive to our patients who are still in need of human interactions to recover and thrive?

Social distancing is important, but so is social interaction. What strategies do we have in place to combat loneliness? How do we help our hospitalized patients who feel connected to the "outside world?" Is battling loneliness worth the risks of additional exposure to COVID-19? These dilemmas cannot be easily resolved. However, it is important for us to recognize the negative impacts of loneliness and identify measures to help our patients.

In our mission to fulfill the beneficence and nonmaleficence principles of caring for patients affected by COVID-19, patients like Mrs. M. lose much of their autonomy during hospital admission. Despite our best efforts, our isolated patients during the pandemic remain alone, which further heightens their feeling of loneliness.

Clinical implications of loneliness

With the advancements in technology, our capabilities to substitute personal human interactions have grown exponentially. The use of telemedicine, video- and audio-conferencing communications have changed the landscape of our capacities to exchange information.

This could be a blessing and a curse. While the use of digital platforms for virtual communication is tempting, we should preserve human interactions as much as possible, particularly when caring for patients affected by COVID-19. Interpersonal "connectedness" plays a crucial role in providing psychological and psychotherapeutic support, particularly when the number of human encounters is already limited.

Social distancing requirements have magnified loneliness. Several studies demonstrate that the perception of loneliness leads to poor health outcomes, including lower immunity, increased peripheral vascular resistance, and higher overall mortality. Loneliness can lead to functional impairment, such as poor social skills, and even increased inflammation.

The negative emotional impact of SARS-CoV-2 echoes the experiences of patients affected by the severe acute respiratory syndrome (SARS) outbreak in 2003. However, with COVID-19, we are witnessing the amplified effects of loneliness on a global scale. The majority of affected patients during the 2003 SARS outbreak in Canada reported loneliness, fear, aggression, and boredom: They had concerns about the impacts of the infection on loved ones, and psychological support was required for many patients with mild to moderate SARS disease.

Nonpharmacological management strategies for battling loneliness

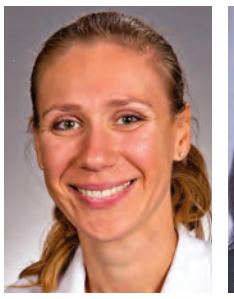
Utilization of early supportive services has been well described in literature and includes extending additional resources such as books, newspapers, and most importantly, additional in-person time to our patients. Maintaining rapport with patients' families is also helpful in reducing anxiety and fear. The following measures have been suggested to prevent the negative impacts of loneliness and should be considered when caring for hospitalized patients diagnosed with COVID-19.

- Screen patients for depression and delirium and utilize delirium prevention measures throughout the hospitalization.
- Educate patients about the signs and symptoms of loneliness, fear, and anxiety.
- Extend additional resources to patients, including books, magazines, and newspapers.
- Keep the patient's cell or hospital phone within their reach.
- Adequately manage pain and prevent insomnia.
- Communicate frequently, utilizing audio- and visual-teleconferencing platforms that simultaneously include the patient and their loved ones.
- For patients who continue to exhibit feelings of loneliness despite the above interventions, consider consultations with psychiatry to offer additional coping strategies.
- Ensure a multidisciplinary approach when applicable – proactive consultation with the members of a palliative care team, ethics, spiritual health, and social and ancillary services.

It is important to recognize how vulnerable our patients are. Diagnosed with COVID-19, and caught in the midst of the current pandemic, not only do they suffer from the physical effects of this novel disease, but they also have to endure prolonged confinement, social isolation, and uncertainty – all wrapped in a cloak of loneliness and fear.

With our main focus being on the management of a largely unknown viral illness, patients' personal experiences can be easily overlooked. It is vital for us as health care providers on the front lines to recognize, reflect, and reform to ease our patients' journey through COVID-19.

For a complete list of the references for this article, please see the online version at www.the-hospitalist.org.



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Blood glucose predicts COVID-19 severity

By Miriam E. Tucker

Hyperglycemia at hospital admission – regardless of diabetes status – is a key predictor of COVID-19–related death and severity among noncritical patients, new research finds.

The observational study, the largest to date to investigate this association, was published in Annals of Medicine by Francisco Javier Carrasco-Sánchez, MD, PhD, and colleagues (doi: 10.1080/07853890.2020.1836566).

Among more than 11,000 patients with confirmed COVID-19 from March to May 2020 in a nationwide Spanish registry involving 109 hospitals, admission hyperglycemia independently predicted progression from noncritical to critical condition and death, regardless of prior diabetes history.

Those with abnormally high glucose levels were more than twice as likely to die from the virus than those with normal readings (41.4% vs 15.7%). They also had an increased need for a ventilator and ICU admission.

"These results provided a simple and practical way to stratify risk of death in hospitalized patients with COVID-19. Hence, admission hyperglycemia should not be overlooked, but rather detected and appropriately treated to improve the outcomes of COVID-19 patients with and without diabetes," Dr. Carrasco-Sánchez and colleagues wrote.

The findings confirm those of previous retrospective observational studies, but the current study "has, by far, the biggest number of patients involved in this kind of study [to date]. All conclusions are consistent to other studies," Dr. Carrasco-Sánchez, of University Hospital Juan Ramón Jiménez, Huelva, Spain, said in an interview.

However, a surprising finding, he said, "was how hyperglycemia works in the nondiabetic population and [that] glucose levels over 140 [mg/dL] increase the risk of death."

Even mild hyperglycemia on admission may affect outcome

The study also differs from some of the prior observational ones in that it examines outcome by admission glycemia rather than during the hospital stay, therefore eliminating the effect of any inpatient treatment, such as dexamethasone.

Although blood glucose measurement at admission is routine for all patients in Spain, as it is in the United States and elsewhere, a mildly elevated level in a person without a diagnosis of diabetes may not be recognized as important.

"In patients with diabetes we start the protocol to control and treat hyperglycemia during hospitalization. However, in nondiabetic patients blood glucose levels under 180 [mg/dL], and even greater, are usually overlooked. This means there is not a correct follow-up of the patients during hospitalization. After this study we learned that we need to pay attention to this population ... who develop hyperglycemia from the beginning," he said.

The study was limited in that patients who had previously undiagnosed diabetes couldn't always be distinguished from those with acute "stress hyperglycemia."

Progress to critical care higher with hyperglycemia

The retrospective, multicenter study was based on data from 11,312 adult patients with confirmed COVID-19 in 109 hospitals participating in Spain's SEMI-COVID-19 registry as of May 29, 2020. They had a mean age of 67 years, 57% were male, and 19% had a diagnosis of diabetes. A total of 20% (n = 2,289) died during hospitalization.

Overall all-cause mortality was 41.1% among those with admission blood glucose levels above 180 mg/dL, 33.0% for those with glucose levels 140-180 mg/dL, and 15.7% for levels below 140 mg/dL. All differences were significant ($P < .0001$), but there were no differences in mortality rates within each blood glucose category between patients with or without a previous diagnosis of diabetes.

After adjustment for confounding factors, elevated admission blood glucose level remained a significant predictor of death.

A version of this article originally appeared on Medscape.com.

In the Literature

Clinician reviews of HM-centric research

By Krishna A. Chokshi, MD; Andrew Chung, MD; Ariel Y. Elyahu, MD; Rex Hermansen, MD; Michael Herscher, MD; Andrew Kim, MD; Amit S. Narayan, MD; David Portnoy, MD; Elizabeth Yoo, MD

Division of Hospital Medicine, Mount Sinai Health System, New York

IN THIS ISSUE

By Krishna A. Chokshi, MD

1 Bedside frailty assessment can determine when CPR will be nonbeneficial

CLINICAL QUESTION: How does frailty impact survival after inpatient cardiac arrest in older adults?

BACKGROUND: Although average survival after in-hospital cardiac arrest is 17%-20%, many clinicians feel that survival is lower in older patients or patients with multiple comorbidities. The Clinical Frailty Scale (CFS) is a simple bedside visual tool that encapsulates patients' mobility and functional status, with a score greater than 4 indicating frailty. How this measure of frailty correlates with outcomes after in-hospital cardiac arrest is unknown.

Dr. Chokshi

STUDY DESIGN: Retrospective review.

SETTING: Tertiary referral center in England.

SYNOPSIS: The study included patients over 60 years old who received CPR between May 2017 and December 2018. CFS was retroactively applied based on available chart data. The patients' median age was 77 years old, and 71% were male. The initial cardiac rhythm was nonshockable in 82% of cases, and overall in-hospital mortality was 86%. Frailty was independently associated with increased mortality when controlling for age, comorbidities, and rhythm. No frail patients survived to hospital discharge, while 26% of patients with CFS greater than 4 survived. Although patients with a shockable rhythm had a better chance of survival overall, compared with those with a nonshockable rhythm (92% vs. 23%, *P* less than .001), 15% of frail patients had a shockable rhythm, and none survived to discharge. Limitations of the study include relatively small sample size and the possibility of confounding variables, such as comorbid conditions.

BOTTOM LINE: When adjusted for age and rhythm, no frail patients older than 60 who received CPR for cardiac arrest survived to hospital discharge. Clinicians should discuss the limited chance of survival and potential burdens of resuscitation with frail patients and their families to avoid inappropriate CPR at the end of life.

CITATION: Ibitoye SE et al. Frailty status predicts futility of cardiopulmonary resuscitation in older adults. Age Ageing. 2020 Jun 5;[e-pub]. doi: doi.org/10.1093/ageing/afaa104.

Dr. Chokshi is a hospitalist in the Division of Hospital Medicine, Mount Sinai Health System, New York.

By Andrew Chung, MD

2 Tranexamic acid does not reduce risk of death in GI bleed

CLINICAL QUESTION: In patients with GI bleeding, does high-dose tranexamic acid (TXA) reduce the risk of death?

BACKGROUND: TXA is an anti-fibrinolytic agent that decreases surgical bleeding and reduces death resulting from bleeding in trauma and postpartum hemorrhage. A 2012 Cochrane review suggested a reduction in mortality with use of TXA in patients with GI bleed, but previous trials were small with a high risk of bias.

Dr. Chung

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial.

SETTING: 164 hospitals in 15 countries.

SYNOPSIS: A total of 12,009 patients presenting with suspected significant upper or lower GI bleeding were randomized to receive either high-dose TXA or placebo. Death resulting from bleeding within 5 days (primary outcome) was similar in the two groups (3.7% with TXA and 3.8% with placebo; relative risk, 0.99; 95% confidence interval, 0.82-1.18). All-cause mortality at 28 days was also similar (9.5% with TXA and 9.2% with placebo; RR, 1.03; 95% CI, 0.92-1.16).

There was an increase in venous thromboembolism (VTE; deep vein thrombosis or pulmonary embolism) in the TXA group versus the placebo group (0.8% with TXA and 0.4% with placebo; RR, 1.85; 95% CI, 1.15-2.98), as well as an increase in seizure events (0.6% with TXA and 0.4% with placebo; RR, 1.73; 95% CI, 1.03–2.93).

BOTTOM LINE: TXA did not reduce mortality risk in patients with upper or lower GI bleeding and should not be used in the routine management of GI bleed.

CITATION: Roberts I et al. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet. 2020;395(10241):1927-1936. doi: 10.1016/S0140-6736(20)30848-5.

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By Ariel Y. Elyahu, MD

3 Antibiotics vs. placebo in acute uncomplicated diverticulitis

CLINICAL QUESTION: Does antibiotic therapy decrease length of hospital stay for patients with acute uncomplicated diverticulitis?

BACKGROUND: Antibiotic therapy is considered the standard of care for acute uncomplicated diverticulitis. Over the past decade, randomized clinical trials have suggested that treatment with antibiotics may be noninferior to observation with supportive care; however, there have not been any blinded, placebo-controlled trials to provide high-quality evidence.

Dr. Elyahu

STUDY DESIGN: Placebo-controlled, double-blinded, randomized noninferiority trial.

SETTING: Four centers in New Zealand and Australia.

SYNOPSIS: Researchers randomized 180 patients hospitalized for acute uncomplicated diverticulitis with Hinchey 1a CT findings (i.e., phlegmon without abscess) into two groups treated with either antibiotics (intravenous cefuroxime and oral metronidazole followed by oral amoxicillin/clavulanic acid) or placebo for 7 days. Median lengths of stay between the antibiotic (40.0 hours) and placebo (45.8 hours) groups were not significantly different (5.9 hours difference between groups; 95% CI, –3.7 to 15.5; *P* = .2). Additionally, there were no significant differences in the secondary outcomes of readmission at 7 days and 30 days or in need for procedural intervention, mortality, pain scores at 24 hours, or change in white blood cell count.

Notably, though this study was adequately powered to detect differences in length of stay, it was not powered to detect differences in clinical outcomes, including death or the need for surgery. The exclusion of patients with language barriers

raises concerns regarding the generalizability of the results.

BOTTOM LINE: Antibiotic therapy does not decrease length of hospital stay when compared with placebo for patients with acute uncomplicated diverticulitis.

CITATION: Jaung R et al. Antibiotics do not reduce length of hospital stay for uncomplicated diverticulitis in a pragmatic double-blind randomized trial. Clin Gastroenterol Hepatol. 2020 Mar;S1542-3565(20):30426-2. doi: 10.1016/j.cgh.2020.03.049.

Dr. Elyahu is a hospitalist in the Division of Hospital Medicine, Mount Sinai Health System, New York.

By Rex Hermansen, MD

4 Apixaban noninferior to low-molecular-weight heparin in cancer-associated VTE

CLINICAL QUESTION: Is oral apixaban as safe and effective as subcutaneous dalteparin in treating venous thromboembolism (VTE) in patients with underlying cancer?

BACKGROUND: VTE is common in patients with cancer and can lead to serious complications and death. Relatively recently, the use of edoxaban or rivaroxaban was recommended by major guidelines for the treatment of cancer-associated VTE. Previous studies have demonstrated a higher risk of major bleeding when compared with low-molecular-weight heparin. Whether oral apixaban can be safely used in this setting is unknown.

Dr. Hermansen

STUDY DESIGN: Randomized, controlled, open-label, noninferiority clinical trial.

SETTING: Multinational study with patients enrolled in nine European countries, Israel, and the United States.

SYNOPSIS: Adult patients with confirmed cancer who had a new diagnosis of proximal lower-limb deep vein thrombosis or pulmonary embolism were enrolled in the trial. Of those enrolled, 1,170 patients underwent randomization to receive either oral apixaban twice daily or subcutaneous dalteparin once daily. The primary outcome was recurrent deep vein thrombosis or pulmonary embolism. The principal safety outcome was major bleeding. Researchers followed patients for 7 months after randomization. The primary outcome occurred in 32 of 576 patients (5.6%) in the apixaban group and 46 of 579 patients (7.9%) in the dalteparin group (hazard ratio, 0.63; 95% CI, 0.37-1.07). Major bleeding occurred in 22 patients (3.8%) in the apixaban group and 23 patients (4.0%) in the dalteparin group (HR, 0.82; 95% CI, 0.40-1.69). Limitations were the open-label trial design; the exclusion of patients with primary brain tumors, cerebral metastases, or acute leukemia; and the sample size being powered for the primary outcome, rather than to allow definitive conclusions about bleeding. Additionally, long-term data are needed as patients were followed for only 7 months.

BOTTOM LINE: Apixaban was noninferior to subcutaneous dalteparin for the treatment of VTE in patients with cancer and did not increase bleeding.

CITATION: Agnelli G et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med. 2020 Apr 23;382:1599-607. doi: 10.1056/NEJMoa1915103.

Dr. Hermansen is a hospitalist in the Division of Hospital Medicine, Mount Sinai Health System, New York.

By Michael Herscher, MD

5 Compression therapy prevents recurrence of cellulitis

CLINICAL QUESTION: Do compression garments prevent recurrent cellulitis in patients with lower-extremity edema?

BACKGROUND: Recurrent cellulitis is a common condition in patients with lower-extremity edema. Although some clinicians recommend compression garments as a preventative treatment, there are no data evaluating their efficacy for this purpose.

Dr. Herscher

STUDY DESIGN: Participants were randomized to receive either education alone or education plus compression therapy. Neither the participants nor the assessors were blinded to the treatment arm.

SETTING: Single-center study in Australia.

SYNOPSIS: Participants with cellulitis who also had at least two previous episodes of cellulitis in the previous 2 years and had lower-extremity edema were enrolled. Of participants, 84 were randomized. Both groups received education regarding skin care, body weight, and exercise, while the compression therapy group also received compression garments and instructions for their use. The primary outcome was recurrent cellulitis. Patients in the control group were allowed to cross over after an episode of cellulitis. The trial was stopped early for efficacy. At the time the trial was halted, 17 of 43 (40%) participants in the control group had recurrent cellulitis, compared with only 6 of 41 (15%) in the intervention (hazard ratio, 0.23; 95% CI, 0.09-0.59; P = .002). Limitations include the lack of blinding, which could have introduced bias, although the diagnosis of recurrent cellulitis was made by clinicians external to the trial. This study supports the use of compression garments in preventing recurrent cellulitis in patients with lower-extremity edema.

BOTTOM LINE: Compression garments can be used to prevent recurrent cellulitis in patients with edema.

CITATION: Webb E et al. Compression therapy to prevent recurrent cellulitis of the leg. N Engl J Med. 2020;383(7):630-9. doi:10.1056/NEJMoa1917197.

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By Andrew Kim, MD

6 Timing of initiation of renal-replacement therapy in acute kidney injury

CLINICAL QUESTION: In critically ill patients, does early renal-replacement therapy (RRT), compared with standard therapy, improve death from any cause at 90 days?

Dr. Kim

BACKGROUND: Acute kidney injury (AKI) is a common complication that occurs in seriously ill patients admitted to the ICU, and many of these patients eventually require RRT. When complicated by major metabolic disorders, it is usually clear when therapy should be initiated. However, when these complications are absent, the most appropriate time to initiate

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RRT is unclear. There are potential advantages to performing early RRT in patients with severe AKI, such as restoring acid-base balance, preventing fluid accumulation, and preventing major electrolyte disturbances.

STUDY DESIGN: Multinational, randomized, controlled trial.

SETTING: 168 hospitals in 15 countries.

SYNOPSIS: Eligible patients were adults admitted to an ICU with severe AKI. Patients were randomly assigned to an accelerated strategy of RRT (initiated within 12 hours, 1,465 patients) or a standard strategy of RRT (held until conventional indications developed or AKI lasted more than 72 hours, 1,462 patients). RRT was performed in 1,418 (96.8%) in the accelerated group and 903 (61.8%) in the standard group. At 90 days, 643 deaths (43.9%) occurred in the accelerated group and 639 deaths (43.7%) occurred in the standard group (RR, 1.00; 95% CI, 0.93-1.09; *P* = .92). Among survivors at 90 days, 85 out of 814 accelerated patients (10.4%) and 49 of 815 standard patients (6.0%) continued to require RRT (RR, 1.75; 95% CI, 1.24-2.43), suggesting the possibility of increased dependence on long-term RRT if introduced early. Limitations include use of clinical equipoise to confirm full eligibility, introducing possible patient heterogeneity into the trial. In addition, broad discretion was given to clinicians on when to start RRT in the standard group resulting in variable initiation times.

BOTTOM LINE: In critically ill patients with severe AKI, earlier RRT did not result in lower mortality at 90 days compared with standard therapy and increased the risk of requiring RRT at 90 days.

CITATION: Bagshaw SM et al. Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med. 2020;383:240-51. doi: 10.1056/NEJMoa2000741.

Dr. Kim is a hospitalist in the Division of Hospital Medicine, Mount Sinai Health System, New York.

By Amit S. Narayan, MD

7 Apixaban a reasonable alternative to warfarin in patients with severe renal impairment

CLINICAL QUESTION: Is apixaban a safe alternative to warfarin in patients with severe renal impairment?

BACKGROUND: Over 6 million Americans are prescribed anticoagulation; however, available anticoagulation options for patients with concomitant renal impairment are limited. Until recently, warfarin was the only recommended option because of a lack of data to support the use of alternative agents in such patients. This study evaluates the safety and effectiveness of apixaban, compared with warfarin, in patients with severe renal dysfunction.

Dr. Narayan

STUDY DESIGN: Multicenter retrospective cohort study.

SETTING: Seven hospitals in Michigan between January 2013 and December 2015 and including adult patients with CrCl less than 25 cc/min who were newly initiated on apixaban or warfarin.

SYNOPSIS: Patients in the apixaban group (n=128) had a higher rate of heart failure, atrial fibrillation, stent placement, and hyperlipidemia, while the warfarin group (n=733) had a higher rate of prior venous thromboembolism. The primary outcome was time to first bleeding or thrombotic event. Apixaban was associated with a lower risk of thrombotic or bleeding events, compared with warfarin (HR, 0.47). Post-hoc analysis controlling for patient differences showed similar results. There was no statistical difference in the severity of events or overall mortality. Further subgroup analysis showed that 5 mg B.I.D. dosing was not associated with higher risk of bleeding than 2.5 mg B.I.D.

The main limitation is the retrospective observational design, which may have introduced confounding variables that were not accounted for in the analyses. The study also did not account for patient nonadherence to medication.

BOTTOM LINE: Apixaban is a reasonable alternative to warfarin in patients with severe renal impairment.

CITATION: Hanni C et al. Outcomes associated with apixaban vs. warfarin in patients with renal dysfunction. Blood Adv. 2020;4(11): 2366-71. doi: 10.1182/bloodadvances.2019000972.

Dr. Narayan is a hospitalist in the Division of Hospital Medicine, Mount Sinai Health System, New York.

By David Portnoy, MD

8 Anticoagulant choice in antiphospholipid syndrome–associated thrombosis

CLINICAL QUESTION: Are direct oral anticoagulants (DOACs) as efficacious and safe as vitamin K antagonists (VKAs) in treating thrombosis secondary to antiphospholipid syndrome (APS)?

BACKGROUND: DOACs have largely replaced VKAs as first-line therapy for venous thromboembolism in patients with adequate renal function. However, there is concern in APS that DOACs may have higher rates of recurrent thrombosis than VKAs when treating thromboembolism.

Dr. Portnoy

STUDY DESIGN: Randomized noninferiority trial.

SETTING: Six teaching hospitals in Spain.

SYNOPSIS: Of adults with thrombotic APS, 190 were randomized to receive rivaroxaban or warfarin. Primary outcomes were thrombotic events and major bleeding. Follow-up after 3 years demonstrated new thromboses in 11 patients (11.6%) in the DOAC group and 6 patients (6.3%) in the VKA group (*P* = .29). Major bleeding occurred in six patients (6.3%) in the DOAC group and seven patients (7.4%) in the VKA group (*P* = .77). By contrast, stroke occurred in nine patients in the DOAC group while the VKA group had zero events, yielding a significant relative RR of 19.00 (95% CI, 1.12-321.90) for the DOAC group.

The DOAC arm was not proven to be noninferior with respect to the primary outcome of thrombotic events. The higher risk of stroke in this group suggests the need for caution in using DOACs in this population.

BOTTOM LINE: DOACs have a higher risk of stroke than VKAs in patients with APS without a significant difference in rate of a major bleed.

CITATION: Ordi-Ros J et. al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome. Ann Intern Med. 2019;171(10):685-94. doi: 10.7326/M19-0291.

Dr. Portnoy is a hospitalist in the Division of Hospital Medicine, Mount Sinai Health System, New York.

By Elizabeth Yoo, MD

9 Oral step-down therapy for infective endocarditis

CLINICAL QUESTION: What is oral step-down therapy's relative clinical effectiveness, compared with prolonged IV antibiotics for infective endocarditis (IE)?

BACKGROUND: The standard of care for IE has been a prolonged course of IV antibiotics. Recent literature has suggested that oral antibiotics might be a safe and effective step-down therapy for IE.

Dr. Yoo

STUDY DESIGN: Systematic review.

SETTING: Literature review in October 2019, with update in February 2020, consisting of 21 observational studies and 3 randomized controlled trials.

SYNOPSIS: Three RCTs and 21 observational studies were reviewed, with a focus on the effectiveness of antibiotics administered orally for part of the therapeutic course for IE patients. Patients included in the study had left- or right-sided IE. Pathogens included viridians streptococci, staphylococci, and enterococci, with a minority of patients infected with methicillin-resistant Staphylococcus aureus. Treatment regimens included beta-lactams, linezolid, fluoroquinolones, trimethoprim-sulfamethoxazole, or clindamycin, with or without rifampin.

In studies wherein IV antibiotics alone were compared with IV antibiotics with oral step-down therapy, there was no difference in clinical cure rate. Those given oral step-down therapy had a statistically significant lower mortality rate than patients who received only IV therapy.

Limitations include inconclusive data regarding duration of IV lead-in therapy, with the variance before conversion to oral antibiotics amongst the studies ranging from 0 to 24 days. The limited number of patients with MRSA infections makes it difficult to draw conclusions regarding this particular pathogen.

BOTTOM LINE: Highly orally bioavailable antibiotics should be considered for patients with IE who have cleared bacteremia and achieved clinical stability with IV regimens.

CITATION: Spellberg B et al. Evaluation of a paradigm shift from intravenous antibiotics to oral step-down therapy for the treatment of infective endocarditis: a narrative review. JAMA Intern Med. 2020;180(5):769-77. doi: 10.1001/jamainternmed.2020.0555.

Dr. Yoo is a hospitalist in the Division of Hospital Medicine, Mount Sinai Health System, New York.

Upper GI bleeds in COVID-19 not related to increased mortality

By Jim Kling
MDedge News

A Spanish survey of COVID-19 patients suggests that upper gastrointestinal bleeding (UGB) does not affect in-hospital mortality. It also found that fewer COVID-19–positive patients underwent endoscopies, but there was no statistically significant difference in in-hospital mortality outcome as a result of delays.

"In-hospital mortality in COVID-19 patients with upper GI bleeding seemed to be more influenced by COVID-19 than by upper GI bleeding, and that's something I think is important for us to know," Gyanprakash Ketwaroo, MD, associate professor at Baylor College of Medicine, Houston, said in an interview. Dr. Ketwaroo was not involved in the study.

The results weren't a surprise, but they do provide some reassurance. "Initially, we thought there might be some COVID-19–related [GI] lesions, but that didn't seem to be borne out. So we thought the bleeding was related to [the patient] being in a hospital or the typical reasons for bleeding. It's also what I expected that less endoscopies would be performed in these patients, and even though fewer endoscopies were performed, the outcomes were still similar. I think it's what most people expected," said Dr. Ketwaroo.

The study was published online in the Journal of Clinical Gastroenterology (2020 Nov. doi: 10.1097/MCG.0000000000001465), and led by Rebeca González González, MD, of Severo Ochoa University Hospital in Leganés, Madrid, and Pascual Piñera-Salmerón, MD, of Reina Sofia University General Hospital in Murcia, Spain. The researchers retrospectively analyzed data on 71,904 COVID-19 patients at 62 emergency departments in Spain, and compared 83 patients who had COVID-19 and UGB to two control groups: 249 randomly selected COVID-19 patients without UGB, and 249 randomly selected non-COVID-19 patients with UGB.

They found that 1.11% of COVID-19 patients presented with UGB, compared with 1.78% of non–COVID-19 patients at emergency departments. In patients with COVID-19, risk of UGB was associated with hemoglobin values <10 g/L (odds ratio, 34.255, 95% confidence interval, 12.752-92.021), abdominal pain (OR, 11.4; 95% CI, 5.092-25.944), and systolic blood pressure <90 mm Hg (OR, 11.096; 95% CI, 2.975-41.390).

Compared with non–COVID-19 patients with UGB, those COVID-19 patients with UGB were more likely to have interstitial lung infiltrates (OR, 66.42; 95% CI, 15.364-287.223) and ground-glass opacities (OR, 21.27; 95% CI, 9.720-46.567) in chest radiograph, as well as fever (OR, 34.67; 95% CI, 11.719-102.572) and cough (OR, 26.4; 95% CI, 8.845-78.806).

Gastroscopy and endoscopic procedures were lower in patients with COVID-19 than in the general population (gastroscopy OR, 0.269; 95% CI, 0.160-0.453: endoscopy OR, 0.26; 95% CI, 0.165-0.623). There was no difference between the two groups with respect to endoscopic findings. After adjustment for age and sex, the only significant difference between COVID-19 patients with UGB and COVID-19 patients without UGB was a higher rate of intensive care unit admission (OR, 2.98; 95% CI, 1.16-7.65). Differences between COVID-19 patients with UGB and non–COVID-19 patients with UGB included higher rates of ICU admission (OR, 3.29; 95% CI, 1.28-8.47), prolonged hospitalizations (OR, 2.02; 95% CI, 1.15-3.55), and in-hospital mortality (OR, 2.05; 95% CI, 1.09-3.86).

UGB development was not associated with increased in-hospital mortality in COVID-19 patients (OR, 1.14; 95% CI, 0.59-2.19).

A limitation to the study is that it was performed in Spain, where endoscopies are performed in the emergency department, and where there are different thresholds for admission to the intensive care unit than in the United States.

Pediatric HM highlights from the 2020 *State of Hospital Medicine* Report

By Sandra Gage, MD, PhD, SFHM, FAAP

To improve the pediatric data in the *State of Hospital Medicine* (*SoHM*) Report, the Practice Analysis Committee (PAC) developed a pediatric task force to recommend content specific to pediatric practice and garner support for survey participation. The pediatric hospital medicine (PHM) community responded with its usual enthusiasm, resulting in a threefold increase in PHM participation (99 groups), making the data from 2020 *SoHM* Report the most meaningful ever for pediatric practices.

However, data collection for the 2020 *SoHM* Report concluded in February, just before the face of medical practice and hospital care changed dramatically. A recent report at the virtual Pediatric Hospital Medicine meeting stated that pre–COVID-19 hospital operating margins had already taken a significant decline (from 5% to 2%-3%), putting pressure on pediatric programs in community settings that typically do not generate much revenue. After COVID-19, hospital revenues took an even greater downturn, affecting many hospital-based pediatric programs. While the future direction of many PHM programs remains unclear, the robust nature of the pediatric data in the 2020 *SoHM* Report defines where we were and where we once again hope to be. In addition, the PAC conducted a supplemental survey designed to assess the impact of COVID-19 on the practice of hospital medicine. Here's a quick review of PHM highlights from the 2020 *SoHM* Report, with preliminary findings from the supplemental survey.

Diversity of service and scope of practice: Pediatric hospitalist programs continue to provide a wide variety of services beyond care on inpatient wards, with the most common being procedure performance (56.6%), care of healthy newborns (51.5%), and rapid response team (38.4%) coverage. In addition, most PHM programs have a role in comanagement of a wide variety of patient populations, with the greatest presence among the surgical specialties. Approximately 90% of programs report some role in the care of patients admitted to general surgery, orthopedic surgery, and other surgical subspecialties.

SURVEY INSIGHTS

"Pediatric hospitalist programs continue to provide a wide variety of services beyond care on inpatient wards."

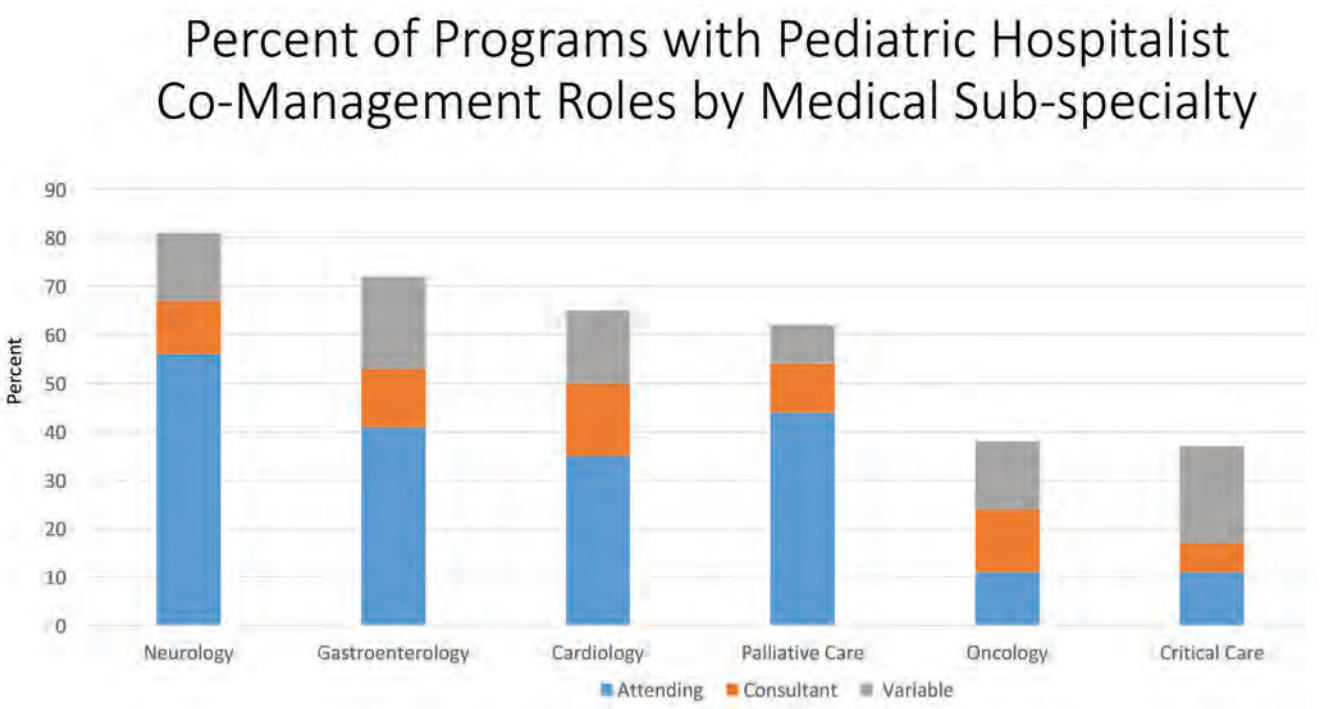
The role for comanagement with medical specialties remains diverse, with PHM programs routinely having some role in caring for patients hospitalized for neurologic, gastroenterological, cardiac concerns, and others (see graphic below). With the recent decline in hospital revenues affecting PHM practices, one way to ensure program value is to continue to diversify. Based on data from the 2020 *SoHM* report, broadening of clinical coverage will not require a significant change in practice for most PHM programs.

PHM board certification: With the first certifying exam for PHM taking place just months before *SoHM* data collection, the survey sought to establish a baseline percentage of providers board certified in PHM. With 98 groups responding, an average of 26.4% of PHM practitioners per group were reported to be board certified. While no difference was seen based on academic status, practitioners in PHM programs employed by a hospital, health system, or integrated delivery system were much more likely to be board certified than those employed by a university or medical school (31% vs. 20%). Regional differences were noted as well, with the East region reporting a much higher median proportion of PHM-certified physicians. It will be interesting to watch the trend in board certification status evolve over the upcoming years.

Anticipated change of budgeted full-time equivalents in the next year/post–COVID-19 analysis: Of the PHM programs responding to the *SoHM* Survey, 46.5% predicted an increase in budgeted full-time equivalents in the next year, while only 5.1% anticipated a decrease. Expecting this to change in response to COVID-19, the supplemental survey sought to update this information. Of the 30 PHM respondents to the supplemental survey, 41% instituted a temporary hiring freeze because of COVID-19, while 8.3% instituted a hiring freeze felt likely to be permanent. As PHM programs gear up for the next viral season, we wait to see whether the impact of COVID-19 will continue to be reflected in the volume and variety of patients admitted. It is clear that PHM programs will need to remain nimble to stay ahead of the changing landscape of practice in the days ahead. View all data by obtaining access to the 2020 *SoHM* Report at hospitalmedicine.org/sohm.

Many thanks to pediatric task force members Jack Percelay, MD; Vivien Kon-Ea Sun, MD; Marcos Mestre, MD; Ann Allen, MD; Dimple Khona, MD; Jeff Grill, MD; and Michelle Marks, MD.

Dr. Gage is director of faculty development, pediatric hospital medicine, at Phoenix Children's Hospital, and associate professor of pediatrics at the University of Arizona, Phoenix.



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Editor's Desk

Leading hospitalists during a pandemic

By Weijen W. Chang, MD, SFHM, FAAP

As I write this, we are entering the third surge of the COVID-19 pandemic, with new cases, hospitalizations, and deaths from COVID-19 skyrocketing around the country. Worst of all, this surge has been most severely affecting areas of the nation least prepared to handle it (rural) and populations already marginalized by the health care system (Latinx and Black). Despite the onslaught of COVID-19, "pandemic fatigue" has begun to set in amongst colleagues, friends, and family, leading to challenges in adhering to social distancing and other infection-control measures, both at work and home.

Royal Geographic Society, public domain, via Wikimedia

Endurance final sinking in Antarctica, November 1915. The dogs were later shot to conserve supplies.

In the face of the pandemic's onslaught, hospitalists – who have faced the brunt of caring for patients with COVID-19, despite the absence of reporting about the subspecialty's role – are faced with mustering the grit to respond with resolve, coordinated action, and empathy. Luckily, hospitalists are equipped with the very characteristics needed to lead teams, groups, and hospitals through the crisis of this pandemic. Ask yourself, why did you become a hospitalist? If you wanted steady predictability and control, there were many office-based specialties you could have chosen. You chose to become a hospitalist because you seek the challenges of clinical variety, problem-solving, systems improvement, and you are a natural team leader, whether you have been designated as such or not. In the words of John Quincy Adams, "if your actions inspire others to dream more, learn more, do more, and become more, you are a leader."

As a leader, how can you lead your team through the series of trials and tribulations that this year has thrown at you? From COVID-19 to racism directed against Black and Latinx people to the behavioral health crisis, 2020 has likely made you feel as if you're stuck in a ghoulish carnival fun house without an exit.

Yet this is where some leaders hit their stride, in what Bennis and Thomas describe as the "crucible of leadership."[1] There are many types of "crucibles of leadership," according to Bennis and Thomas, and this year has thrown most of these at us: prejudice/bias, physical fatigue and illness, sudden elevation of responsibility to lead new processes, not to mention family stressors. Leaders who succeed in guiding their colleagues through these challenges have manifested critical skills: engaging others in shared meaning, having a distinctive and compelling voice, displaying integrity, and having adaptive capacity.

What exactly is adaptive capacity, the most important of these, in my opinion? Adaptive capacity requires understanding the new context of a crisis and how it has shifted team members' needs and perceptions. It also requires what Bennis and Thomas call hardiness and what I call grit – the ability to face adversity, get knocked down, get up, and do it again.

There is probably no better example of a crisis leader with extraordinary adaptive capacity than Anglo-Irish explorer Sir Ernest Shackleton. Bitten by the bug of exploration, Shackleton failed at reaching the South Pole (1908-1909) but subsequently attempted to cross the Antarctic, departing South Georgia Island on Dec. 5, 1914. Depressingly for Shackleton, his ship, the Endurance, became stuck in sea ice on Jan. 19, 1915, before even reaching the continent. Drifting with the ice floe, his crew had set up a winter station hoping to be released from the ice later, but the Endurance was crushed by the pressure of sea ice and sank on Nov. 21, 1915. From there, Shackleton hoped to drift north to Paulet Island, 250 miles away, but eventually was forced to take his crew on lifeboats to the nearest land, Elephant Island, 346 miles from where the Endurance sank. He then took five of his men on an open-boat, 828-mile journey to South Georgia Island. Encountering hurricane-force winds, the team landed on South Georgia Island 15 days later, only to face a climb of 32 miles over mountainous terrain to reach a whaling station. Shackleton eventually organized his men's rescue on Elephant Island, reaching them on Aug. 30, 1916, 4½ months after he had set out for South Georgia Island. His entire crew survived, only to have two of them killed later in World War I.

You might consider Shackleton a failure for not even coming close to his original goal, but his success in saving his crew is regarded as the epitome of crisis leadership. As Harvard Business School professor Nancy F. Koehn, PhD, whose case study of Shackleton is one of the most popular at HBS, stated, "He thought he was going to be an entrepreneur of exploration, but he became an entrepreneur of survival."[2] Upon realizing the futility of his original mission, he pivoted immediately to the survival of his crew. "A man must shape himself to a new mark directly the old one goes to ground," wrote Shackleton in his diary.[3]

Realizing that preserving his crew's morale was critical, he maintained the crew's everyday activities, despite the prospect of dying on the ice. He realized that he needed to keep up his own courage and confidence as well as that of his crew. Despite his ability to share the strategic focus of getting to safety with his men, he didn't lose sight of day-to-day needs, such as keeping the crew entertained. When he encountered crew members who seemed problematic to his mission goals, he assigned them to his own tent.

Despite the extreme cold, his decision-making did not freeze – he acted decisively. He took risks when he thought appropriate, twice needing to abandon his efforts to drag a lifeboat full of supplies with his men toward the sea. "You can't be afraid to make smart mistakes," says Dr. Koehn. "That's something we have no training in."[4] Most importantly, Shackleton took ultimate responsibility for his men's survival, never resting until they had all been rescued. And he modeled a culture of shared responsibility for one another[5] – he had once offered his only biscuit of the day on a prior expedition to his fellow explorer Frank Wild.

Dr. Chang is chief of pediatric hospital medicine at Baystate Children's Hospital in Springfield, Mass., and associate professor of pediatrics at the University of Massachusetts, also in Springfield.

As winter arrives in 2020 and deepens into 2021, we will all be faced with leading our teams across the ice and to the safety of spring, and hopefully a vaccine. Whether we can get there with our entire crew depends on effective crisis leadership. But we can draw on the lessons provided by Shackleton and other crisis leaders in the past to guide us in the present.

Author disclosure: I studied the HBS case study "Leadership in Crisis: Ernest Shackleton and the Epic Voyage of the Endurance" as part of a 12-month certificate course in Safety, Quality, Informatics, and Leadership (SQIL) offered by Harvard Medical School.

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Community PHM

The importance of community pediatric hospital medicine

By Gregory Welsh, MD, FAAP

According to data from the American Academy of Pediatrics, over 2,000 physicians – or approximately 70% of all physicians practicing pediatric hospital medicine – do so in a community hospital. Like all areas of hospital medicine, community pediatric hospital medicine (CPHM) strives to fulfill one of our field's central tenets – providing high-quality, evidence-based care to our patients.

A phrase often used among CPHM practitioners is that, "if you've seen one CPHM program, you've seen one CPHM program." Every CPHM program is different. While this phrase may seem rather simplistic, it quite accurately portrays a unique aspect of our place in the hospital medicine field. CPHM programs usually require their practitioners to perform a broader range of roles and responsibilities than our colleagues who practice in university or children's hospitals. Typically, these roles are aligned with the unique needs of each hospital within which we practice and the communities we serve. Factors such as the distance to a tertiary care referral center, access to subspecialists, availability and expertise of ancillary services for children, and the particular needs of each community further shape the role that CPHM practitioners may be asked to play.

In 2014, the American Academy of Pediatrics section on hospital medicine's subcommittee on community hospitalists surveyed all CPHM programs to understand the unique roles that practitioners play within their institutions. Under the leadership of Clota Snow, MD, and Jacques Corriveau, MD, the aim was to contact every hospital in the country using the American Hospital Directory to see if they had a PHM program and to identify what roles the program was responsible for within their hospital.

Of the 535 programs identified, the primary responsibilities included inpatient care (85%), ED consultations (76%), and newborn nursery care (73%). Other common roles not typically associated with a university-based hospitalist's responsibilities included delivery room attendance/neonatal resuscitations (44%), neonatal ICU management (47%), and subspecialty or surgical comanagement (52%). In some communities, even pediatric ICU management, sedation, and patient transport are part of our role. Because of the large breadth of roles that a CPHM practitioner may cover, we have often been referred to as "pediatric hospital–based generalists."

"A career in CPHM provides physicians with the opportunity to work together with a close-knit group to provide exceptional care to children and to advocate for the medical needs of children in their hospital and their community."

Ideally, the presence of a pediatric hospitalist in a community hospital allows children to obtain high-quality, evidence-based care within their home communities. Most hospitalized children do not require direct access to subspecialists or all the pediatric-specific resources only available within a university or children's hospital. Thus, if these resources are not required for the child's care, CPHM practitioners can provide the care that a child needs in a setting that is less disruptive to the family and typically more cost effective.

CPHM physicians are often drawn to a career in a community hospital because it allows them to use their entire skill set to care for children with a wide variety of conditions. As they are often the only physicians in an adult hospital with a full understanding of the unique aspects of care that children require, it is important that they be comfortable in their role of managing the majority of pediatric care independently. Yet they also need to understand the limitations of their own ability, as well as their institution's level of expertise in pediatric-specific care. They must be confident and vocal advocates for pediatric-specific needs throughout their institution and its numerous committees, and form close working relationships with colleagues and administrators in the different fields with whom we share care of our patients (e.g., ED, obstetrics, radiology, trauma, and other medical and surgical subspecialties).

CPHM physicians are particularly well suited to partner with local outpatient providers as well as tertiary care physicians to provide coordinated transitions between the inpatient and outpatient management of a child's illness. In addition, a CPHM physician can often bring a unique and valuable perspective of the particular ethnic, cultural, and socioeconomic diversity of their community, as well as its available resources, to facilitate a greater level of engagement with the child's needs and ultimate success of their care.

The 2014 survey of CPHM programs identified several major challenges to recruitment and career satisfaction as a CPHM physician. These include a lack of access to subspecialists, a lack of pediatric-specific ancillary services and the perception that our importance as community hospital providers was not valued as much in the PHM community as PHM physicians working in a university/children's hospital setting. With the recent recognition of PHM as an official subspecialty by the American Board of Pediatrics, the concern has intensified within our field that a two-tiered system will develop with some PHM physicians being board certified and others not.

While the development of board subspecialization was not meant to limit the pool of providers available to staff community hospital sites, there is nowhere near the number of fellowship-trained physicians to provide an adequate workforce to staff CPHM programs. This means that many CPHM physicians will not be board certified in pediatric hospital medicine but does not mean that CPHM programs will be unable to provide high-quality local care that benefits children and their families, including safe care for children who require the skills that an immediately available CPHM physician can provide.

Many pediatric residency programs do not currently provide their trainees with exposure to community hospital medicine. Further, with increased sub-specialization throughout pediatrics, fewer residents are developing the necessary skill set to perform roles integral to a caring for children in community hospitals such as stabilization of a critically ill child prior to transport and complex neonatal resuscitation.

A career in CPHM provides physicians with the opportunity to work together with a close-knit group to provide exceptional care to children and to advocate for the medical needs of children in their hospital and their community. The AAP's subcommittee has made it a priority to engage physicians during all parts of their pediatric training about why a career in CPHM is exciting, fulfilling and a great life, as well as continuing to educate training programs at every level – as well as the larger PHM community – about why CPHM is a valuable and important part of pediatric medicine.

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prior to treatment, or dual antiplatelet therapy. XARELTO is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical efficacy and safety studies. Monitoring for the anticoagulation effect of rivaroxaban using a clotting test (PT, INR or aPTT) or anti-factor Xa (FXa) activity is not recommended.

Spinal/Epidural Anesthesia or Puncture

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

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

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

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

Use in Patients with Renal Impairment

Nonvalvular Atrial Fibrillation

Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly *[see Dosage and Administration (2.1) in Full Prescribing Information]*. Consider dose adjustment or discontinuation of XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations]*.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO in these patients.

Discontinue XARELTO in patients who develop acute renal failure while on treatment *[see Use in Specific Populations]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO in these patients.

Discontinue XARELTO in patients who develop acute renal failure while on treatment *[see Use in Specific Populations]*.

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO in these patients.

Discontinue XARELTO in patients who develop acute renal failure while on treatment *[see Use in Specific Population]*.

Use in Patients with Hepatic Impairment

No clinical data are available for patients with severe hepatic impairment.

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

Use with P-gp and Strong CYP3A Inhibitors or Inducers

Avoid concomitant use of XARELTO with known combined P-gp and strong CYP3A inhibitors *[see Drug Interactions]*.

Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A inducers *[see Drug Interactions]*.

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Risk of Pregnancy-Related Hemorrhage

In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress) *[see Warnings and Precautions and Use in Specific Populations]*.

Patients with Prosthetic Heart Valves

On the basis of the GALILEO study, use of XARELTO is not recommended in patients who have had transcatheter aortic valve replacement (TAVR) because patients randomized to XARELTO experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen. The safety and efficacy of XARELTO have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO is not recommended in patients with prosthetic heart valves.

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

Initiation of XARELTO is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including XARELTO, 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 also discussed in other sections of the labeling:

- Increased Risk of Stroke After Discontinuation in Nonvalvular Atrial Fibrillation *[see Boxed Warning and Warnings and Precautions]*
- Bleeding Risk *[see Warnings and Precautions]*
- Spinal/Epidural Hematoma *[see Boxed Warning and Warnings and Precautions]*

Clinical Trials Experience

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

During clinical development for the approved indications, 31,691 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 6962 patients who received XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily to treat DVT or PE (EINSTEIN DVT, EINSTEIN PE), 10 mg or 20 mg orally once daily (EINSTEIN Extension, EINSTEIN CHOICE) to reduce the risk of recurrence of DVT and/or PE; 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3); 3997 patients who received 10 mg orally once daily for prophylaxis of VTE and VTE-related death in acutely ill medical patients (MAGELLAN) and 9134 patients who received XARELTO 2.5 mg orally twice daily, in combination with aspirin 100 mg once daily, for the reduction in risk of major cardiovascular events in patients with chronic CAD or PAD (COMPASS).

Hemorrhage

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

Nonvalvular Atrial Fibrillation

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

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

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

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

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

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

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

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

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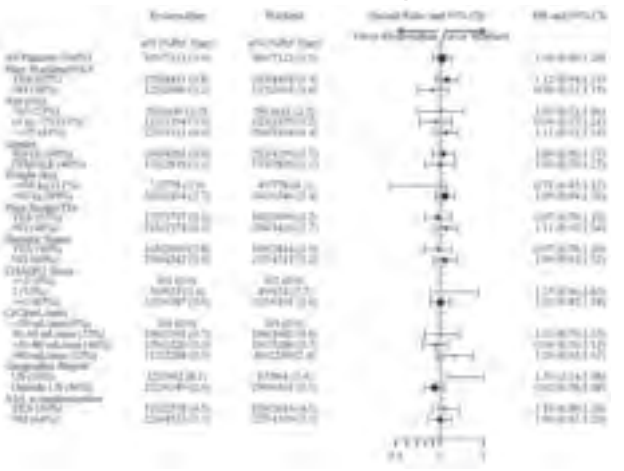
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

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

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

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

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



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

EINSTEIN DVT and EINSTEIN PE Studies

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

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

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

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

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

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

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

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

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

EINSTEIN CHOICE Study

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

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

Table 3: Bleeding Events* in EINSTEIN CHOICE

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

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.
† Treatment schedule: XARELTO 10 mg once daily or aspirin 100 mg once daily.
§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥ 2 units of whole blood or packed red blood cells.
¶ Bleeding which was clinically overt, did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

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

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

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

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

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

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In the MAGELLAN study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events. Cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed. Patients with bronchiectasis/pulmonary cavitation, active cancer (i.e., undergoing acute, in-hospital cancer treatment), dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months all had an excess of bleeding with XARELTO compared with enoxaparin/placebo and are excluded from all MAGELLAN data presented in Table 5. The incidence of bleeding leading to drug discontinuation was 2.5% for XARELTO vs. 1.4% for enoxaparin/placebo.

Table 5 shows the number of patients experiencing various types of bleeding events in the MAGELLAN study.

Table 5: Bleeding Events in MAGELLAN* Study–Safety Analysis Set - On Treatment Plus 2 Days

MAGELLAN Study¶	XARELTO 10 mg N=3218 n (%)	Enoxaparin 40 mg / placebo N=3229 n (%)
Major bleeding‡†	22 (0.7)	15 (0.5)
Critical site bleeding	7 (0.2)	4 (0.1)
Fatal bleeding§	3 (<0.1)	1 (<0.1)
Clinically relevant non-major bleeding events (CRNM)	93 (2.9)	34 (1.1)

* Patients at high risk of bleeding (i.e. bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastroduodenal ulcer or any bleeding in the previous three months) were excluded.
† Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.
‡ Defined as clinically overt bleeding associated with a drop in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.
§ Fatal bleeding is adjudicated death with the primary cause of death from bleeding.
¶ Patients received either XARELTO or placebo once daily for 35 ±4 days starting in hospital and continuing post hospital discharge or received enoxaparin or placebo once daily for 10 ±4 days in the hospital.

Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD

In the COMPASS trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 2.7% for XARELTO 2.5 mg twice daily in combination with aspirin 100 mg once daily vs. 1.2% for aspirin 100 mg once daily.

Table 6 shows the number of patients experiencing various types of major bleeding events in the COMPASS trial.

Table 6: Major Bleeding Events* in COMPASS - On Treatment Plus 2 days

Parameter	XARELTO plus aspirin† N=9134 n (%/year)	Aspirin alone† N=9107 n (%/year)	XARELTO plus aspirin vs. Aspirin alone HR (95 % CI)
Modified ISTH Major Bleeding‡	263 (1.6)	144 (0.9)	1.84 (1.50, 2.26)
- Fatal bleeding event	12 (<0.1)	8 (<0.1)	1.51 (0.62, 3.69)
Intracranial hemorrhage (ICH)	6 (<0.1)	3 (<0.1)	2.01 (0.50, 8.03)
Non-intracranial	6 (<0.1)	5 (<0.1)	1.21 (0.37, 3.96)
- Symptomatic bleeding in critical organ (non-fatal)	58 (0.3)	43 (0.3)	1.36 (0.91, 2.01)
ICH	23 (0.1)	21 (0.1)	1.09 (0.61, 1.98)
Hemorrhagic Stroke	18 (0.1)	13 (<0.1)	1.38 (0.68, 2.82)
Other ICH	6 (<0.1)	9 (<0.1)	0.67 (0.24, 1.88)
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	7 (<0.1)	6 (<0.1)	1.17 (0.39, 3.48)
- Bleeding leading to hospitalization (non-fatal, not in critical organ, not requiring reoperation)	188 (1.1)	91 (0.5)	2.08 (1.62, 2.67)
Major GI bleeding	117 (0.7)	49 (0.3)	2.40 (1.72, 3.35)

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.
† Treatment schedule: XARELTO 2.5 mg twice daily plus aspirin 100 mg once daily, or aspirin 100 mg once daily
‡ Defined as i) fatal bleeding, or ii) symptomatic bleeding in a critical area or organ, such as intraarticular, intramuscular with compartment syndrome, intraspinal, intracranial, intraocular, respiratory, pericardial, liver, pancreas, retroperitoneal, adrenal gland or kidney; or iii) bleeding into the surgical site requiring reoperation, or iv) bleeding leading to hospitalization.
CI: confidence interval; HR: hazard ratio; ISTH: International Society on Thrombosis and Hemostasis

Figure 2 shows the risk of modified ISTH major bleeding events across major subgroups.

Figure 2: Risk of Modified ISTH Major Bleeding Events by Baseline Characteristics in COMPASS – On Treatment Plus 2 Days

Other Adverse Reactions

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies are shown in Table 7.

Table 7: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies

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

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

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 8.

Table 8: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

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

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication
† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Postmarketing Experience

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

Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia
Gastrointestinal disorders: retroperitoneal hemorrhage
Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury)
Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema
Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS)

DRUG INTERACTIONS

General Inhibition and Induction Properties

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.

Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems

Interaction with Combined P-gp and Strong CYP3A Inhibitors

Avoid concomitant administration of XARELTO with known combined P-gp and strong CYP3A inhibitors (e.g., ketoconazole and ritonavir) *[see Warnings and Precautions and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Although clarithromycin is a combined P-gp and strong CYP3A inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with XARELTO as the change in exposure is unlikely to affect the bleeding risk *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Interaction with Combined P-gp and Moderate CYP3A Inhibitors in Patients with Renal Impairment

XARELTO should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk *[see Warnings and Precautions and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Drugs that Induce Cytochrome P450 3A Enzymes and Drug Transport Systems

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Anticoagulants and NSAIDs/Aspirin

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Fetal/Neonatal Adverse Reactions

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

Labor or Delivery

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

Data

Human Data

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

XARELTO® (rivaroxaban) tablets

Animal Data

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In EINSTEIN CHOICE, approximately 39% were 65 years and over and about 12% were >75 years. In the MAGELLAN study, approximately 67% were 65 years and over and about 37% were >75 years. In the COMPASS study, approximately 76% were 65 years and over and about 17% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients *[see Clinical Pharmacology (12.3) and Clinical Studies (14) in Full Prescribing Information]*.

Renal Impairment

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

Nonvalvular Atrial Fibrillation

Patients with Chronic Kidney Disease not on Dialysis

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

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study *[see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.

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

In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of XARELTO is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery

The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. In the RECORD 1-3 trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of XARELTO 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 mL/min.

XARELTO® (rivaroxaban) tablets

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

Patients with CrCl values <30 mL/min at screening were excluded from the MAGELLAN study. In patients with CrCl <30 mL/min a dose of XARELTO 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid use of XARELTO in patients with CrCl <15 mL/min.

Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD

Patients with Chronic Kidney Disease not on Dialysis

Patients with a CrCl <15 mL/min at screening were excluded from COMPASS, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min) *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, whose efficacy and safety outcomes were similar to those with preserved renal function.

Patients with End-Stage Renal Disease on Dialysis

No clinical outcome data is available for the use of XARELTO with aspirin in patients with ESRD on dialysis since these patients were not enrolled in COMPASS. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 2.5 mg twice daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in moderate renal impaired patients in the COMPASS study *[see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]*. It is not known whether these concentrations will lead to similar CV risk reduction and bleeding risk in patients with ESRD on dialysis as was seen in COMPASS.

Hepatic Impairment

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

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

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

OVERDOSAGE

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

Product of Germany

Finished Product Manufactured by:
Janssen Ortho LLC
Gurabo, PR 00778

or

Bayer AG
51368 Leverkusen, Germany

Manufactured for:
Janssen Pharmaceuticals, Inc.
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Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

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cp-62545v7

IMPORTANT SAFETY INFORMATION

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

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

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

B. Spinal/epidural hematoma

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

- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants, *see* Drug Interactions**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery**
- **Optimal timing between the administration of XARELTO® and neuraxial procedures is not known**

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue in patients with active pathological hemorrhage.
  - An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable.
  - Concomitant use of other drugs that impair hemostasis increases risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).
  - Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding: Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of XARELTO® for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage; active cancer (ie, undergoing acute, in-hospital cancer treatment); active gastroduodenal ulcer or history of bleeding in the three months prior to treatment; or dual antiplatelet therapy. XARELTO® is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. To reduce the potential risk of bleeding associated with concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Monitor frequently to detect signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.
- **Use in Patients with Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation in patients who develop acute renal failure while on XARELTO®. Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl <30 mL/min or end-stage renal disease (ESRD) on dialysis.
  - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
  - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
  - **Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
  - **Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD:** For patients with CrCl <15 mL/min, no data are available, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO® twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min), whose efficacy and safety outcomes were similar to those with preserved renal function. Clinical efficacy and safety studies with XARELTO® did not enroll patients with end-stage renal disease (ESRD) on dialysis.
- **Use in Patients with Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use with P-gp and Strong CYP3A Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A inhibitors or inducers.
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing. Promptly evaluate signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients with Prosthetic Heart Valves:** Use of XARELTO® is not recommended in patients who have had transcatheter aortic valve replacement (TAVR), based on the results of the GALILEO study, which reported higher rates of death and bleeding in patients randomized to XARELTO® compared to those randomized to an antiplatelet regimen. Safety and efficacy of XARELTO® have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO® is not recommended in patients with prosthetic heart valves.
- **Acute PE in Hemodynamically Unstable Patients/Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO® is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

Please read accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS for XARELTO®.

Xarelto®
rivaroxaban tablets

Xarelto® rivaroxaban tablets

BECAUSE A THROMBOTIC EVENT DOESN'T ALWAYS COME WITH A WARNING

CHOOSE XARELTO® TO HELP PROTECT THEM FROM THE UNEXPECTED

The DOAC with the most FDA-approved indications to treat and help protect against thrombotic events

▸ **APPROVED** in acutely ill medical patients*

INDICATIONS

XARELTO® (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).

There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.

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

*XARELTO® is indicated for the prophylaxis of venous thromboembolism (VTE) and VTE-related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE, and not at high risk of bleeding.

XARELTO® is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

XARELTO® is indicated, in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular [CV] death, myocardial infarction [MI], and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Increased Risk of Thrombosis in Patients with Antiphospholipid Syndrome:** Direct-acting oral anticoagulants (DOACs), including XARELTO®, 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.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase risk of bleeding.
- Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase risk of thromboembolic events.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase risk of bleeding.
- Avoid concurrent use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

USE IN SPECIFIC POPULATIONS

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

OVERDOSAGE

- Overdose of XARELTO® may lead to hemorrhage. Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

ADVERSE REACTIONS IN CLINICAL STUDIES

- Most common adverse reactions with XARELTO® were bleeding complications.

Please read accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS for XARELTO®.

cp-62551v6

DOAC = direct oral anticoagulant.

XARELTO® is licensed from Bayer HealthCare AG, 51368 Leverkusen, Germany.

 April 2020 cp-112772v3

Xarelto® rivaroxaban tablets

Janssen Pharmaceuticals, Inc.

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