ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS IN COVID-19 PATIENTS

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Objectives

- Recognize patients at risk
- Understand the mechanism of increased coagulation in patients with COVID-19
- Appropriately prophylax and treat patients for VTE in COVID-19
- Know when vascular surgery is needed

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VENOUS THROMBOSIS

Prevalence of VTE in COVID-19

- Numbers vary throughout the literature
  - 6-86%
  - Most studies between 15-40%
    - Other viral illnesses in critically ill patients
      - 5-30%

- Reason for the variation: lack of standardization
  - Population of patients- ICU, hospitalized, community
  - Different imaging modalities- Screening protocols
  - Different prophylactic regimens

*Elevated D-Dimer associated with VTE and mortality *

Prevalence

Zhang, et al review of 40 studies with 7966 patients

	All patients	ICU	Wards
VTE	13%	31%	7%
PE	8%	17%	4%
DVT	7%	25%	7%

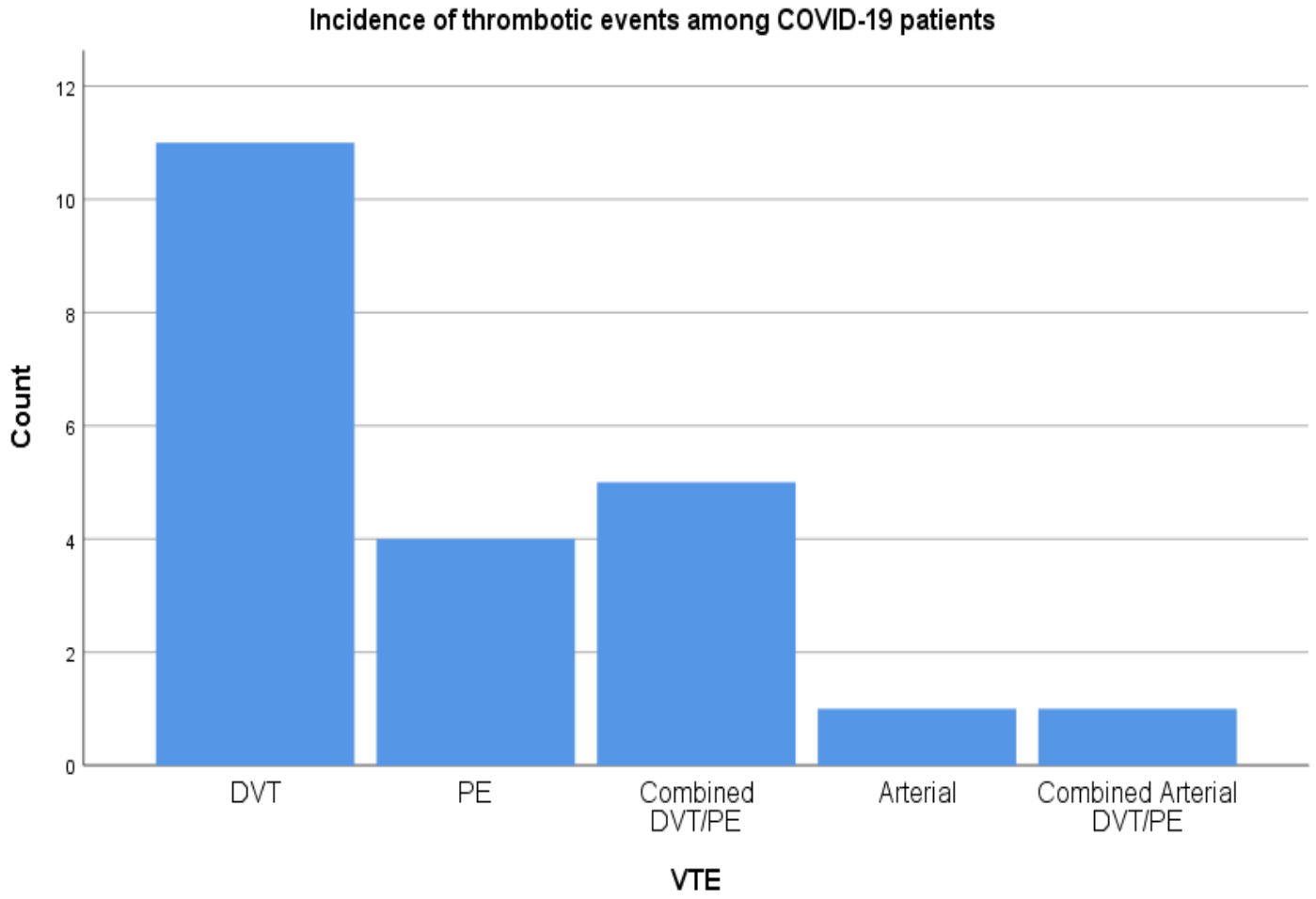
- Noted that in articles where screening was performed there was 3 fold increase in detection of VTE
  - PE: 37% ICU vs. 10% non-ICU
  - DVT: 40% ICU vs. 12% non-ICU

- Upper extremity DVT
- PE without DVT- pulmonary thrombosis

Zhang R, Ni L, Di X, Wang X, Ma B, Niu S, Liu C. Systematic review and meta-analysis of the prevalence of venous thromboembolic events in novel coronavirus disease-2019 patients. J Vasc Surg Venous Lymphat D 2021 Mar;9(2):289-298.e5. doi: 10.1016/j.jvsv.2020.11.023. Epub 2020 Dec 9. PMID: 33309903; PMCID:

Buffalo Numbers

- April1-May 31st 2020
  - 336 patients admitted to BGMC with COVID-19
  - 22 thrombotic events (6.5%)



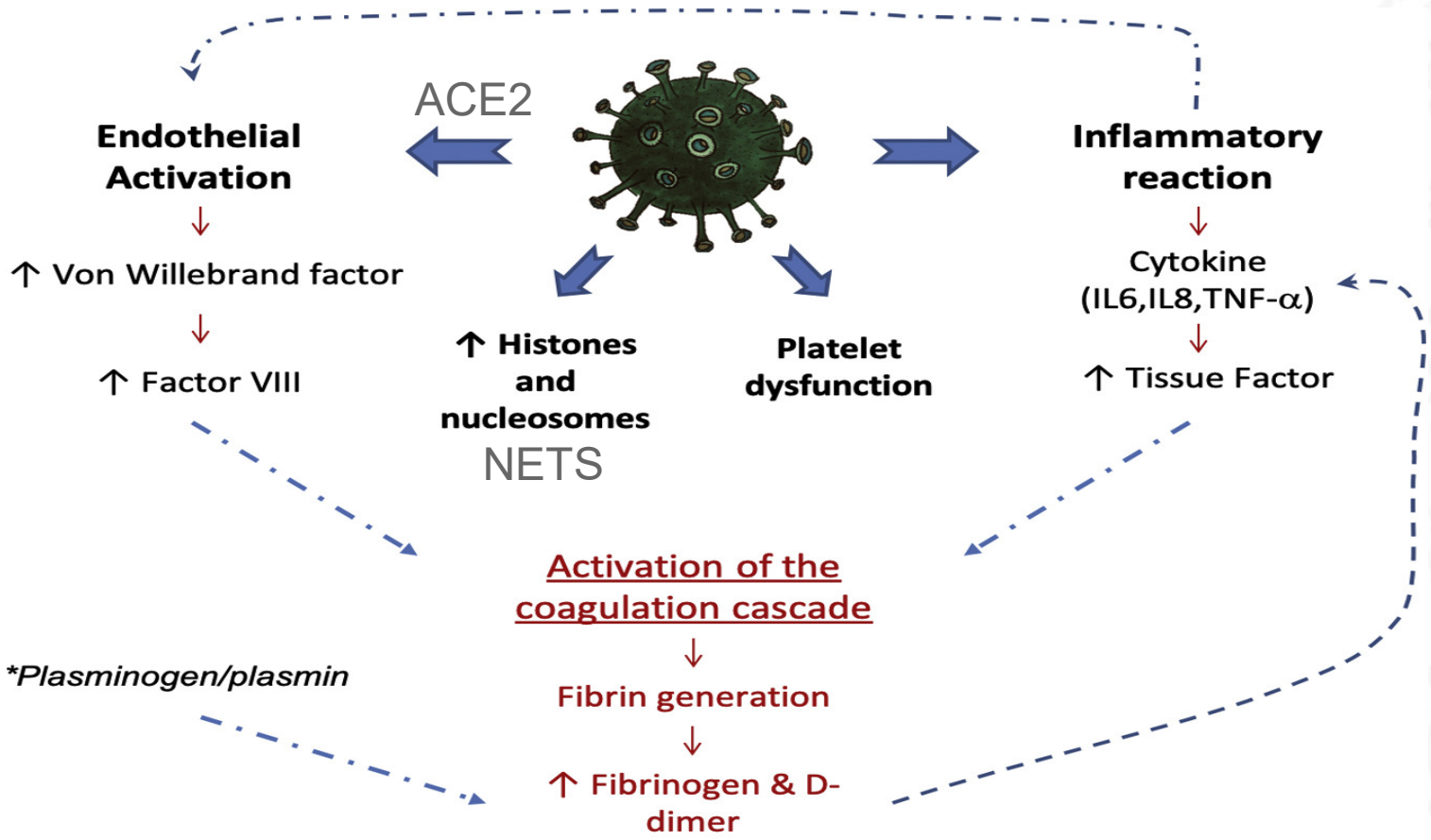
Risk factors

- Age > 65
- Male gender
- African and Latin Americans
- Obesity
- Cancer
- ICU admission
- Immunosuppressants
- CAD/prior MI
- DM

BUFFALO COHORT

- Race
  - Asian Americans least affected
  - Caucasian most prominent in the cohort
  - African American population is smaller in our community so higher percentage
- Hx of HTN, DM, CAD, ESRD
- Mean age: 62
- 37% history of smoking
  - 13.7% active smokers

Pathophysiology- COVID-19 Activated Coagulopathy (CAC)



Luca Costanzo, MD, Francesco Paolo Palumbo, MD, Giorgio Ardita, MD, Pier Luigi Antignani, MD, Enrico Arosio, MD, Giacomo Failla, MD :Coagulopathy, thromboembolic complications, and the use of heparin in COVID-19 pneumonia Journal of Vascular Surgery: Venous and Lymphatic Disorders Volume 8 Issue 5 Pages 711-716 (September 2020)

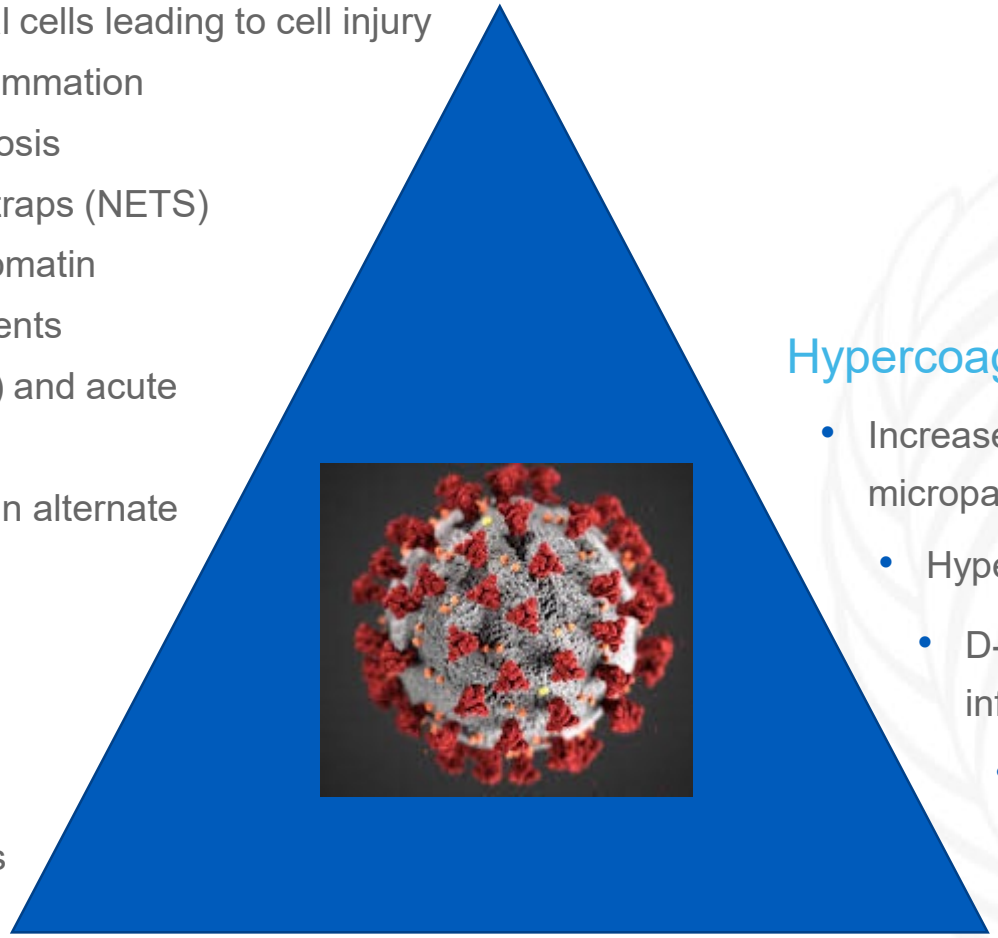
Virchow's Triad

Endothelial Injury

- Virus invades endothelial cells leading to cell injury
  - Microvascular inflammation
  - Endothelial exocytosis
- Neutrophil Extracellular traps (NETS)
  - Decondensed chromatin
- Catheterization in ill patients
- Increase cytokines (IL-6) and acute phase reactants
- Spike protein activates an alternate complement pathway

Stasis

- Immobility of critically ill and hospitalized patients

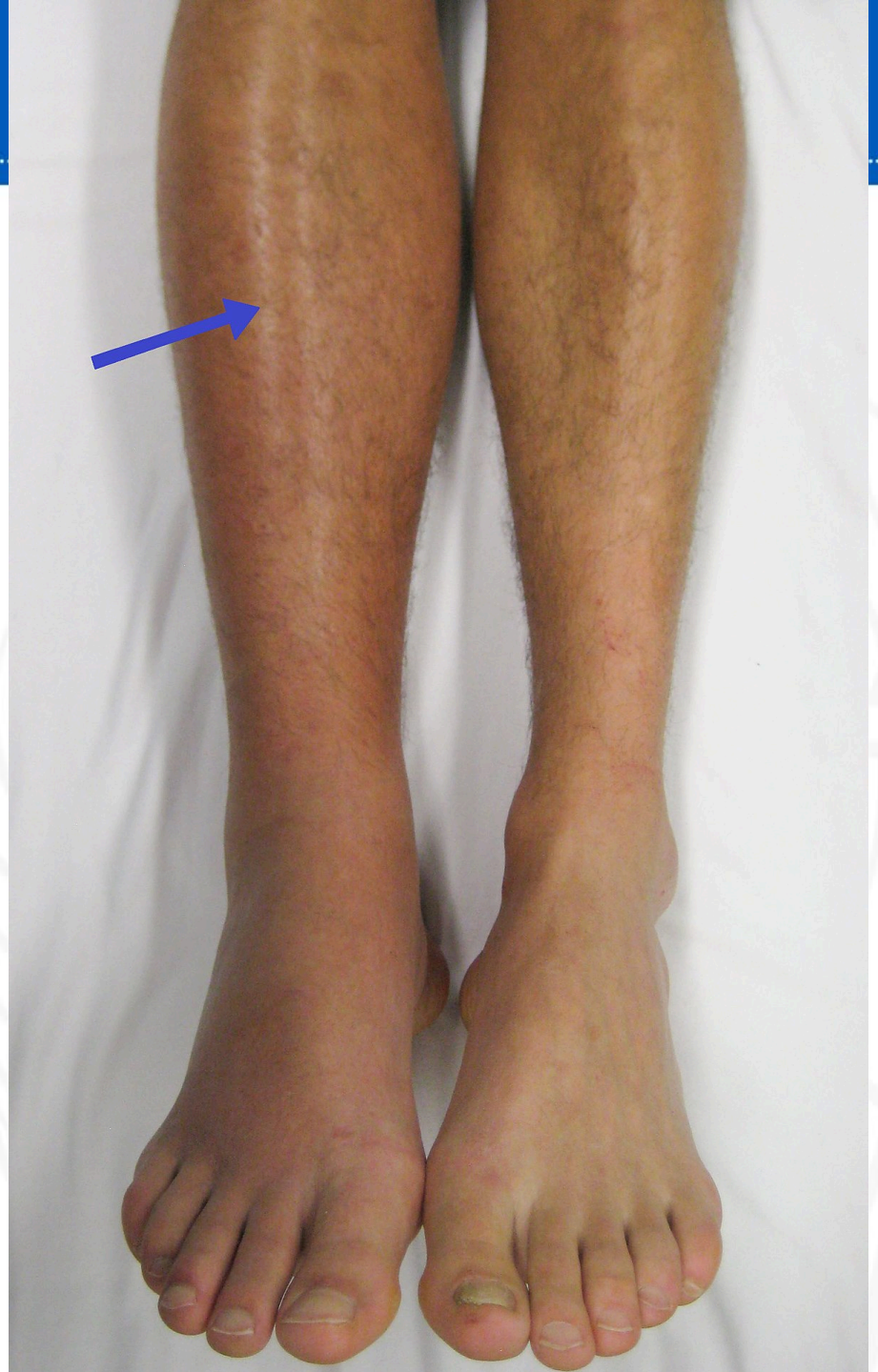


Hypercoagulability

- Increased factor VIII, fibrinogen, prothrombotic microparticles, NETs
  - Hyperviscosity of blood
  - D-Dimer elevated with acutely ill 2/2 inflammatory or infectious processes
    - Anti-phospholipid antibodies transiently positive

Presentation

- Can present late in course
  - Higher rates in the ICU patient
- May also be presenting symptoms with otherwise asymptomatic disease
- Our patients varied:
  - Some noted on admission
  - Others as late as HD 26



Buffalo: Hospital resource use, LOS, morbidity and mortality in COVID 19 Patients with and without VTE

	Patients with VTE	Without VTE	P-Value
Indicator	N%	N%	
	22 (6.5%)	314 (93.5%)	
Intubation	15 (68.2%)	72(22.9%)	<.001
ICU admission	20 (91%)	132(42%)	<.001
Hospital LOS (Days)	30.1± 22.4	12.2 ± 12.1	<.001
CVA	2 (9.1%)	4(1.3%)	0.007
Sepsis	12 (54.5%)	106(33.8%)	0.48
Multisystem Organ Failure	10 (45.5%)	48(15.3%)	<.001
Death	12 (54.5%)	71(22.6%)	0.001

Mortality:

- DVT: 5/11 (54.5%)
- PE: 7/10 (70%)

Markers & Screening

- Routine duplex screening of all patients is not recommended
  - Some studies have suggested screening ICU patients as the prevalence is highest

- Any concerning finding for DVT (edema) duplex is suggested
- Concern for PE- CTA if able, duplex or initiate treatment if not

Table 1 Blood markers of coagulation, fibrinolysis and inflammation in COVID-19

Blood test	Direction of change	Comparator (case vs control)
D-dimer	↑	Severe versus non-severe
Fibrinogen	↑	ICU versus ref range
Platelets	→ / ↓	Severe versus non-severe
aPTT	→	Severe versus non-severe
PT	→ / ↑	Severe versus non-severe
Antithrombin	→ / ↑	COVID-19 versus healthy control
PAI-1	↑	Autopsy versus ref range
Leucocytes	↑	Severe versus non-severe
Lymphocytes	↓	Severe versus non-severe
Neutrophils	↑	Severe versus non-severe
Factor VIII	↑	ICU versus non-ICU
VWF	↑	ICU versus non-ICU
Soluble P-selectin	↑	ICU versus non-ICU
CRP	↑	Severe versus non-severe
Procalcitonin	↑	Severe versus non-severe
Ferritin	↑	Severe versus non-severe
Complement	↑	Autopsy versus ref range

Arrows indicate the direction of change (↑=increase, ↓=decrease, →=no change) in COVID-19 with respect to a control group or column. The magnitude of change (ie, marked increase vs mild increase) is not indicated in this table.
aPTT, activated partial thromboplastin time; CRP, C reactive protein; ICU, intensive care unit; PAI-1, plasminogen activator inhibito von Willebrand factor.

Loo J, Spittle DA, Newnham M
COVID-19, immunothrombosis and venous thromboembolism: biological mechan
Thorax 2021;**76:**412-420.

Treatment: Prophylaxis

- Low molecular weight heparin* or Unfractionated heparin
  - Anticoagulation
  - Anti-inflammatory (lessen cytokine storm) and offers endothelial protection
  - Proposed antiviral effects also proposed

- Dosing is controversial- there are currently >30 clinical trials ongoing for antithrombotic therapy in hospitalized patients with COVID-19
  - Ppx dose is currently recommended over therapeutic dosing for hospitalized and critically ill patients
    - Intermediate dose is recommended for high risk patients by some societies
  - Thrombotic complications remain high despite ppx
    - 16/17 patients in our cohort who developed VTE were on ppx
    - 1 patients had SCDs ordered
  - Some recommend monitoring Anti Xa to assess for adequate dosing
    - 0.2-0.4units/mL
  - Following D-dimer has been recommended by others

Treatment: Prophylaxis

- Following discharge:
  - Currently NIH does not recommend continuing ppx following discharge, unless they qualify as high risk without COVID
  - CHEST guidelines: extended ppx may be considered
  - Italian expert consensus: continued for 7-14 days following discharge

TABLE 1 Society Recommendations for COVID-19 Thromboprophylaxis

Societies (Guidance mo/y)	Universal thromboprophylaxis in acutely ill inpatients	Pharmacologic prophylaxis options in acutely ill inpatients	Role for intensification of pharmacologic prophylaxis in acutely ill inpatients	Universal thromboprophylaxis in labor and delivery
NIH (5/2020)[1]	No; follow the standard of care; data suggest use when the sepsis-induced coagulopathy score ≥ 4	Follow the standard of care	No	No; manage pregnant patients with COVID-19 for the same conditions that require anticoagulation in pregnancy; follow guidance recently published by ASH/ACOG
ACC (4/2020)[2]	No; for patients with moderate or severe COVID-19 without DIC, use risk stratification tools (Caprini, IMPROVE model, or Padua model) to assess risk	For hospitalized patients with COVID-19 without DIC, use prophylactic doses/ regimens: DOAC (prophylactic doses), enoxaparin (40 mg SC daily), dalteparin (5,000 U SC daily), or heparin (5,000 U SC 2-3 times daily if renal dysfunction present [CrCl < 30 mL/min])	No	Not discussed
Anticoagulation Forum (5/2020)[3]	Yes; use for all nonpregnant hospitalized patients with confirmed or highly suspected COVID-19	Standard dose VTE prophylaxis	Not discussed	Yes; follow guidance recently published by the RCOG; close collaboration with obstetric and anesthesiology colleagues is recommended in the event of delivery and/or need for epidural anesthesia during hospitalization
ISTH (5/2020)[4]	Yes	Standard dose UFH or LMWH should be used after careful assessment of bleed risk; LMWH is preferred agent; regimens: enoxaparin (40 mg SC daily), or heparin (5,000-7,500 SC every 8-12 h); modify recommendations based on extremes of body weight, severe thrombocytopenia (ie, platelet counts of 10,000 x 10^9/L or 25,000 x 10^9/L) or deteriorating renal function	Yes; intermediate dose LMWH may be reasonable in non-ICU hospitalized COVID-19 patients	Not discussed
CHEST (6/2020)[5]	Yes	LMWH or fondaparinux over UFH; and additionally recommends LMWH, fondaparinux, or UFH, over a DOAC	No	Not discussed

Benge C, Ragheb B. COVID-19 and Venous Thromboembolism Pharmacologic Thromboprophylaxis. Fed Pract. 2020 Nov;37(11):506-511. doi: 10.12788/fp.0063. PMID: 33328716; PMCID: PMC7735460.

Societies (Guidance mo/y)	Intervention when pharmacologic thromboprophylaxis is contraindicated	Universal thromboprophylaxis in critical illness	Pharmacologic prophylaxis options in critical illness	Role for pharmacologic and mechanical thromboprophylaxis
NIH (5/2020)[1]	Not discussed	Universal thromboprophylaxis in critical illness	There are insufficient data to recommend for or against the use of increasing anticoagulant doses; LMWH or UFH may be preferred due to shorter half-lives, ability to be administered IV or SC, and fewer drug-drug interactions compared with oral anticoagulants	Not discussed
ACC (4/2020)[2]	Intermittent pneumatic compression	Yes; for patients with moderate or severe COVID-19 without DIC, use risk stratification tools (Caprini, IMPROVE model, or Padua model) to assess risk; Yes; for patients with moderate or severe COVID-19 and DIC (note: the diagnosis of DIC is best established using the ISTH DIC score calculator)	Use standard doses/regimens: enoxaparin (SC 40 mg daily), dalteparin (5,000 U SC daily), heparin (5,000 U 2-3 times SC daily if renal dysfunction present [CrCl < 30 mL/min])	Yes; combination in severe COVID-19 is reasonable
Anticoagulation Forum (5/2020)[3]	Intermittent pneumatic compression devices with regular reassessment for conversion to pharmacologic prophylaxis	Yes	Suggest increased doses: enoxaparin (40 mg SC twice daily), enoxaparin (0.5 mg/kg SC twice daily), heparin (7,500 U SC 3 times daily), or low-intensity heparin infusion	Yes; combination in critically ill patients is reasonable
ISTH (5/2020)[4]	Not discussed	Yes	Use standard prophylactic doses of UFH or LMWH; an intermediate dose can be considered in high-risk ICU patients: enoxaparin (40 mg 1-2 times daily), enoxaparin (0.5 mg/kg 1-2 times daily), prophylactic or treatment dose DOAC, or heparin (5,000-7,500 U every 8-12 h)[a]	Yes
CHEST (6/2020)[5]	Mechanical thromboprophylaxis in critically ill, COVID-19	Yes	Use standard dose anticoagulant thromboprophylaxis over intermediate or full treatment dosing, per existing guidelines; suggest LMWH over UFH and LMWH or UFH over fondaparinux or a DOAC	No

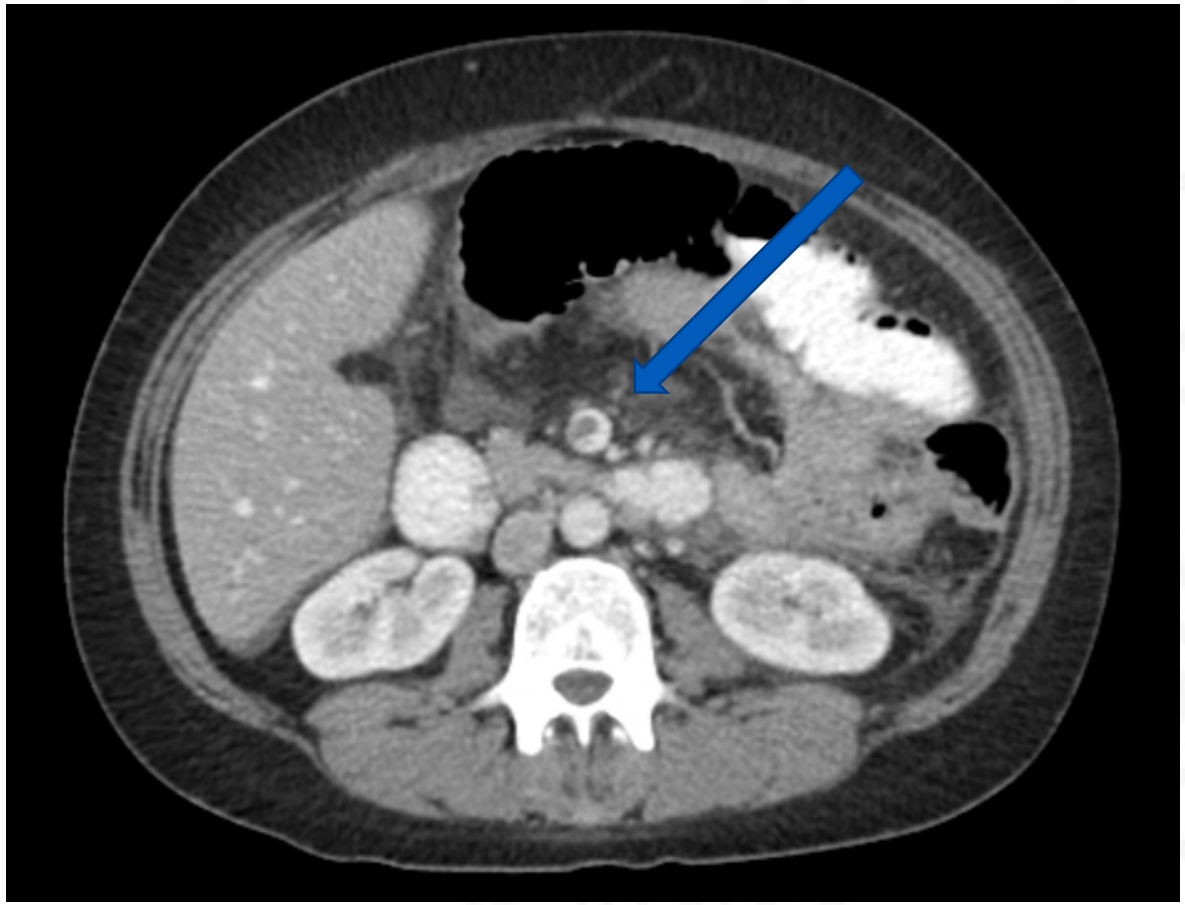
Benge C, Ragheb B. COVID-19 and Venous Thromboembolism Pharmacologic Thromboprophylaxis. Fed Pract. 2020 Nov;37(11):506-511. doi: 10.12788/fp.0063. PMID: 33328716; PMCID: PMC7735460.

Treatment of confirmed VTE

- LMWH standard dosing is recommended
  - Over UFH due to exposure risk to the staff
  - Apixaban/ Rivaroxaban can be used at discharge
  - 3 month treatment period
- Suspected massive PE- systemic thrombolysis is recommended
  - If DIC catheter directed thrombolysis is recommended due to lower doses of thrombolytics
- Intervention for DVT is limited to threatened limbs

Abnormal Venous Thrombosis

- Cerebral venous sinus thrombosis
  - Headache
  - Neurologic deficit
  - Intracranial hemorrhage with seizures
- Splanchnic venous thrombosis- portal vein, SMV, IMV
  - Colicky abdominal pain
  - Gastrointestinal bleeding
- Renal vein
- Gonadal veins



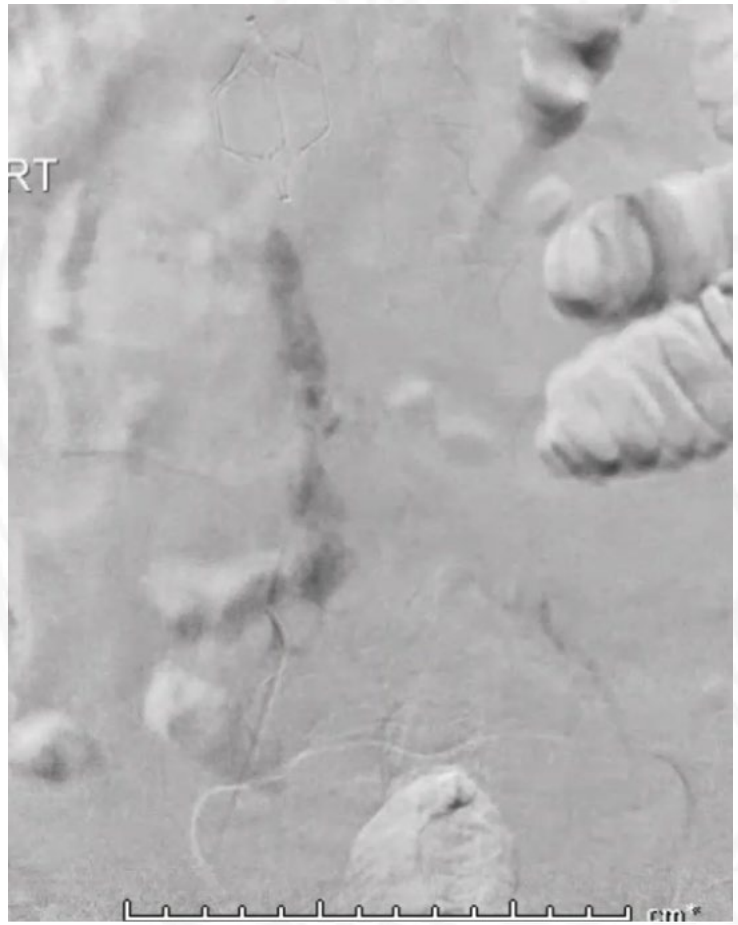
Case Presentation:

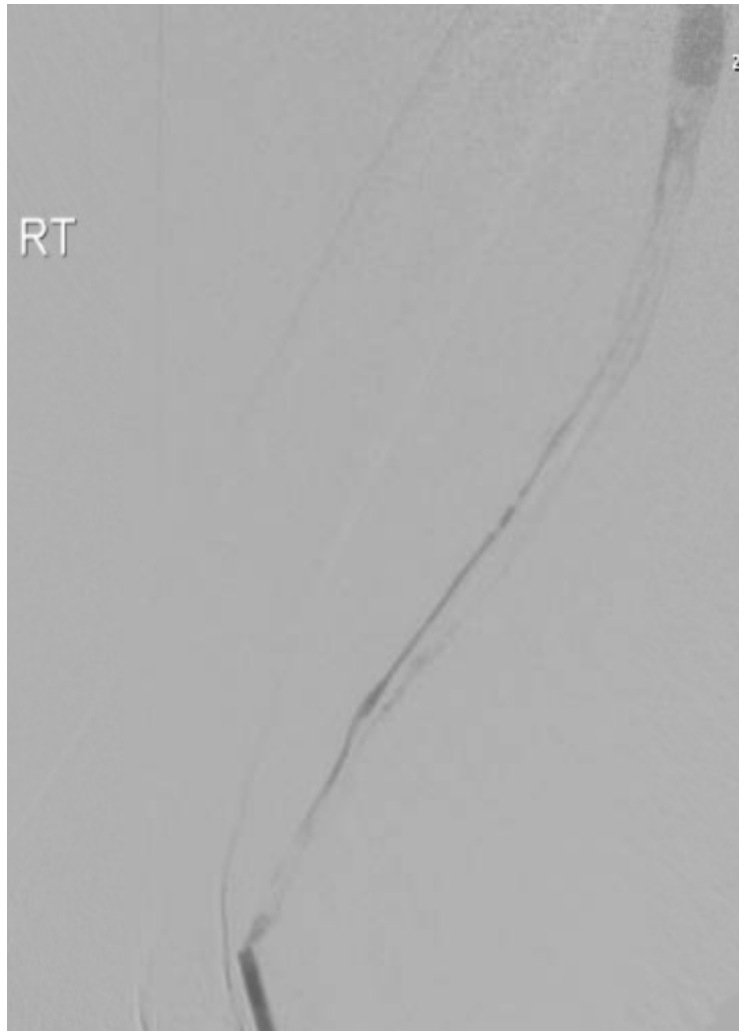
47yo obese male with Hx of DVT PE and IVC filter placed in 2011 not on AC

- Presented to outside facility with several days of worsening bilateral leg edema, pain, difficulty ambulating and hematuria
- Lab findings of acute renal failure with Cr of 10, K 6.2- underwent emergent dialysis
- Worsening edema with blistering and discoloration
- Duplex showed bilateral iliofemoral DVT

- Denied complaints of CP or SOB but preoperative lab workup noted to be COVID +

- Due to the phlegmesia and concern for suprarenal caval thrombosis leading to acute kidney failure he was taken for venogram

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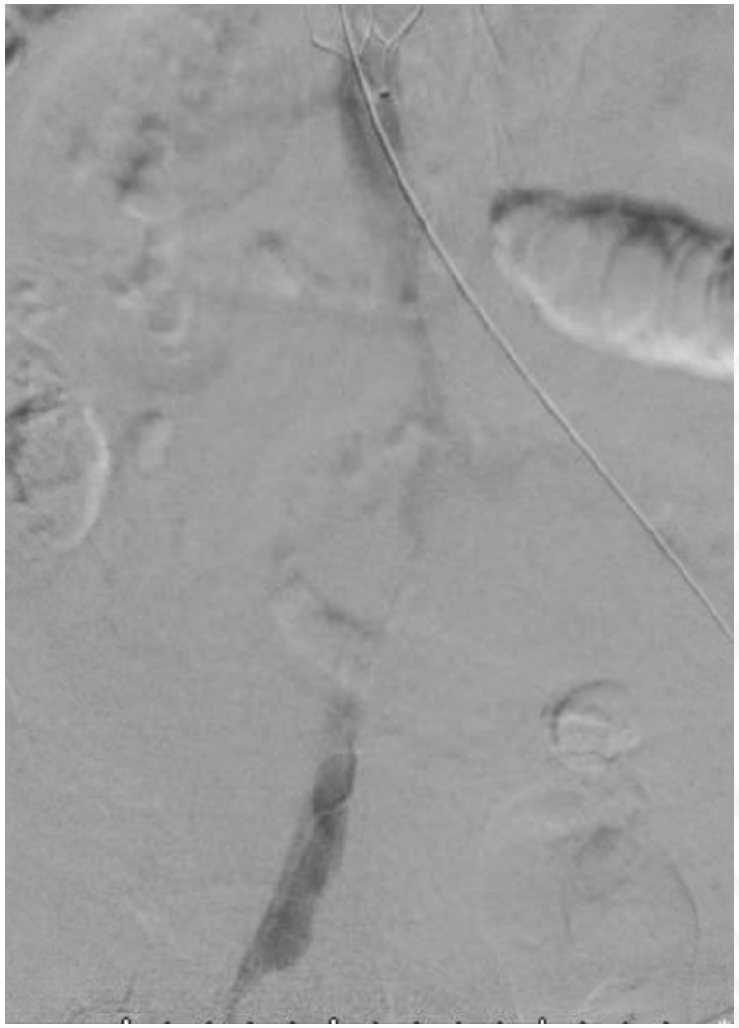

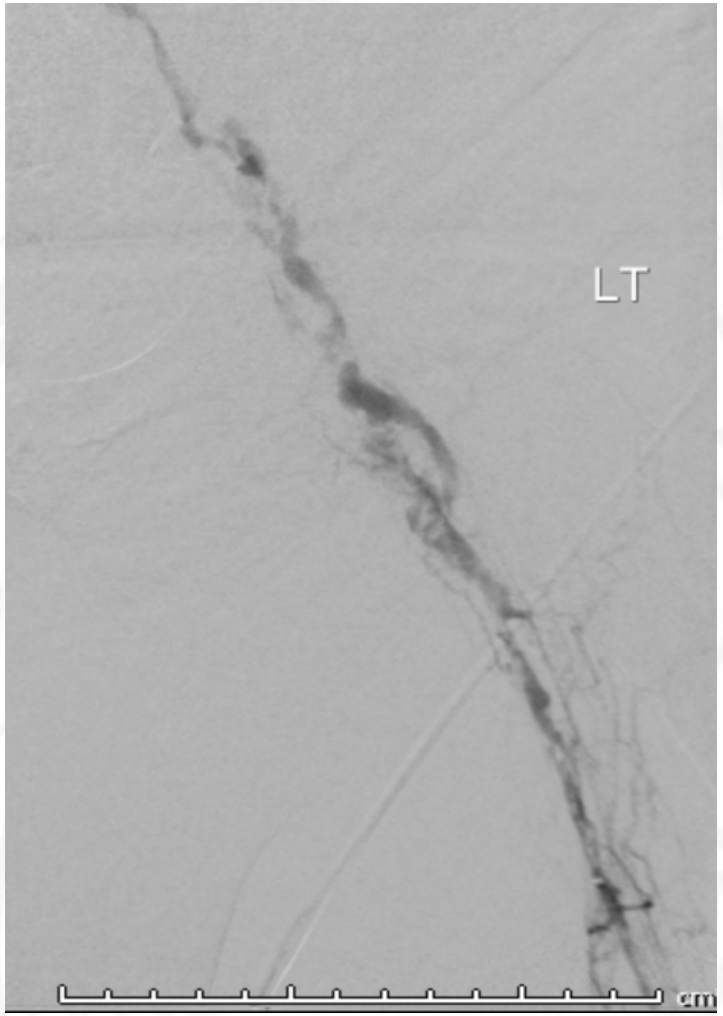
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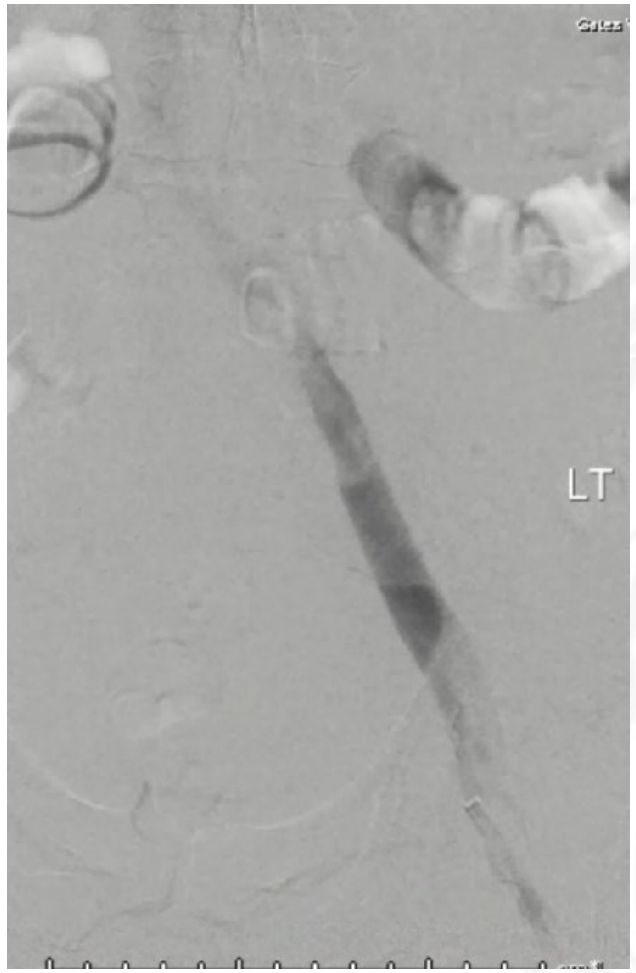
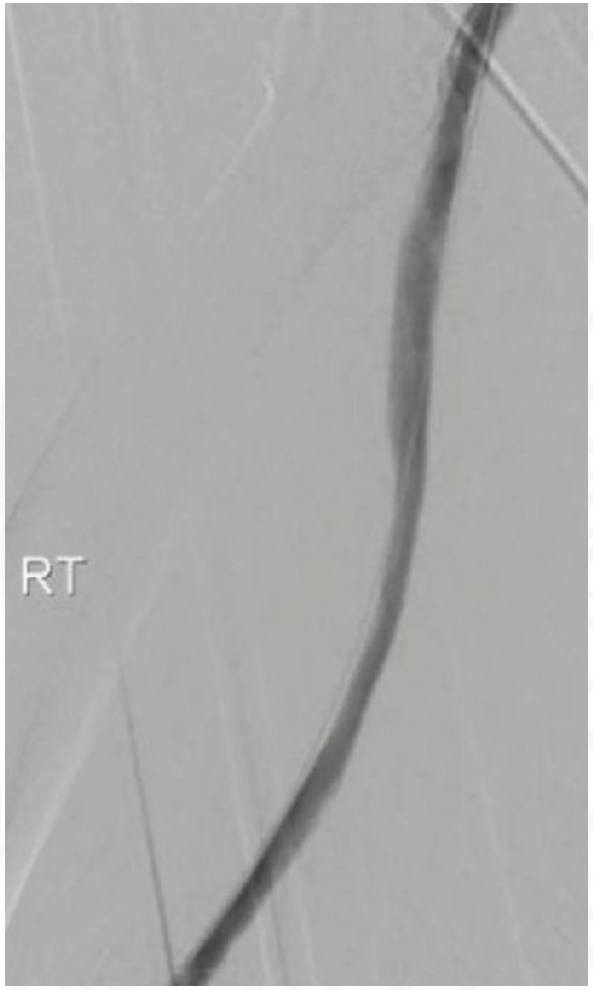
cm

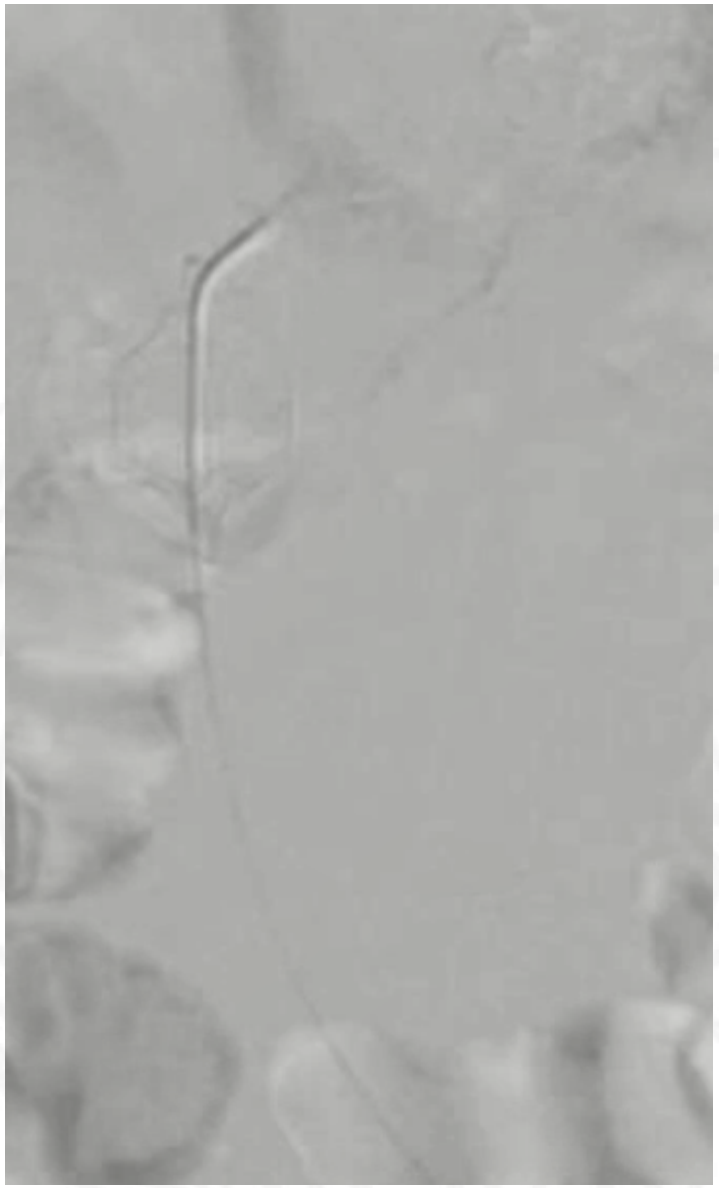
- Mechanical suction thrombectomy to decrease clot burden
- 24 hours of thrombolysis





- Significant improvement in the bilateral iliofemoral clot
- Improvement in edema and pain in the bilateral lower extremities
- Resolution of the caval thrombus
- Improvement in renal failure with normalization of kidney function

- Will require lifelong AC



SUMMARY RECOMMENDATIONS BY THE NIH

Laboratory Testing

- In nonhospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) **(AIII)**.
- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend either for or against using this data to guide management decisions.

Chronic Anticoagulant and Antiplatelet Therapy

- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 **(AIII)**.

Venous Thromboembolism Prophylaxis and Screening

- For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIII)**.
- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation **(AIII)** (see the recommendations for pregnant individuals below). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.
- There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.
- Hospitalized patients with COVID-19 should not routinely be discharged from the hospital while on VTE prophylaxis **(AIII)**. Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered for patients who are at low risk for bleeding and high risk for VTE, as per the protocols for patients without COVID-19 (see details on defining at-risk patients below) **(BI)**.
- There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers.
- For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated **(AIII)**.

Hospitalized Children With COVID-19

- For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 **(BIII)**.

Treatment

- When diagnostic imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy **(AIII)**.
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Special Considerations During Pregnancy and Lactation

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued **(AIII)**.
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated (see below) **(BIII)**.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients **(AIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, considering concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy **(AIII)**.
- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding individuals with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**. In contrast, use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data **(AIII)**.

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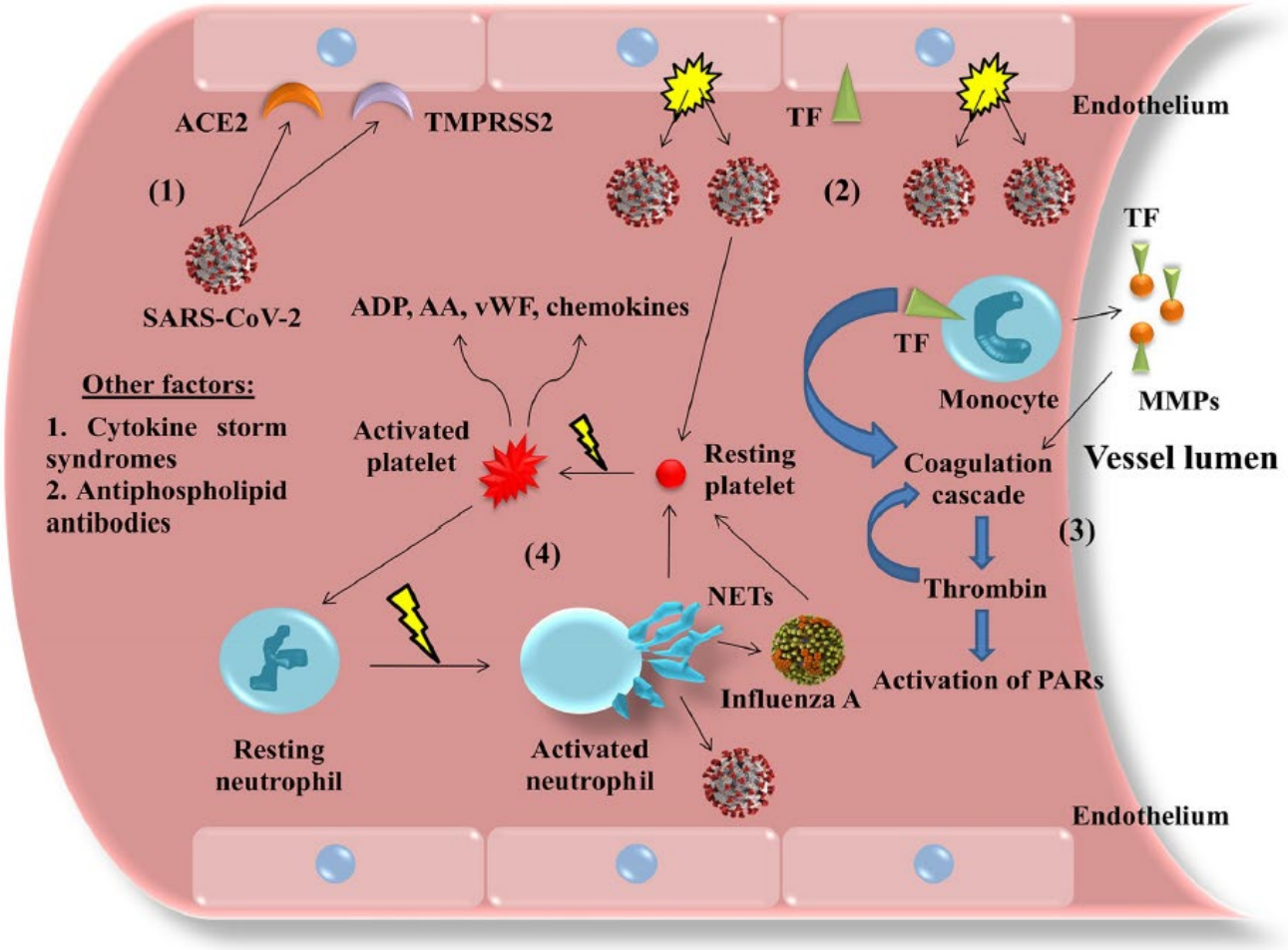
ARTERIAL THROMBOSIS

SARS-CoV-2 and Arterial Thrombosis

- Endothelial cell activation
- Platelet activation
- Neutrophil extracellular traps
- Cytokine storm
- Complement activation
- Thrombin generation
- Antiphospholipid syndrome

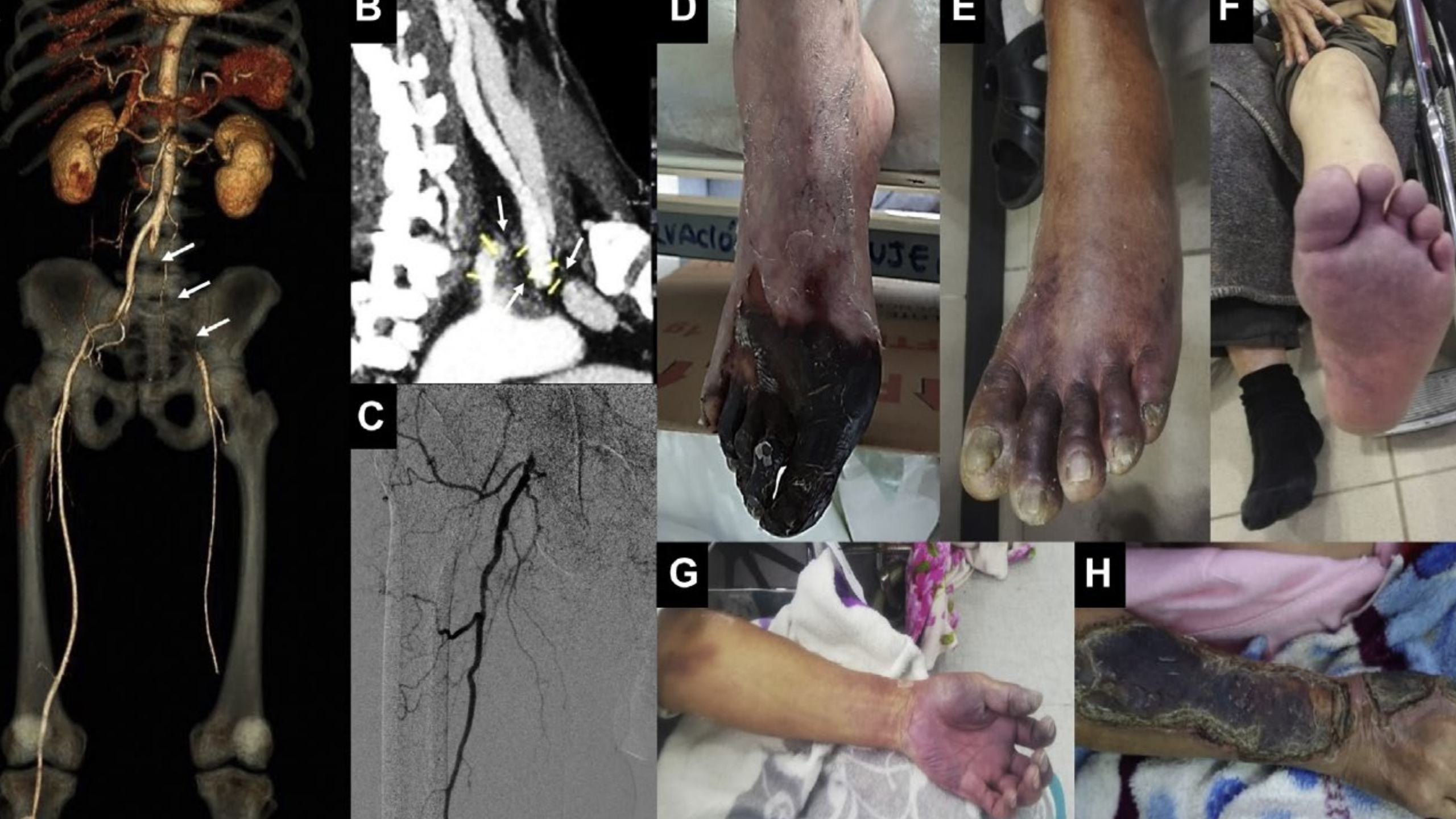


Presentation

- ALI in COVID-19 can occur in two situations.
  - During the in-hospital evolution of severe COVID-19 infection
  - Present to ER with ALI, and have mild or no respiratory symptoms, some have history of respiratory symptoms (median of 19, ranging from 11-23 days)

Distribution

- More frequent arterial involvement in the lower limbs, predominantly the popliteal, anterior, and posterior tibial and superficial femoral, iliac, and distal aorta
- Concerning the upper limbs, frequent involvement of the subclavian, brachial, radial, and ulnar arteries
- aortic arch, descending thoracic aorta, aortobifemoral bypass, femoropopliteal bypass and stent, renal artery, mesenteric, and splenic arteries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Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c], M.S. Arbous[d], D.A.M.P.J. Gommers[e], K.M. Kant[f], F.H.J. Kaptein[a], J. van Paassen[d], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[e,1]

Thrombosis Research 191 (2020) 145–147

- 184 ICU patients
- 31% had thrombotic complications despite prophylaxis with LMWH
  - 27% VTE (mostly PE)
  - 4% arterial (strokes)

Acute Arterial Thromboembolism in Patients with COVID-19 in the New York City Area

Yana Etkin, Allan M. Conway[1] Jeffrey Silpe, Khalil Qato, Alfio Carroccio, Pallavi Manvar-Singh, Gary Giangola, Jonathan S. Deitch, Luis Davila-Santini, Jonathan A. Schor, Kuldeep Singh, Firas F. Mussa, and Gregg S. Landis, Hempstead

Annals of Vascular Surgery Volume 70, January 2021

- 12630 hospitalized patients (7 hospital system)
- 49 arterial ischemic complications
- 76% Men, mean age 67 (58-75)
- Median d-dimer 2763 (720-7140)
- Upper 14%, lower 71% Mesenteric 4% (both died), cerebral 10%
- 6% multiple locations
- 16% concomitant DVT
- 45% were subsequently diagnosed with COVID, 55% had ischemia during hospital stay
- 27% revascularization, 10% primary amputation, 63% systemic anticoagulation
- 46% died (77% in d-dimer over 5000ng/mL), 18% limb loss

Vascular Surgery During COVID-19 Emergency in Hub Hospitals of Lombardy: Experience on 305 Patients

Andrea Kahlberg [a,*], Daniele Mascia [a], Raffaello Bellosta [b], Luca Attisani [b], Matteo Pegorer [b], Anna M. Socrate [c], Matteo Ferraris [c], Piero Trabattoni [d], Enrico Rinaldi [a], Andrea Melloni [a], Fabrizio Monaco [e], Germano Melissano [a], Roberto Chiesa [a]

- 4 Hub hospitals in Lombardy, 7 week period
- 64 COVID, 241 non-COVID
- COVID more acute (64% vs 23%), higher mortality (25% vs 6%)
- 14% of COVID treated medically (vs 6% non-COVID)

Seda Bilaloglu, MS

Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System

JAMA August 25, 2020 Volume 324, Number 8

- 4 NYC Hospitals March-April 2020
- 3334 patients 60% male
- 16% thrombotic complications (6% venous, 9% MI, 1.6% stroke, 1% peripheral)
- In 829 ICU patients 30% had thrombotic complications
- Mortality 43% in thrombotic complications, vs 21%

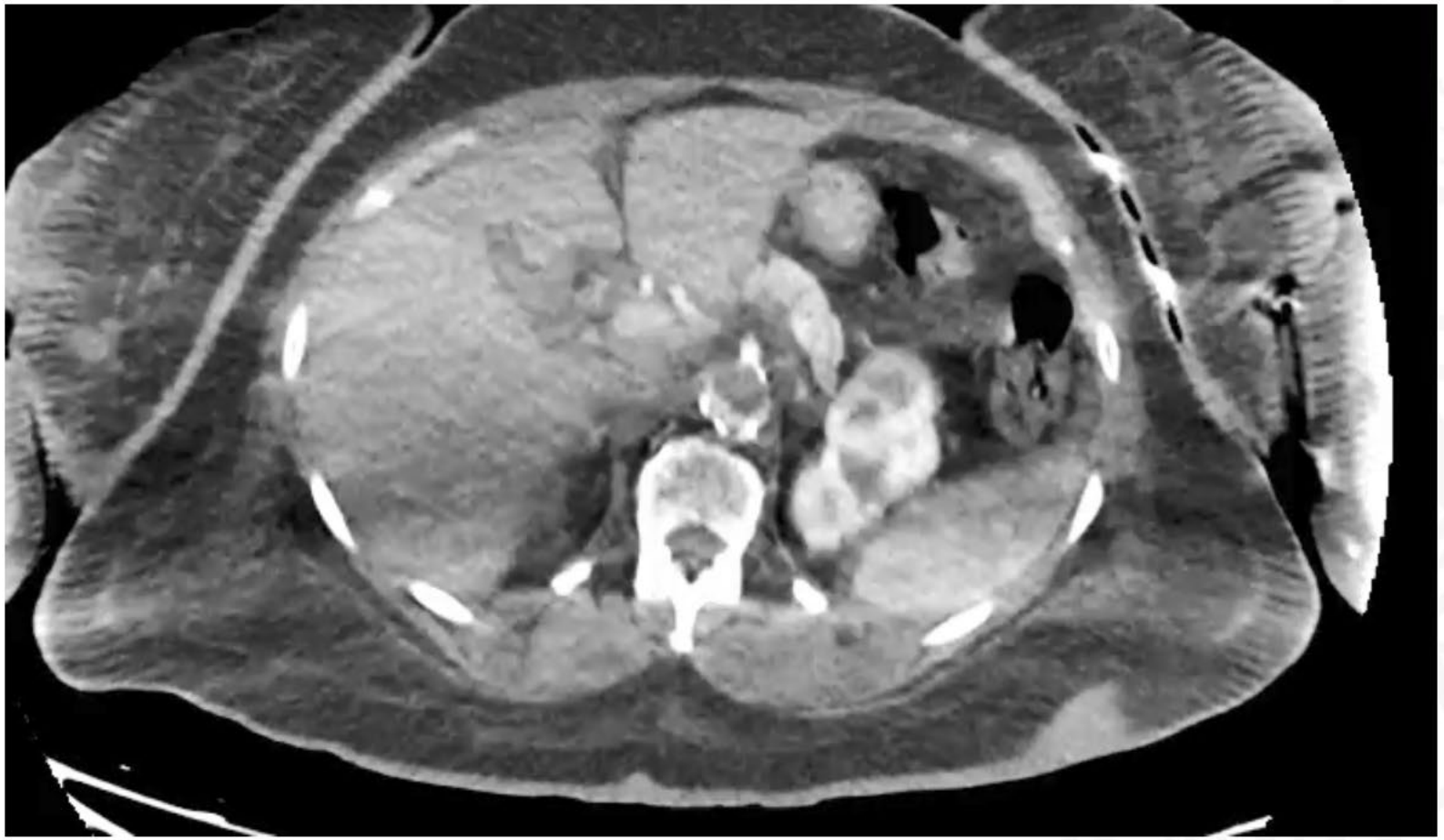
Treatment

- Anticoagulation
- Primary amputation
- Endovascular (thrombolysis and intervention)
- Open thrombectomy

- Outcomes worse than patients without COVID

- HPI: 78 y.o Female with PMH of HTN, HLD, CHF, cardiac thrombus on anticoagulation presented to the ED with 8 hour hx of abdominal pain and bilateral lower extremity pain. She had COVID but with mild symptoms, and was not hospitalized

CTA



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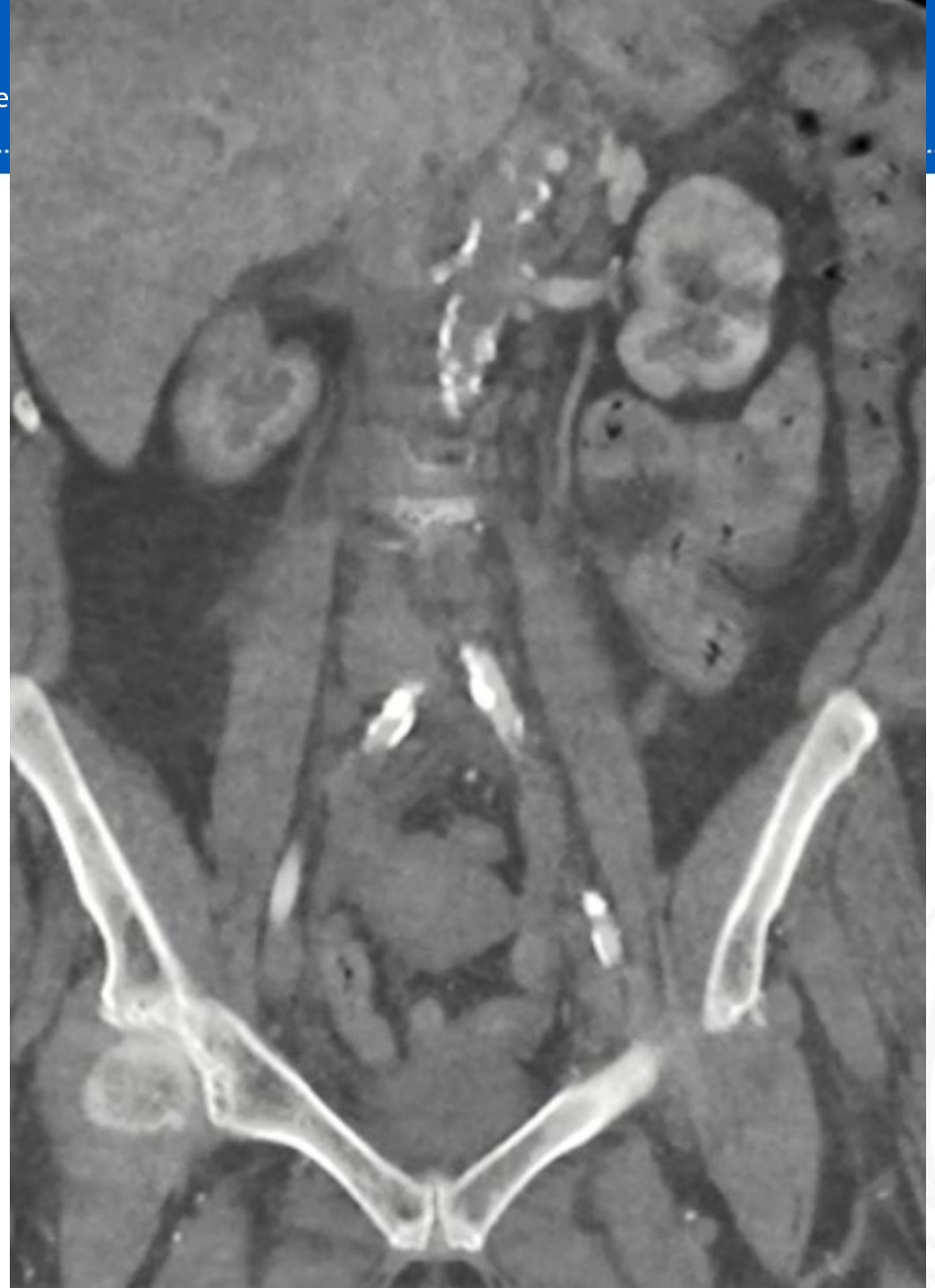
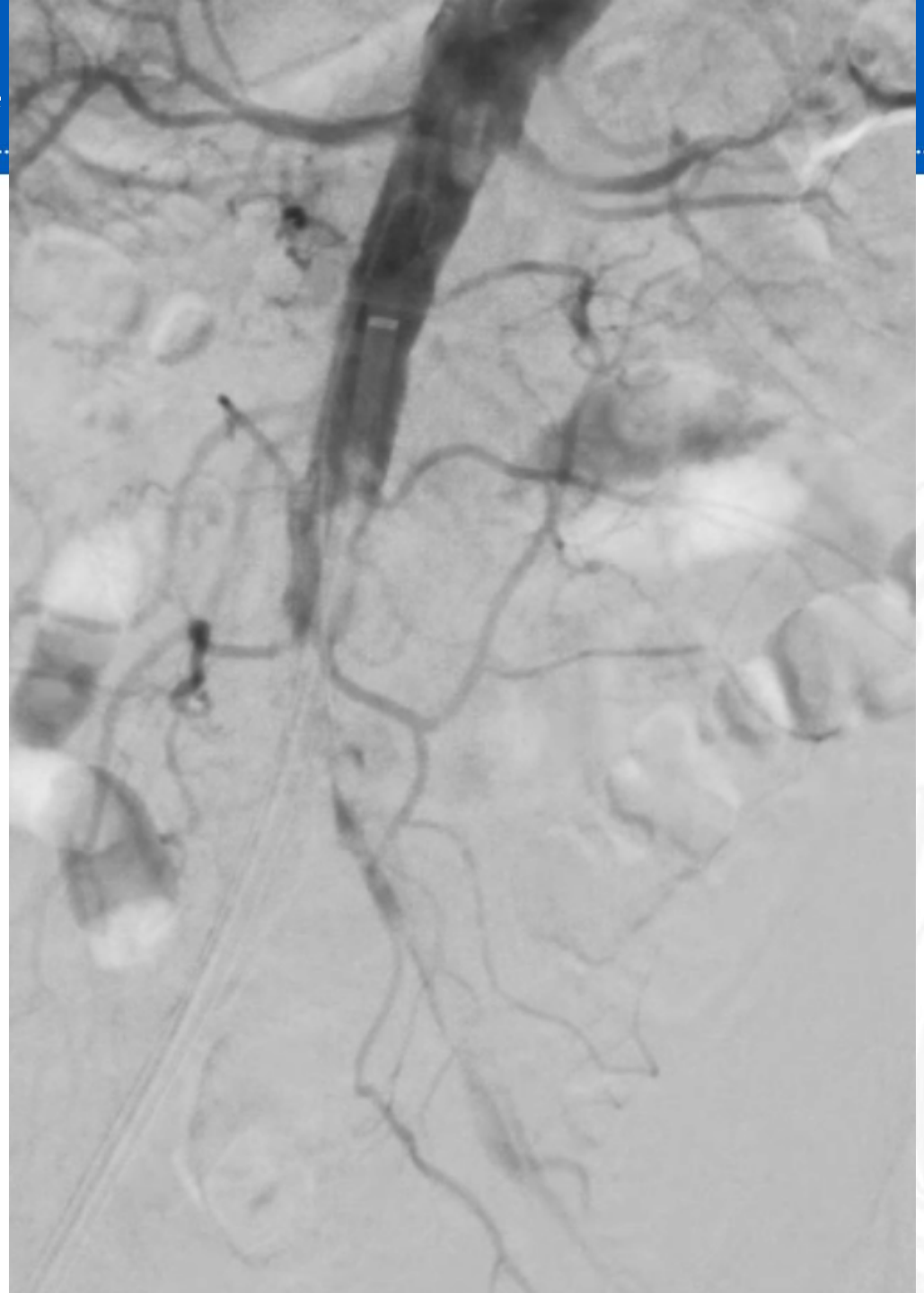
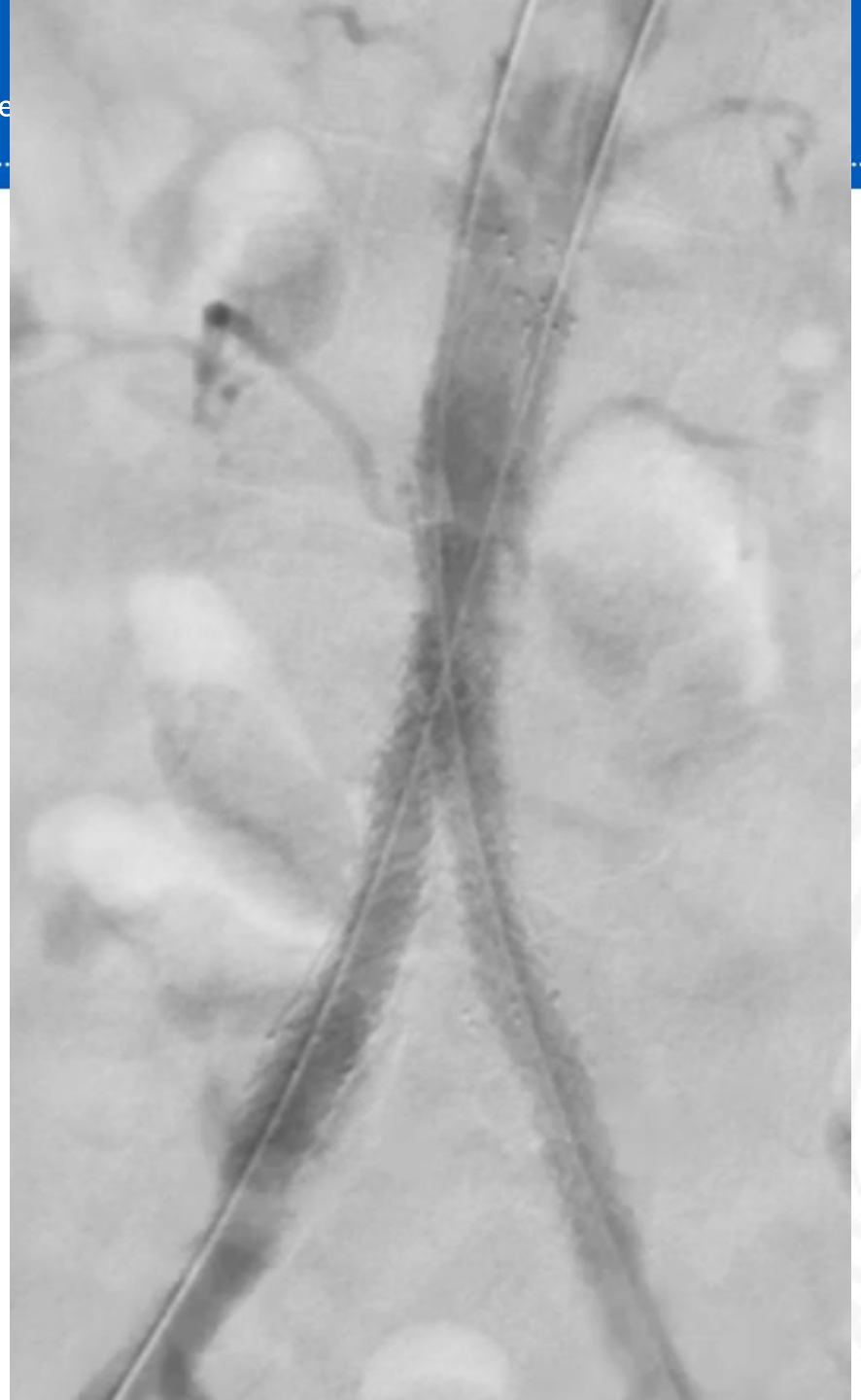
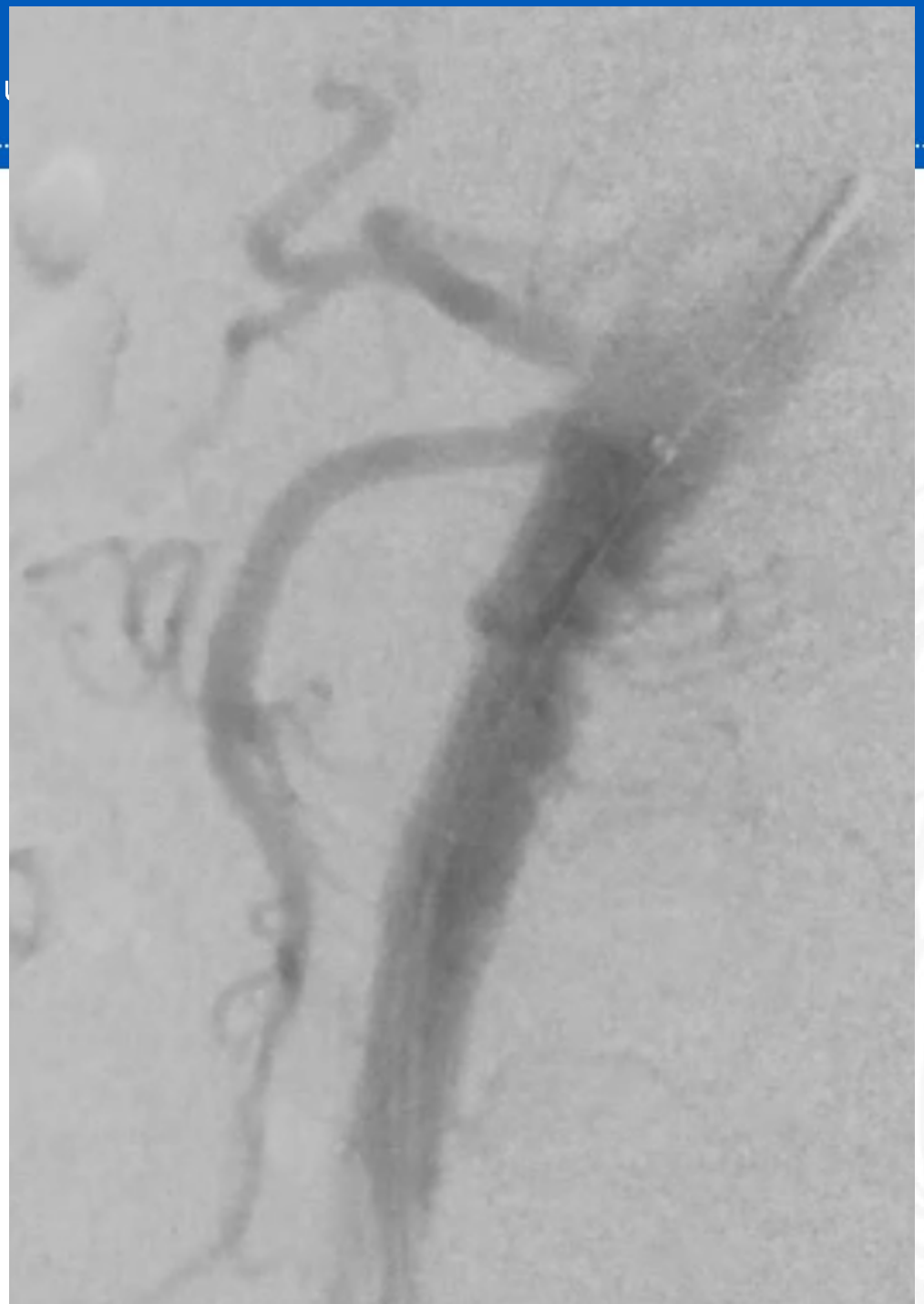
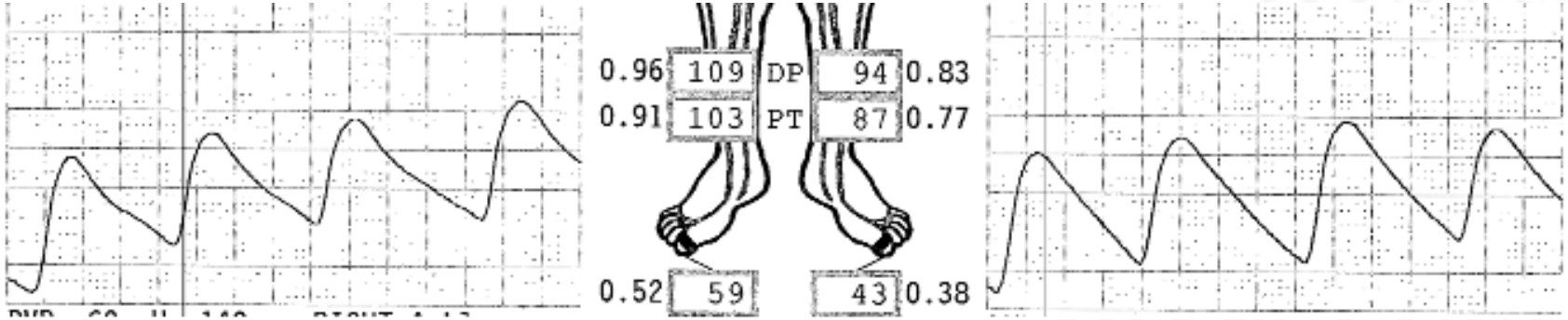




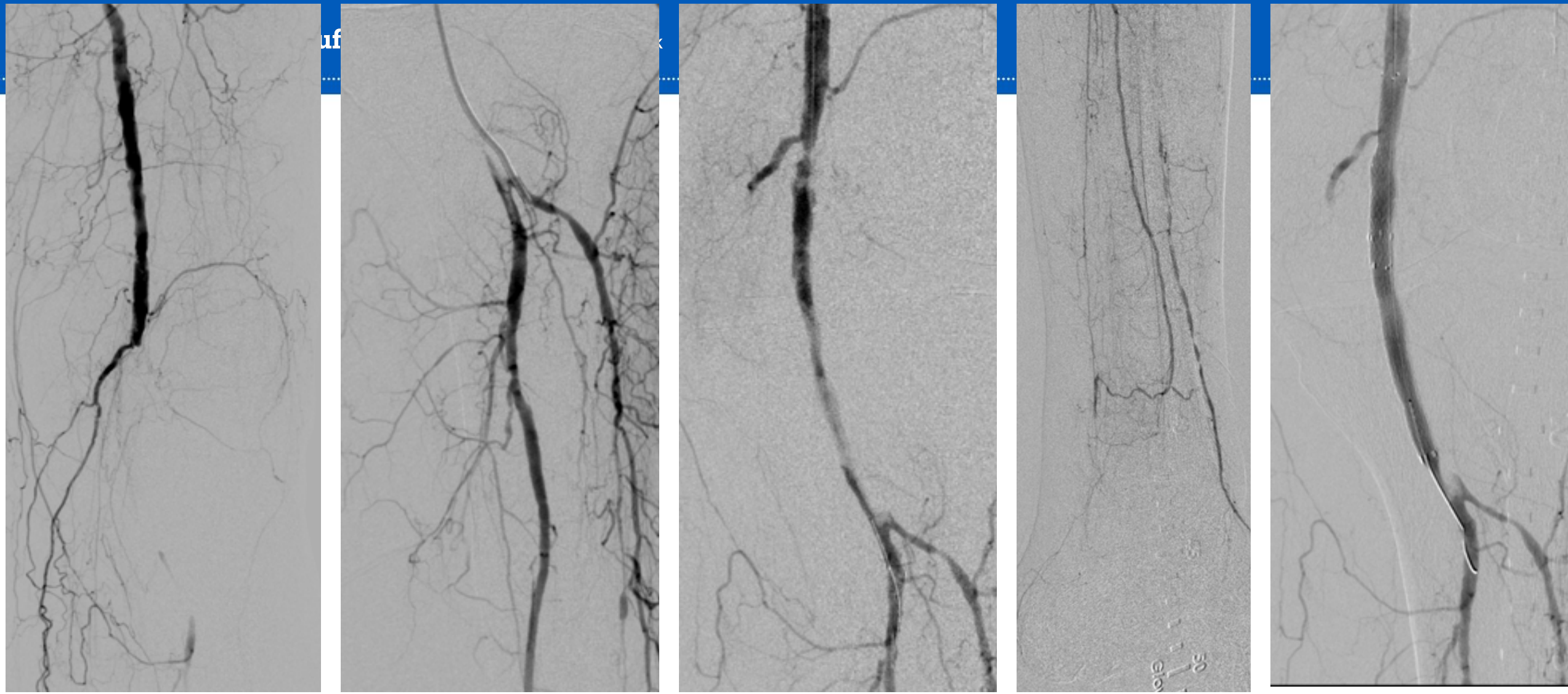




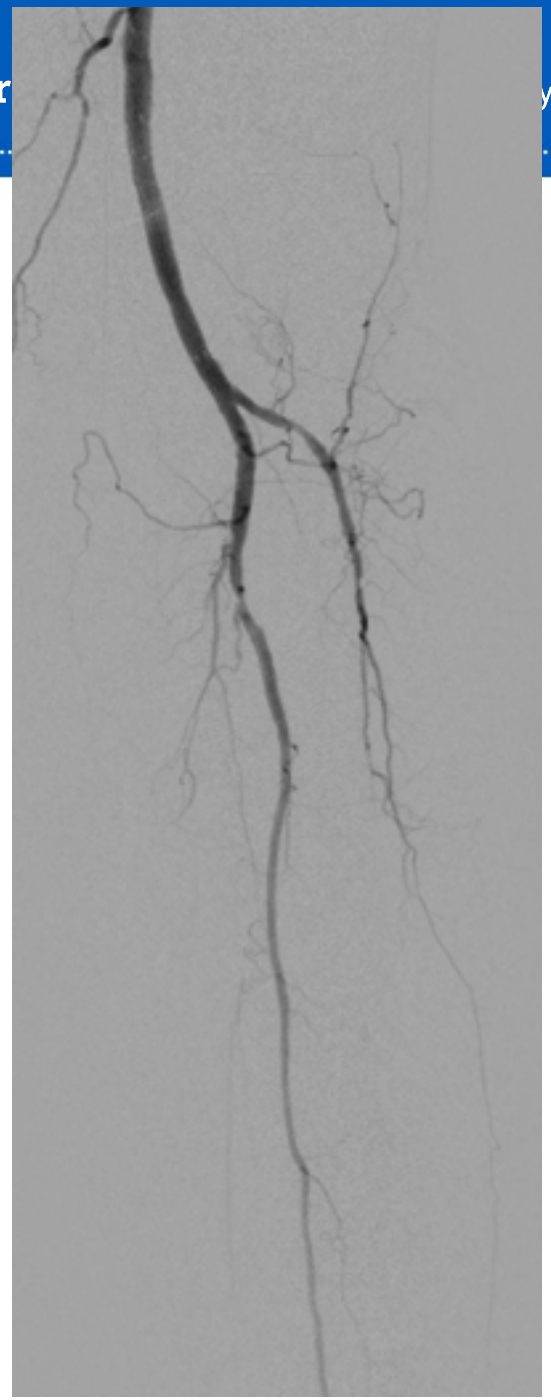
Post-op ABIs

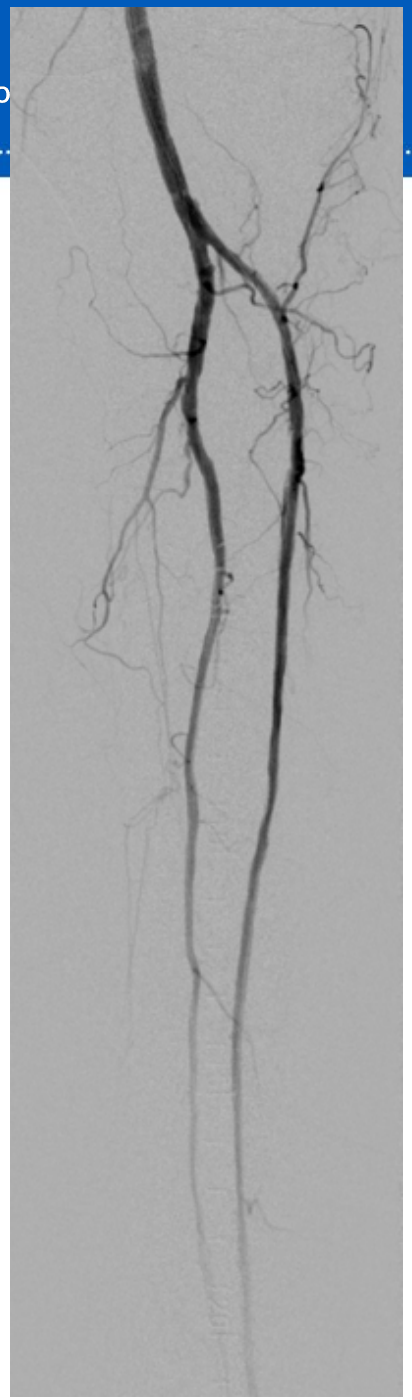


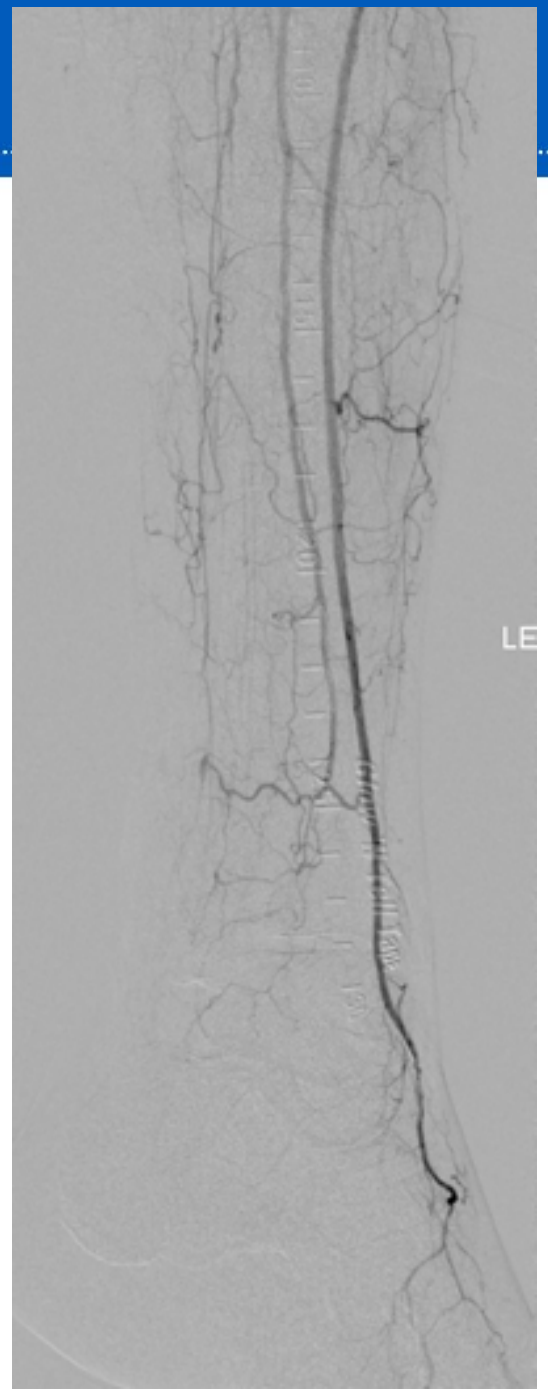
- 72 year old with DM, htn, history of DVT, who was admitted for COVID pneumonia, and was discharged returned with 3 days history of bilateral leg “weakness” which was new, and was found to have no signals in either feet, but had minimal pain. He was started on heparin drip.



12 hr thrombolysis







Outcomes

- Primary amputation rates 5-15% (higher mortality)
- Secondary amputation rates 3-5%
- Mortality 20-45%

Questions?