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Updates in the Literature

2nd Annual Inpatient Medicine for NPs & PAs:
Hospital Care from Admission to Discharge

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Sawgrass Marriott Hotel • Ponte Vedra Beach, Florida
Disclosures

• None
Which of the following statements is true?

1. Lung ultrasound can help diagnose pleural effusion or heart failure, but not pneumonia or pneumothorax

2. Most patients with diverticulitis require surgery after the second episode

3. Procalcitonin can help differentiate between pneumonia and CHF in the dyspneic patient in the ED

4. There are no FDA approved antidotes for the direct oral anticoagulants (e.g. dabigatran)

5. The recommended duration of antibiotic therapy for an abdominal abscess after drainage is 14-21 days
Which of the following statements is true?

1. Lung ultrasound can help diagnose pleural effusion or heart failure, but not pneumonia or pneumothorax
2. Most patients with diverticulitis require surgery after the second episode
3. Procalcitonin can help differentiate between pneumonia and CHF in the dyspneic patient in the ED
4. There are no FDA approved antidotes for the direct oral anticoagulants (e.g., dabigatran)
5. The recommended duration of therapy for an abdominal abscess after drainage is 14-21 days
Case Presentation

• You are called by the Emergency Center to admit a 78-year-old man with heart failure versus pneumonia and cellulitis.

• He has a history of hypertension, obesity, obstructive sleep apnea, ischemic cardiomyopathy with an ejection fraction of 45% treated medically, atrial fibrillation, previously on warfarin, currently on apixaban.
Case Presentation

• He was admitted for heart failure exacerbation last year following a respiratory infection and nonadherence with his diuretic.

• As far as you can tell, he is treated with appropriate medical therapy including an ACE inhibitor, diuretic, beta blocker, spironolactone.

• The patient has a history of sigmoidectomy 2 years ago.
Case Presentation

• He presented at that time with perforated diverticulitis which was complicated by an intra-abdominal abscess that was drained percutaneously. He was treated subsequently with intravenous antibiotics for 14 days.

• Last year, he had an episode of thigh cellulitis that was treated with Bactrim as an outpatient; he has a remote history of MRSA skin/soft tissue infections.
Case Presentation

- Two days ago, he developed a fever and he has been more short of breath; examination of his left thigh revealed cellulitis and his lung exam shows crackles bilaterally. His doctor was concerned about heart failure exacerbation, possible pneumonia and cellulitis.

- He was sent to the emergency room in a wheelchair. He is mildly hypoxic on room air, he does have leukocytosis.
Case Presentation

- Chest x-ray - difficult to interpret due to body habitus - low lung volumes, basilar opacities that may represent consolidation versus heart failure versus atelectasis, “clinical correlation suggested”.

- You take your history, examine the patient, order appropriate studies, admit the patient.
Case Presentation

• He has congestive heart failure exacerbation and mild cellulitis.

• You treat him with diuretics and antibiotics and he is discharged home in the next 2 days, back to his baseline.
Questions about this case, addressed in the literature published in the last few years

• Are there any other diagnostic modalities that we could use at the point-of-care to differentiate between pneumonia and heart failure to aid your clinical exam?
Questions

• Is Trimethoprim/Sulfamethoxazole a good drug for cellulitis in the outpatient setting? How about in a patient with congestive heart failure? How about if my patient is bacteremic?

• Are there any new antibiotics for cellulitis with MRSA coverage that can be used parenterally without the need for a PICC line?
Questions

• What is the natural history of sigmoid diverticulitis?

• What is the appropriate duration of antibiotic treatment after source control for an intra-abdominal infection?

• When this patient had sigmoid surgery after abscess drainage, did he really need “bridging” with LMWH?

• Are there any new agents capable of reversing DOAC activity?
Question 1

• Are there any other diagnostic modalities that we could use at the point-of-care to differentiate between pneumonia and heart failure to aid your clinical exam? –Point of Care Ultrasound, Procalcitonin
Pivetta E et al. Lung ultrasound-implemented diagnosis of acute decompensated heart failure in the ED

• Lung ultrasound can be used to diagnose congestive heart failure (CHF) via detection of B-lines — vertical hyperechoic lines extending from the pleural line to the bottom of the ultrasound screen that result from reverberation artifact owing to interstitial fluid in otherwise aerated lungs.

• Multicenter Italian study: assess the accuracy of lung ultrasound for detecting CHF in patients presenting with acute dyspnea.
Pivetta E et al. Lung ultrasound-implemented diagnosis of acute decompensated heart failure in the ED

- Ultrasound was performed in the emergency department by trained emergency physicians.
- Adjudication by two experts who relied on all available data (but were blinded to lung ultrasound results) was the gold standard.
- Among 1005 patients, the final diagnosis was acute decompensated heart failure in 46%. The negative and positive predictive values of clinical assessment plus lung ultrasound were both 97%.
Pivetta E et al. Lung ultrasound-implemented diagnosis of acute decompensated heart failure in the ED

• Lung ultrasound alone had negative and positive predictive values of 92%, which were significantly higher than the values of 76% and 77%, respectively, for chest x-ray alone.

• Accuracy is operator-dependent

• Training is required
Nazerian P et al. Accuracy of lung ultrasound for the diagnosis of consolidations when compared to chest computed tomography.

• Prospective study; compared lung ultrasound to CT and CXR among adult patients presenting with unexplained respiratory symptoms to an academic emergency department in Italy.

• CT served as the gold standard for diagnosis of an infiltrate consistent with pneumonia. Patients were enrolled when a CT scan was planned.
Nazerian P et al. Accuracy of lung ultrasound for the diagnosis of consolidations when compared to chest computed tomography.

• Bedside lung ultrasound was performed within 3 hours of the CT scan by either emergency physicians or internists, and chest x-ray was performed at the discretion of the treating physician.

• 8-month study. 285 patients underwent CT and ultrasound, and, of these, 190 also had a chest x-ray. Chest CT was positive for pneumonia in 87 patients.
Nazerian P et al. Accuracy of lung ultrasound for the diagnosis of consolidations when compared to chest computed tomography.

- **Sensitivity** for diagnosing pneumonia was significantly higher with ultrasound than x-ray (81% vs. 64%), while specificities were statistically similar (94% and 90%).

- Requires external validation. Suggests that ultrasound may be superior to x-ray for diagnosing pneumonia.
Lung ultrasound—Normal Lung and Consolidation
Lung ultrasound- Consolidation

http://www.criticalecho.com/content/tutorial-9-lung-ultrasound
Lung ultrasound-Consolidation

http://www.criticalecho.com/content/tutorial-9-lung-ultrasound
Lung ultrasound- Interstitial Edema
Lung ultrasound - M mode Normal Lung
Lung ultrasound- M mode Pneumothorax
Alba GA et al. Diagnostic and prognostic utility of procalcitonin in patients presenting to the emergency department with dyspnea

- Pooled data from two studies point to the potential value of a 0.10-ng/mL cutoff value of procalcitonin, but clearer outcomes data are needed.

- To better explore the value of measuring procalcitonin to diagnose pneumonia in patients with acute dyspnea, researchers pooled data from 453 patients enrolled in two previous ED-based investigations: PRIDE and BIONICS-HF.
Alba GA et al. Diagnostic and prognostic utility of procalcitonin in patients presenting to the emergency department with dyspnea

- A maker of procalcitonin assays funded the analysis.

- The final diagnosis was acutely decompensated HF in 212 patients (47%), pneumonia in 30 (6.5%), and both HF and pneumonia in another 30 (6.5%). The median procalcitonin level was significantly higher in patients with pneumonia than in those without pneumonia (0.38 ng/mL vs. 0.06 ng/mL).
Alba GA et al. Diagnostic and prognostic utility of procalcitonin in patients presenting to the emergency department with dyspnea

• Among patients whose clinical likelihood of HF exceeded 75%, a procalcitonin cutoff value of 0.10 ng/mL had a sensitivity for identifying pneumonia of 95% and a negative predictive value (NPV) of 99%

• For patients with a <25% likelihood of HF, that procalcitonin cutoff value had a specificity of 85% and an NPV of 95%.

• The effect on outcomes of procalcitonin measurement is unknown.
Questions -2

• Is trimethoprim sulfamethoxazole a good drug for cellulitis in the outpatient setting? –**Reasonable option in selected cases, in otherwise healthy patients**

• How about in a patient with congestive heart failure? –**Careful- hyperkalemia, excess mortality**

• How about if my patient is bacteremic? –**No**

• Are there any new antibiotics that can be used parenterally without the need for a PICC line? - *Dalbavancin, Oritavancin; Tedizolid*
Miller LG et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections.

• For skin abscesses, methicillin-resistant Staphylococcus aureus (MRSA) is a predominant pathogen in many areas of the U.S.; for cellulitis, its role is less certain.

• To compare clindamycin with trimethoprim-sulfamethoxazole (TMP/SMX) for the treatment of uncomplicated skin infections, investigators conducted a prospective, randomized, double-blind clinical trial at four medical centers located in areas where community-acquired MRSA is endemic.
Miller LG et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections.

- 524 outpatients (mean age, 27.1 years; 30% aged <18), of whom 54% had cellulitis only, 30% had abscess only, and 16% had both. The pathogen most commonly recovered from positive cultures was S. aureus (41%).

- The medications were given for 10 days; all abscesses were incised and drained.

- In the intention-to-treat cohort, the cure rate 7 to 10 days after completion of therapy (the primary study outcome) was 80% in the clindamycin arm and 78% in the TMP/SMX arm (P=0.52).
Miller LG et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections.

- Adverse effects –mostly GI complaints -19% of both treatment groups. Neither *Clostridium difficile* infection, nor serious adverse events were reported in either group, and skin rash was uncommon (~1%) in both.

- Monotherapy with TMP-SMX may be a treatment option for nonpurulent cellulitis — for a very select younger subpopulation with uncomplicated infections, without systemic manifestations, and with few or no comorbid conditions.
Miller LG et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections.

• β-lactam antibiotics with activity against β-hemolytic streptococci and S. aureus (e.g., cephalexin or dicloxacillin) are the first-line empirical treatment options for nonpurulent cellulitis.
Fralick M et al. Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system

• Old study in 2010. Hospitalization for hyperkalemia was associated with TMP/SMX use in patients who took ACE inhibitors or ARBs.

• Population-based, case-control study, investigators examined whether TMP/SMX plus ACE inhibitors or ARBs is associated with excess risk for sudden death.

• 1994 to 2012, 1.6 million older patients (age, ≥65) in Ontario were treated with ACE inhibitors or ARBs.
Fralick M et al. Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system

- 1110 and 1827 of these patients died suddenly within 7 or 14 days, respectively, after receiving outpatient prescriptions for one of five common antibiotics.

- Each case was matched by age, sex, presence of kidney disease, and presence of diabetes with at least one living control who also received one of the antibiotics.
Compared with amoxicillin (used as the reference exposure because it is not associated with hyperkalemia), TMP/SMX was associated with significantly greater risk for sudden death within 7 days (adjusted odds ratio, 1.4) and within 14 days (AOR, 1.5) of exposure.

The results were similar after excluding patients with congestive heart failure at excess risk for sudden death.
Fralick M et al. Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system

• In older patients taking ACE inhibitors and ARBs, TMP/SMX use was associated with excess risk for sudden death — presumably from trimethoprim-induced hyperkalemia.

• 3 sudden deaths with TMP/SMX versus 1 sudden death with amoxicillin per 1000 prescriptions. Large number of patients are receiving ACE inhibitors and ARBs and TMP/SMX is also prescribed often.
Antoniou T et al. Trimethoprim–sulfamethoxazole and risk of sudden death among patients taking spironolactone.

• 18-year period, 349 patients (age, ≥66) died suddenly while taking both spironolactone and one of five antibiotics (TMP/SMX, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin).

• Each case was matched with as many as four age- and sex-matched controls who took spironolactone plus one of the aforementioned antibiotics but did not die.

• In adjusted analyses, **TMP/SMX** was associated with highly significant **excess risk for sudden death compared with amoxicillin**, the reference standard (adjusted odds ratio, 2.5).
Antoniou T et al. Trimethoprim–sulfamethoxazole and risk of sudden death among patients taking spironolactone.

- Ciprofloxacin (which can prolong the QT interval) and nitrofurantoin (which was associated with hyperkalemia in a prior study) were associated with excess sudden-death risks of borderline statistical significance (adjusted ORs, 1.6 and 1.7, respectively). Norfloxacin was not associated with sudden death.

- Avoid coadministration of TMP/SMX and spironolactone

- Residual confounding could explain these results, but spironolactone and trimethoprim interfere with renal potassium excretion.
Paul M et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant Staphylococcus aureus

• Vancomycin - MRSA infections.
• Issues: monitoring levels, toxicity
• MRSA usually sensitive to TMP/SMX-effective in treating MRSA skin infections.
• How does it compare for severe MRSA infections (bacteremia or pneumonia)?
Paul M et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant Staphylococcus aureus

- Israel - open-label, controlled trial
- 252 participants (including 91 with MRSA bacteremia) at four hospitals were randomized to receive vancomycin (starting at 1 g) or high-dose TMP/SMX (starting at 320 mg of TMP/1600 mg of SMX) intravenously twice daily.
Paul M et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant Staphylococcus aureus

- Overall, rates of the primary outcome — clinical treatment failure (measured by several indices) at 7 days — were similar between arms (38% with TMP/SMX and 27% with vancomycin).

- 30-day all-cause mortality was also similar between groups (14% and 11%, respectively).
Paul M et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant Staphylococcus aureus

- In the patients with bacteremia, the 30-day mortality rate was nearly twice as high in the TMP/SMX group as in the vancomycin group (risk ratio, 1.90; 95% confidence interval, 0.92–3.93).

- The predefined 15% non-inferiority criterion was not met.
Boucher HW et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection

- 2 multicenter, multinational, double-blind, double-dummy, randomized trials

- Compared dalbavancin (1 dose intravenously on days 1 and 8) with vancomycin (1 dose intravenously every 12 hours, with an option to switch to oral linezolid after ≥3 days, for a total of 10–14 days).

- Overall, an early clinical response indicating treatment success (the primary end point) was seen in 79.7% and 79.8% of the dalbavancin and vancomycin/linezolid groups, respectively.

- Adverse events were more common in the vancomycin/linezolid group
Corey GR et al. Single-dose oritavancin in the treatment of acute bacterial skin infections

- Multinational, randomized, double-blind trial comparing oritavancin (1 dose intravenously on day 1) with vancomycin (administered intravenously twice daily for 7–10 days).
- Based on a prespecified non-inferiority margin of 10 percentage points, oritavancin was non-inferior to vancomycin on all three efficacy end points.
- Serious adverse events were comparable between groups; the proportion of participants discontinuing the study drug due to adverse events was lower in the oritavancin group.
Questions-3

• What is the natural history of sigmoid diverticulitis? – At 4 years, 7% recurrence, 2% surgery that was emergent

• What is the appropriate duration of antibiotic treatment after source control for an intra-abdominal infection? -4 days
Li D et al. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: A population-based analysis

- Debatable role elective surgery after one or two episodes of uncomplicated diverticulitis to prevent recurrences.
- Ontario retrospective study: population-based administrative database.
- The cohort included 14,121 patients who were hospitalized with first episodes of acute diverticulitis between 2002 and 2012 and were managed nonoperatively.
Li D et al. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: A population-based analysis

- Patients readmitted within 30 days of index admissions were excluded because these cases likely represented persistent rather than recurrent disease.

- During median follow-up of 4 years, 6.8% of patients were readmitted once, and 1.3% were readmitted more than once; only 1.8% required emergency surgery.
Li D et al. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: A population-based analysis

- Readmissions were most likely during the first 2 years and declined subsequently.
- Patients whose index episodes of diverticulitis were complicated by perforation or abscess were about three times more likely to require emergency surgery during follow-up than those with uncomplicated index episodes.
Li D et al. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: A population-based analysis

• Risk for recurrent hospitalization or need for emergency surgery - low.

• Does not answer the question of number of recurrent episodes that should indicate surgery

• Suggests a benign course for most patients — even those whose with initial complicated episodes.

• Outpatient managed recurrences -not captured in this study.

Ann Surg 2014 Sep; 260:423
The lifetime risk for diverticulitis in patients with diverticulosis is about 5%.

About 20% of patients with acute uncomplicated diverticulitis will have a recurrence, and most recurrences are not complicated.

Routine use of broad-spectrum antibiotics for uncomplicated acute diverticulitis may not reduce symptom duration but may reduce complications and recurrences; the latter remains uncertain.
• The risk for a major complication from elective surgical resection after recovery from acute diverticulitis is about 10%.

• Factors that may reduce the risk for recurrence include a high-fiber diet, avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs), avoidance of aspirin, and regular use of probiotics.
Rifaximin may prevent recurrences, but the data are limited.

The evidence does not show a benefit for mesalamine in preventing recurrences.

Data on avoidance of seeds, nuts, corn, and popcorn are extrapolated from the data on prevention of first episodes, which suggest that nut and popcorn consumption improves outcomes whereas corn consumption may have a negative effect on outcomes.
Simianu VV et al. The impact of elective colon resection on rates of emergency surgery for diverticulitis

• Elective sigmoid colectomy was advocated in patients who had experienced two episodes of uncomplicated diverticulitis - it would prevent subsequent episodes of complicated diverticulitis leading to higher-risk emergency surgery.

• 2006- ASCRS guidelines-advised against elective “prophylactic” surgery after an arbitrary number of episodes of uncomplicated diverticulitis
Simianu VV et al. The impact of elective colon resection on rates of emergency surgery for diverticulitis

- Population-based retrospective study using a hospital database from Washington state
- 1987-2012, the annual rate of elective colectomy for diverticulitis went from 8 to 17 procedures per 100,000 people.
- If elective colectomy had prevented subsequent emergency surgery for diverticulitis, the rate of emergency surgery should have fallen between 1987 and 2012
Simianu VV et al. The impact of elective colon resection on rates of emergency surgery for diverticulitis

• However, the annual rate of emergency surgery also increased — from 7 to 10 procedures per 100,000 people. Rates of hospital admissions for acute diverticulitis and rates of percutaneous drainage procedures also increased over time.

• These results suggest that elective colon resection for a patient with previous uncomplicated diverticulitis does not prevent subsequent emergency surgery.
Simianu VV et al. The impact of elective colon resection on rates of emergency surgery for diverticulitis

• Surgeons have been performing elective surgery increasingly, despite the ASCRS guideline that discourages it.

• The growing availability of laparoscopic colon surgery might in part explain these findings.
Sawyer RG et al. Trial of short-course antimicrobial therapy for intraabdominal infection

- For complicated intra-abdominal infections, the optimal duration of antimicrobial therapy after achievement of source control remains unclear.

- Open-label trial multicenter - U.S. and Canada

- Compared fixed-duration antimicrobial therapy (4 days) after source control versus traditional strategy (antibiotic administration until 2 days after resolution of fever, leukocytosis, and ileus).

- Randomized in a 1:1 ratio to the fixed-duration (experimental) or the traditional-strategy (control) group, with therapy duration for the control group capped at 10 days.
Sawyer RG et al. Trial of short-course antimicrobial therapy for intraabdominal infection

- 30 day follow-up after the initial source-control procedure and included assessment for infectious complications and all-cause mortality (the composite primary endpoint), as well as for use of antimicrobial therapy.

- 517 patients completed 30-day follow-up. Commonly, infections originated in the colon or rectum; the source-control procedure was percutaneous in one third of each group.

- The composite primary endpoint =22% of patients in each arm.
Sawyer RG et al. Trial of short-course antimicrobial therapy for intraabdominal infection

- The median duration of antimicrobial therapy was 4.0 days (interquartile range, 4.0–5.0) and 8.0 days (interquartile range, 5.0–10.0) in the experimental and control groups, respectively (absolute difference, –4.0 days; 95% confidence interval, –4.7 to –3.3).

- Non-adherence =common — 18.2% in the experimental group and 27.3% in the control group did not receive antibiotics for the specified duration (P=0.02).
Sawyer RG et al. Trial of short-course antimicrobial therapy for intraabdominal infection

- In patients with complicated intra-abdominal infection, *source control is paramount*.
- Shortening therapy does not appear to increase the risk for adverse outcomes.
- Antibiotic overuse is not justified.
Questions- 4

• Did this patient require enoxaparin bridging for his sigmoid surgery? No
• Are there any new agents capable of reversing DOAC activity? Yes
Douketis JD et al. Perioperative bridging anticoagulation in patients with atrial fibrillation

- Randomized trial: 1800 warfarin-treated adults with AF and CHADS$_2$ (congestive heart failure, hypertension, age $\geq 75$, diabetes, stroke) scores $\geq 1$ who were undergoing elective invasive procedures or surgery.

- Patients were bridged with subcutaneous dalteparin (_________) or placebo from 3 days before their procedures until 24 hours before their procedures; bridging was resumed at 1 or 2 days after procedures and was continued until patients achieved full warfarin anticoagulation.

Douketis JD et al. Perioperative bridging anticoagulation in patients with atrial fibrillation

- Patients with recent arterial or venous thromboembolism (within 3 months) or mechanical heart valves were excluded.

- Arterial thromboembolism within 30 days did not differ in the two groups (0.3% and 0.4%).

- Significantly more patients in the bridging group than in the placebo group experienced major bleeding (3.2% vs. 1.3%; number needed to harm [NNH], 53) and minor bleeding (21% vs. 12%; NNH, 11).

- Incidences of acute myocardial infarction, venous thromboembolism, and death were similar in the two groups.
Douketis JD et al. Perioperative bridging anticoagulation in patients with atrial fibrillation

• Forgoing bridging anticoagulation is safe in many AF patients who require surgery.

• Average CHADS$_2$ score in this study was 2.3, and 90% of patients underwent minor procedures (e.g., endoscopic, dermatologic, or dental procedures, or cardiac catheterization).

• Uncertain if results apply to patients with higher CHADS$_2$ scores, to those undergoing major surgery is uncertain or to the subgroup of patients with histories of transient ischemic attacks or stroke.
Temporary interruption of anticoagulation

- Indication for anticoagulation
- The type of anticoagulant
- Estimated bleeding risk for procedure
- Projected duration of interruption
- Individualized decision
Temporary interruption of anticoagulation

- DVT prevention:
  - Thrombophilia disorders
  - Prior history of DVT/PE
  - Cancer
- Stroke Prevention
  - Atrial fibrillation
  - Embolic stroke
- Mechanical heart valves
Temporary interruption of anticoagulation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Excretion</th>
<th>Half life (hours)</th>
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<tbody>
<tr>
<td>UFH</td>
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<td>Enoxaparin</td>
<td>Renal</td>
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</tr>
<tr>
<td>Dalteparin</td>
<td>Renal</td>
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<tr>
<td>Fondaparinux</td>
<td>Renal</td>
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<td>Rivaroxaban</td>
<td>Renal, Biliary</td>
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<td>Renal, Biliary</td>
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<tr>
<td>Edoxaban</td>
<td>Renal</td>
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Procedure Bleeding Risk

- **High risk**
  - Urological procedures and surgery, TURP, nephrectomy, tumor ablations
  - Pacemaker or ICD placement with separation of thoracic fascia
  - Colonic polyp resection, typically large polyps > 1cm, sessile polyps
  - Surgery and procedures in highly vascular organs such as kidneys, liver and spleen
  - Major surgery with extensive tissue injury, cancer surgery, joint arthroplasty, reconstructive plastic surgery
  - Cardiac, intracranial or spinal surgery, where small bleeds can have serious consequences.

- **Low Risk**
  - Superficial procedure
  - Breast procedures
  - Endoscopic procedure
<table>
<thead>
<tr>
<th>RISK ASSESSMENT</th>
<th>Mech. Valve</th>
<th>A. Fib</th>
<th>VTE</th>
</tr>
</thead>
</table>
| **HIGH** (>10% per year) | All except below | · CHADS<sub>2</sub> 5-6 or prior history of stroke with interruption of anticoagulation  
· Stroke/TIA < 3mo  
· Rheumatic valve heart disease  
· Intracardiac thrombus | · VTE < 3mo  
· Severe thrombophilia (protein C or S deficiency, antithrombin III deficiency, antiphospholipid antibody syndrome) |
| **MODERATE** (4-10% per year) | · Bileaflet AV prosthesis and atrial fibrillation | · CHADS<sub>2</sub> 3-4 | · VTE within 3-12 months  
· Heterozygous inherited thrombophilia (factor II or factor V Leiden)  
· Active cancer  
· Recurrent VTE |
| **LOW** (<4% per year) | · Bileaflet AV prosthesis without atrial fibrillation or other risk factors for stroke | · CHADS<sub>2</sub> 0-2 (and no prior stroke or TIA) | · Single VTE >12months (and no other risk factors) |

Prosthetic Heart Valves

- Caged –Ball (ex. Starr-Edwards)
- Tilting Disc (ex. Bjork-Shiley, Medtronic-Hall)
- Bi-leaflet (ex. St. Jude, Carbomedics)
CHADS 2 Score Risk

<table>
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<tr>
<th>CHADS2</th>
<th>Score</th>
<th>Stroke risk/year</th>
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<tr>
<td>Risk Factor</td>
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<tr>
<td>HTN</td>
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<tr>
<td>DM</td>
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<tr>
<td>Stroke, TIA</td>
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# Bridging recommendations

<table>
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<tr>
<td>High</td>
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<td>Consider low dose LMWH</td>
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<tr>
<td>Low</td>
<td>No bridge</td>
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</table>
Bridging regimens

- UFH IV regimen: ESRD patients
- Outpatient LMWH
  - Low dose: prophylactic regimen Enoxaparin 40mg or Dalteparin 5000 units daily
  - Intermediate dose*: Enoxaparin 40mg bid
  - Therapeutic full dose regimen: Enoxaparin 1mg/kg bid or 1.5mg/kg daily or Dalteparin 100u/kg bid or 200 u/kg daily
Temporary interruption of anticoagulation - Warfarin

- Full interruption: Goal normal INR
  - INR < 3.5: Stop 5 days prior to procedure
  - INR > 3.5: Stop 6-7 days prior to procedure
  - Restart usual dose night of procedure or next day

- Partial interruption: Goal INR < 1.5
  - Stop 2-3 days prior to procedure
  - Restart usual dose night of procedure or next day
## Temporary interruption of anticoagulation-DOACs

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Renal function, Cr Cl ml/min; dose in mg</th>
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Temporary interruption of anticoagulation-DOACs

- New oral anticoagulants usually do not require bridge therapy (quick acting agents)
  - Factor Xa inhibitors can be stopped 2-3 days prior to procedure
  - Dabigatran can be stopped 2-3 days prior to procedure with normal renal function but require longer interruption with renal impairment
  - Re-start 48-72 hours after achieving surgical hemostasis
  - Consider LMWH therapy only if prolonged interruption > 10 days
Periprocedural bridging

- Risk assess all patients on anticoagulation going for procedures and individualize therapy.
  - Most patients do not need bridge therapy
  - Reserve bridge therapy for high-risk patients: Recent DVT/stroke, high-risk thrombophilia, CHADS2 score >4, Mechanical valves

- Do not use IVC filter for primary prophylaxis
  - Avoid use and remove early
Oral anti-Xa inhibitors apixaban, edoxaban, and rivaroxaban have advantages over vitamin K antagonists, but the absence of an anti-Xa reversal agent has limited their widespread adoption.

Andexanet is a compound that binds tightly to the active site of these anti-Xa anticoagulants, preventing further inhibition of factor Xa.
Siegal DM et al. Andexanet alfa for the reversal of factor Xa inhibitor activity

- Industry-sponsored, double-blind, placebo-controlled, phase II trial in nonbleeding adults aged 50 to 75.
- Participants received either apixaban (5 mg) or rivaroxaban (20 mg) for 4 days followed by a 400 mg intravenous bolus of andexanet; some subjects then received a 2-hour continuous intravenous infusion of andexanet.
- The primary endpoint was the percent change in anti-Xa activity.
Siegal DM et al. Andexanet alfa for the reversal of factor Xa inhibitor activity

• Within 2 to 5 minutes of receiving the andexanet bolus, participants experienced a >90% decline in the anti-Xa activity of either apixaban or rivaroxaban.

• The reduction of anti-Xa activity persisted for up to 2 hours after the andexanet bolus, whether given with or without an infusion. All andexanet recipients but one, who did not receive the full dose of andexanet, had a ≥80% reversal of anti-Xa activity (P<0.001).

• No serious adverse events were associated with andexanet, but one recipient developed urticaria during the infusion, which resolved with discontinuation of the drug and administration of an antihistamine.
SJ Connolly et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors

- Industry-sponsored, multicenter, prospective, open-label, single-group study of 67 elderly patients (mean age, 77) with major gastrointestinal bleeding (33 patients), intracranial bleeding (28), or other bleeding (6) associated with the use of rivaroxaban, apixaban, or enoxaparin.

- Andexanet was given as a bolus dose and a 2-hour intravenous infusion. Efficacy was examined in the subset of patients with elevated blood levels of these anticoagulants.
SJ Connolly et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors

- In 26 patients given rivaroxaban, median anti–factor Xa levels fell from 277 ng/mL to 16.8 ng/mL after the bolus dose of andexanet, and hemostatic efficiency was rated as excellent or good in 81% of these patients.

- In 20 patients given apixaban, median anti–factor Xa levels fell from 149.7 ng/mL to 10.3 ng/mL, and hemostatic efficiency was excellent or good in 75%.
SJ Connolly et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors

• In one patient given enoxaparin, anti–factor Xa activity declined from 0.61 IU/mL to 0.15 IU/mL, and bleeding was controlled.

• Thrombotic events occurred in 12 (18%) of the patients, but only one had a therapeutic dose of anticoagulant restarted before the event.

• 10 deaths occurred (15%); 6 were cardiovascular-related.
SJ Connolly et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors

- Andexanet rapidly reduced elevated anti–Xa factor levels and controlled bleeding in most of these patients.
- However, the FDA has withheld approval of the drug pending additional manufacturing data and further experience with enoxaparin, so the current clinical trial is continuing.
Glund S et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers

• Dabigatran is a direct thrombin inhibitor that is approved for the prevention of stroke in atrial fibrillation and for the treatment of venous thromboembolism. Bleeding is usually managed by discontinuing the drug or, if severe, by giving a prothrombin complex concentrate.

• Monoclonal antibody fragment, idarucizumab, which tightly binds to dabigatran and nullifies its anticoagulant activity
Glund S et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers

• Trial conducted by the drug manufacturer

• Participants were given dabigatran for 4 days and then intravenous doses of idarucizumab, ranging from 1 to 5 g.

• Coagulation variables (thrombin times, ecarin clotting time, activated clotting time, and partial thromboplastin time) were all prolonged on day 3 of dabigatran dosing, and mild bleeding was observed in four participants (3 with hematuria and 1 with epistaxis).
Glund S et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers

• Infusion of idarucizumab resulted in an immediate and complete reversal of the dabigatran-induced increases in clotting tests, which was maintained for at least 72 hours with all but the 1 g dose of idarucizumab.

• The antidote was well-tolerated; no serious or severe adverse events were observed.
Pollack CV Jr et al. Idarucizumab for dabigatran reversal.

- 90 patients who were being treated with dabigatran: 51 who experienced bleeding (intracranial, 18; gastrointestinal, 20), and 39 who required urgent interventions.
- The median time since the last dose of dabigatran was 15.4 hours, and the dose of idarucizumab used for reversal was 5 g.
Pollack CV Jr et al. Idarucizumab for dabigatran reversal.

• After infusion of the antidote, the dilute thrombin time was normalized in more than 90% of patients, and the concentration of unbound dabigatran was <20 ng/mL at 24 hours in 79%.

• In the patients with hemorrhage, the median time for bleeding cessation was 11.4 hours, and in those undergoing surgery, normal intraoperative hemostasis was reported in 92%. In the 72 hours following administration of idarucizumab, only one patient had a thrombotic event.
Staerk L et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation

- Danish investigators-nationwide registry data to assess the relationship between anticoagulant use after GI bleeding and rates of stroke, recurrent bleeding, and death.

- 4602 patients with AF (mean age 78) who were receiving anticoagulation before a GI bleed, 27% did not resume any antithrombotic therapy within the subsequent 3 months, 21% resumed oral anticoagulation, and the remainder resumed a combination of anticoagulant and antiplatelet therapy.
Staerk L et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation

- Over the next 2 years, approximately 40% died, 12% had a thromboembolic event, 12% had recurrent GI bleeding, and 17% had major bleeding.

- Compared with not restarting antithrombotic treatment, resumption of oral anticoagulation alone was associated with a significantly lower risk for all-cause mortality (hazard ratio, 0.39) and thromboembolism (HR, 0.41) even though it non-significantly increased the risk for recurrent GI bleeding (HR, 1.22; 95% confidence interval, 0.84–1.77) and significantly increased the overall risk for major bleeding (HR, 1.37; 95% CI, 1.06–1.77).
Staerk L et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation

• AF-related strokes are preventable

• One third of AF patients do not receive anticoagulant therapy. One common reason is a history of GI bleeding.

• This study indicates that thromboembolic risk weighs more heavily on AF patients' life expectancy than does bleeding risk (stroke has a fourfold-higher mortality rate than GI bleeding).

• Given the available data, withholding anticoagulant therapy solely on the basis of a prior GI bleed is difficult to justify.
Goette A et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): A randomised, open-label, phase 3b trial

• Elective cardioversion for atrial fibrillation (AF), standard anticoagulation lasts for 3 weeks before and 4 weeks after the procedure.

• TEE guided cardioversion can be performed safely without preprocedural anticoagulation but requires postprocedural anticoagulation.
Goette A et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): A randomised, open-label, phase 3b trial

• Manufacturer-funded multinational trial

• Randomized 2199 patients (AF duration, 2 days to 1 year) undergoing elective cardioversion to receive enoxaparin–warfarin or the direct oral anticoagulant edoxaban (60 mg/day or, in appropriate patients, reduced-dose 30 mg/day).

• Local investigators chose whether to use 3 weeks of preprocedural anticoagulation or a more-immediate TEE-guided approach.
Goette A et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): A randomised, open-label, phase 3b trial

• Incidence of the primary endpoint — stroke, systemic embolism, myocardial infarction, or cardiovascular mortality — was statistically similar with edoxaban (<1%) and enoxaparin–warfarin (1%), as was the incidence of major and clinically relevant non-major bleeding (1% in both groups).

• The choice of 3 weeks of preprocedural anticoagulation or more-immediate TEE-guided cardioversion did not affect the findings.
Goette A et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): A randomised, open-label, phase 3b trial

- Low incidences of thromboembolism and bleeding (about 1%)

- Future questions: role of DOACs in patients with hemodynamic instability undergoing urgent cardioversion, patients with AF lasting <48 hours, and patients with left-atrial thrombus.

- Ongoing: EMANATE trial, comparing apixaban with warfarin
Questions & Discussion
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Title for Chart
Subtitle for Chart

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