Regulate Your Appetite: A GLP-1 Agonist for Adult Weight Loss

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Learning Objectives:

- Identify health problems commonly associated with overweight and obese individuals
- Identify the most common types of side effects associated with GLP-1 agonists used for weight loss
- Identify the place in therapy of GLP-1 agonists for the weight management of adults

Background:

- Obesity prevalence in US:
  - 1999-2000: 30.5%
  - 2017-2020: 41.9%
- 2019 estimated annual medical cost of obesity: $173 billion
- Severe obesity (BMI > 40kg/m^2) increased from 5.7% in 2007 to 9.2% in 2018

Medical complications arising from obesity:

- Hypertension
- Dyslipidemia
- Insulin resistance
- Type 2 diabetes
- Cardiovascular disease
- Reduced life expectancy

COVID-19 specific, increased:

- Hospitalizations
- Need for mechanical ventilation
- Death

Trials / Data:

Trial	Population	Primary Outcome Results
STEP-1	Semaglutide 2.4mg vs. placebo + lifestyle intervention in patients **without diabetes**	Semaglutide: Average 14.9% body weight reduction compared to 2.4% with placebo (P<0.001)

STEP-2	Semaglutide 2.4mg, 1mg, or placebo + lifestyle intervention compared in patients **with type 2 diabetes**	Percent body weight reduction (P<0.001): Semaglutide 2.4mg: 9.64% Semaglutide 1mg: 6.99% Placebo: 3.42% Percent achieving ≥ 5% body weight reduction (P<0.001): Semaglutide 2.4mg: 68.8% Semaglutide 1mg: 57.1% Placebo: 28.5%
STEP-3	Semaglutide 2.4mg + intensive behavioral therapy with initial low-calorie diet in patients **without diabetes**	Semaglutide: Average 16% body weight reduction compared to 5.7% with placebo (P<0.001) Percent achieving ≥5% body weight reduction (P<0.001): Semaglutide 2.4mg: 86.6% Placebo: 47.6%
STEP-4	Continuing semaglutide 2.4mg vs. placebo + lifestyle intervention after reaching treatment dose during 20-week run-in in patients **without diabetes**	Mean weight change from week 20-68: Semaglutide 2.4mg: -7.9% Placebo: +6.9%
STEP-8	Semaglutide 2.4mg versus Liraglutide 3.0mg + lifestyle intervention in patients **without diabetes**	Percent body weight reduction (P<0.001): Semaglutide 2.4mg weekly: -15.8% Liraglutide 3.0mg daily: -6.4%
SURMOUNT-1	Tirzepatide 5mg, 10mg, 15mg, or placebo + lifestyle intervention in patients **without diabetes**	Percentage body weight reduction (P<0.001): Tirzepatide 5mg: 15% Tirzepatide 10mg: 19.5% Tirzepatide 15mg: 20.9% Placebo: 3.1%

STEP = **S**emaglutide **T**reatment **E**ffect in **P**eople with obesity

Lifestyle intervention: 500 kcal deficit in daily expenditure (which was determined at trial initiation) + 150 minutes physical activity per week

Intensive behavioral therapy with initial low-calorie diet: 1000-1200 kcal diet for first 8 weeks, transitioned to low-calorie 1200-1800 kcal diet for the remainder of the trial. Physical activity included 100 minutes weekly over 4-5 days, increased by 25 minutes every 4 weeks to reach a goal of 200 minutes per week.

Assessment Questions (Answers with explanations at the end of handout)

1. Which of the following disease states is most likely to improve from a substantial loss in body weight?

A. Chronic Obstructive Pulmonary Disease

B. Cardiovascular Disease

C. Congestive Heart Failure - Stage 3

D. Crohn's Disease

2. Which type of side effect is most common for GLP-1 agonists?

A. Gastrointestinal upset

B. Cardiovascular arrhythmia

C. Hair loss

D. Nephrotoxicity

3. Which of the following FDA approved medications is most effective for weight loss?

A. Qsymia (Phentermine-Topiramate)

B. Contrave (Naltrexone-Bupropion)

C. Wegovy (Semaglutide)

D. Xenical / Alli (Orlistat)

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1. B - Obesity is the number 1 most modifiable risk factor for cardiovascular disease. While weight loss may help some patients with complications from CHF, the damage to the heart cannot be reversed. Weight loss will not help with COPD for similar reasons, and will not help Crohn's disease.

2. A - The most common side effects are nausea, vomiting, diarrhea, and constipation. Tirzepatide can cause alopecia, but in a low percentage of patients.

3. C - Semaglutide on average produces approximately 15% total body weight loss, compared to roughly 10% for Qsymia, and 6% for orlistat or Contrave.

Buprenorphine Microinduction for Chronic Pain

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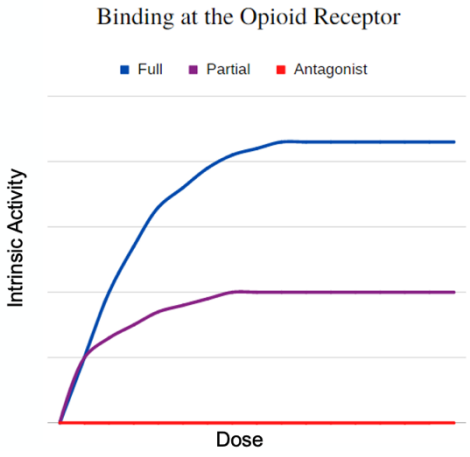
Disclosure: The content of this presentation has not been endorsed or approved by, nor does not directly represent any belief of, the United States Department of Veteran's Affairs

Objectives:

- List proposed benefits of buprenorphine as compared to a full mu agonist
- Describe the theorized mechanism behind microinduction with buprenorphine
- Summarize available data on microinduction strategies in chronic pain

Buprenorphine as an Analgesic

- Mechanism of action of buprenorphine[1,2]
    - Buprenorphine binds to four different receptors
        - Mu – acts like a partial agonist to mediate analgesia while causing less constipation, respiratory depression, and euphoria then full agonists
        - Kappa – acts as an antagonist to lessen dysphoria and constipation
        - Delta – acts as a weak agonist
        - Opioid receptor like-1 – acts as an agonist
- Clinical relevance of partial agonism[1,2]
    - As represented by the blue line, effects of full agonists continue to increase as doses increase, particularly concerning with regards to respiratory depression and constipation
    - As represented by the purple line, effects of partial agonists tend to exhibit more of a 'ceiling' effect given that as doses increase the risk of respiratory depression and constipation does not necessarily continue to climb
        - This translates to
            - Decreased risk of respiratory depression
            - Decreased risk of constipation
            - Decreased euphoria
        - Does not translate to
            - 'Partial' analgesia



- Binding to the receptor[1,2]
    - Has high binding affinity for the receptor
    - Slow dissociation from the receptor
    - High potency at the receptor

- Overview of common buprenorphine products[3,4,5]

Product	Formulation	Available Doses	Typical Dosing Interval	Bioavailability	Notes
Butrans	Transdermal	5 mcg/hr patch 7.5 mcg/hr patch 10 mcg/hr patch 15 mcg/hr patch 20 mcg/hr patch	Every 7 days	15%	A 20mcg/hr patch results in a similar dose of buprenorphine absorbed at the 75 mcg buccal film administered twice daily
Belbuca	Buccal	75 mcg 150 mcg 300 mcg 450 mcg 600 mcg 750 mcg 900 mcg	BID or TID	50%	Administering 300 mcg BID of Belbuca results in a similar dose of buprenorphine absorbed as administering 1 mg/0.25 mg BID
Suboxone	Sublingual	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	BID or TID	30%	Contains naloxone as abuse deterrent

- Receptor occupancy[6]
    - No buprenorphine allows for 100% of receptors to be available for binding
    - 2mg of buprenorphine allows for 59% of receptors to be available for binding
    - 16mg of buprenorphine allows for 20% of receptors to be available for binding
    - 32mg of buprenorphine allows for 16% of receptors to be available for binding
    - Large doses of buprenorphine would be required for saturation of receptors
- FDA Approval and prescribing in pain[7]

Drug	FDA Approval for Pain?	X Waiver Requirement in Civilian Practice	X Waiver Requirement in the VA
Butrans (Transdermal)	Yes	No	No
Belbuca (Buccal)	Yes	No	No
Suboxone (Sublingual)	No	No	Yes

Assessment Question 1

What are the proposed benefits of buprenorphine use as compared to a full mu agonist?

A. Analgesia
B. Decreased risk of side effects including respiratory depression and constipation
C. Decreased euphoria
D. All of the above

Traditional Strategies for Transitioning to Buprenorphine

- Opioid Tapers
    - Overview
        - No agreed upon strategy for doing this
        - Institutions may have some guidance

        - Typically, very patient specific
    - Tapering strategies recommended by different organization
        - Oregon Pain Guidance[8]
            - 5 to 20% dose reduction per month
            - Slower is better
            - Allow for breaks
        - Health and Human Services[9]
            - Slow taper: 10% dose reduction or slower per month
            - Faster taper: 10% dose reduction per week
                - May be more feasible for patients on opioids for weeks to months as compared to those who have been on them for years
        - Stanford School of Medicine[10]
            - Taper of 10% dose reduction per week is probably too fast
            - No clear recommendation but advises to go slower than 10% per week and allow the patient to be involved in the process
    - Higher Opioid Doses Predict Poorer Functional Outcome in Patients with Chronic Disabling Occupational Musculoskeletal Disorders by Kidner et al.[11]
        - 1226 with a chronic disabling musculoskeletal disorder were admitted into an interdisciplinary functional restoration program.
        - Patients were placed into groups based on opioid use
        - At enrollment, 630 patients did not use opioids and 596 patients used opioids at some capacity

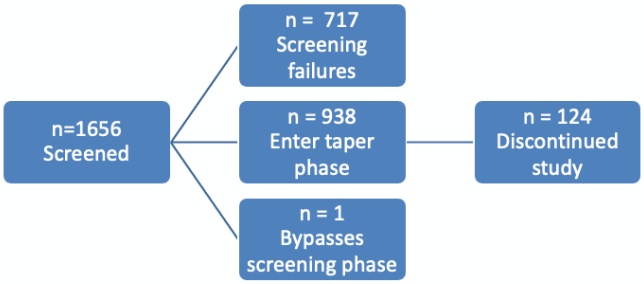
Patients on Opioids at Start of Study	
Opioid Use	**Number of Patients (%)**
Low (≤30 MMEs)	267 (44.8)
Medium (31 to 60 MMEs)	112 (18.8)
High (61 to 120 MMEs)	78 (13.1)
Very High (> 120 MMEs)	59 (9.9)
Unknown dose	80 (13.4)

        - All patients in the medium, high, and very high opioid subgroups were referred to a staff psychiatrist for "organized weaning"

Incompletion of Study/Program	
Group	**Number of Patients/N (%)**
No Opioid Use	117/630 (18.5)
Low (≤30 MMEs)	64/267 (23.3)
Medium (31 to 60 MMEs)	35/112 (31.3)
High (61 to 120 MMEs)	25/78 (31.9)
Very High (> 120 MMEs)	17/59 (29.4)

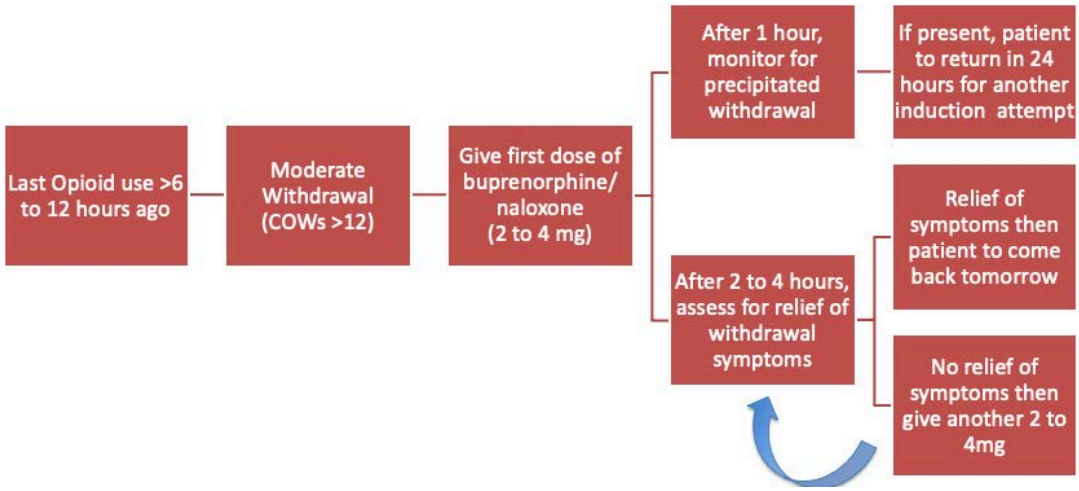
        - Participants requiring opioid taper were about 1.5x less likely to complete the study. The authors attributed incompletion of study in opioid use group due to refusal to taper or failure of taper.
    - Efficacy and Tolerability of Buccal Buprenorphine in Opioid-Experienced Patients with Moderate to Severe Low Back Pain by Gimbel et al.[12]
        - Participants in this study had moderate to severe chronic low back pain and had been taking 30 to 160 MMEs of an opioid
        - Participants were required to taper after the initial screening phase of the study

- Taper had to occur within 4 weeks
- Had to decrease to ≤ 30 MMEs
- Once at ≤ 30 MMEs for at least 3 days they were advanced to the open-label phase



- Takeaways
  - In these studies, participants who required an opioid taper were more likely to be unable to complete the study
  - Could potentially be linked to difficulty with opioid taper
  - Limitations
    - No information regarding individual participants reason for incompletion of the study in either study
    - No information regarding symptoms of withdrawal in either study

- Initiation of buprenorphine in opioid use disorder
  - Overview
    - Doses of buprenorphine typically used may be more than is needed for someone who is using for pain
    - Patient is required to exhibit symptoms of withdrawal before initiation of buprenorphine
  - Traditional initiation – in-office initiation[13]



- Clinical Opiate Withdrawal Scale (COWS)[14]

HR: 0 = HR <80 BMP 1 = HR 81-100 2 = HR 101-120 4 = HR >120	**GI Upset in last 30 minutes** 0 = No symptoms 1 = stomach cramps 2 = nausea or loose stool 3 = vomiting or diarrhea 5 = multiple episodes of v/d	**Yawning** (during assessment) 0 = no yawning 1 = yawns 1 to 2x 2 = yawns 3x or more 4 = yawns several times per minute	**Gooseflesh skin** 0 = skin is smooth 3 = piloerrection of skin can be felt or hairs standing up on arms 5 = prominent piloerrection
Tremor 0 = no tremor 1 = tremor can be felt, but not observed 2 = slight tremor observable 4 = gross tremor or muscle twitching	**Sweating in last 30 minutes** 0 = no reports of chills/flushing 1 = subjective report of chills/flushing 2 = flushed or observable moist face 3 = beads of sweat on brow or face 4 = sweat streaming off face	**Restlessness** (during assessment) 0 = able to sit still 1 = reports difficulty with sitting but is able to 3 = frequent shifting or extraneous movement of extremities 5 = unable to sit still for more than a few seconds	**Runny Nose or Tearing** 0 = not present 1 = nasal stuffiness or unusually moist eyes 2 = nose running or tearing 4 = nose constantly running or tears streaming down cheeks
Pupil size 0 = pupils pinned or normal size for room light 1 = pupils possibly larger than normal for room light 2 = pupils moderately dilated 5 = pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 = none 1 = patient reports increasing irritability or anxiousness 2 = patient obviously irritable or anxious 4 = patient so irritable or anxious that assessment is difficult	**Bone or Joint Aches** 0 = not present 1 = mild diffuse discomfort 2 = patient reports severe diffuse aching of joints/muscles 4 = patient is rubbing joints or muscles and is unable to sit still because of discomfort	**SCORING** **5 to 12 = mild** **13 to 24 = moderate** **25 to 36 = moderately severe** **>36 = severe**

  - Relation to buprenorphine use in chronic pain
    - Although this strategy is not typically used for transitioning chronic pain patients on full agonists to buprenorphine, it does provide some insight into symptoms patients can experience in the transitioning process. These symptoms could be worse if withdrawal is precipitated.
- Limitations to traditional strategies
  - Opioid Tapers
    - Can still be challenging for patients to reduce their dose significantly to be able to transition to buprenorphine without concern for precipitated withdrawal
    - Patient may still experience withdrawal symptoms during their taper
    - Patients may experience an increase in their pain
  - Traditional Initiation Strategies
    - Withdrawal is typically not a positive experience
    - Time consuming for both patient and provider
- How to initiate per Lexicomp[7]
  - Dose should be tapered to <30 MMEs then patient should be initiated based on their previous MME daily dose

Microinduction with Buprennorphine

- Theory behind microinduction[15,16]
  - Providing small doses of buprenorphine should only displace small amounts of full mu agonists
    - Study conducted by Mendelson et al gave 0.2 mg of buprenorphine IV to methadone-maintained patients and precipitated withdrawal was not induced
  - Due to the slow dissociation of buprenorphine at the receptor, buprenorphine will accumulate at the receptor
  - Over time, an increasing amount of full mu agonist will be displaced by buprenorphine and allow for discontinuation of the full mu agonist
- The Bernese Method[17]
  - Overview
    - Reported as a case series involving two patients

        - Utilized sublingual buprenorphine
        - Method first introduced in 2010
        - Case series published in 2016
    - Case 1
        - Overview
            - Patient was a 30 year old female
            - Past medical history significant for
                - Post-traumatic stress disorder
                - Historical sexual abuse as a child
                - Polysubstance use disorder
                - Psilocybin, 3,4-methylenedioxy-methamphetamine, cocaine, cannabis, heroin
                - Suicide attempt
                - Bulimia
        - First treatment attempt had occurred as an outside facility
        - Second treatment attempt occurred at study facility
            - Utilized conventional induction strategy
            - Patient had abstained from heroin for more than 8 hours
                - Rhinorrhea
                - Mydriasis
                - Stomach cramps
            - Initiated at 0.4 mg of buprenorphine which was administered four times
                - Diarrhea
                - Severe anxiety
                - Dissociative thinking
            - Additional doses of buprenorphine were administered in addition to supportive medications and patient returned home in stable condition
            - Three weeks later patient had relapsed and presented to clinic with desire to re-initiate buprenorphine use but with concern regarding induction process and related symptoms
        - Third treatment attempt
            - Offers 'Bernese Method'
                - Low doses of buprenorphine overlapping with heroin use
                - Plan to continue to increase buprenorphine dose until sufficient dose of buprenorphine was met and heroin could be abruptly stopped
                - Offered physician support via text message as well
                - See table for dosing utilized

Day	Buprenorphine Dose	Street Heroin (Sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8 + 2 mg	0.5 g
4	2 + 2.5 mg	1.5 g
5	2.5 + 2.5 mg	0.5 g
6	2.5 + 4 mg	0
7	4 + 4 mg	0
8	4 + 4 mg	0
9	8 + 4 mg	0

            - No data with information regarding withdrawal symptoms, but authors report patient tolerated this induction much better than the conventional induction
        - Longer term outcomes

- Relapsed multiple times after initial trial of Bernese method but continued to return for re-induction with this strategy
- Developed major depressive episode for which she was started on escitalopram and initiated psychotherapy
- Then abstained from heroin and was maintained on buprenorphine 12mg/day for 2.5 years
- Desired complete abstinence from opioids and with use of very low dose naltrexone, was able to achieve this

- Case 2
  - Overview
    - Patient was a 49 year old male
    - Past medical history significant for
      - Polysubstance use disorder
      - Cocaine
      - Heroin
      - Tobacco
      - COPD
      - Chronic hepatitis C
      - Recurrent thrombosis due to injection at the groin
    - Had several unsuccessful treatment attempts with methadone and had entered heroin-assisted treatment which had been successful
      - 200mg diacetylmorphine BID and 40mg of methadone at night
      - Wanted to switch to buprenorphine for more flexible pharmacotherapy

- Opioid doses, withdrawal symptoms, and cravings

Day	Buprenorphine Dose	Full Agonist in Methadone Equivalents	SOWS	Cravings Score
1	0.2 mg	160 mg	0	0
2	0.4 + 0.4 mg	140 mg	1	0
3	0.8 + 0.4 mg	140 mg	0	0
4	1.2 + 0.4 mg	140 mg	0	0
5	2 mg	140 mg	0	0
6	2.4 mg	130 mg	0	0
7	2.8 mg	140 mg	0	0
8	3 mg	140 mg	3	0
9	3.4 mg	140 mg	1	0
10	4 mg	140 mg	2	0
11	4.8 mg	180 mg	3	0
12	6 mg	160 mg	0	0
13	6 mg	140 mg	1	0
14	6 mg	140 mg	3	0
15	6 mg	180 mg	7	2
16	6 mg	180 mg	5	2
17-19	6 mg	180 mg, 180 mg, 80 mg	n/a	n/a
20	6 mg	120 mg	0	0
21	6 mg	130 mg	0	0
22	7.2 mg	90 mg	0	0
23	8.8 mg	130 mg	0	0
24	10.8 mg	140 mg	0	0
25	13.2 mg	90 mg	0	0
26	16 mg	140 mg	0	0
27	20 mg	110 mg	0	0
28	24 mg	140 mg	0	0
29	24 mg	0	1	0
30	24 mg	0	0	0

- Discussion
  - Case 1 patient was one who had history of previous difficulties with conventional induction strategies. The Bernese method was better tolerated by her.
  - Case 2 patient was using very high amounts of opioids. Despite this, he was still able to convert to buprenorphine with minimal withdrawal symptoms over a longer titration period.
- Strengths and limitations
  - Strengths
    - Introduced new method that was generally well tolerated in these two patients
    - No reported incidences of overdose
    - Mild withdrawal symptoms
    - Called for further research on this method
  - Limitations
    - Only two cases

- Limited information regarding rationale of full agonist dosing in Case 2
- No comparison information from conventional induction strategies
- Patients are utilizing for OUD, not chronic pain

- Buprenorphine Micrdose Induction for the Management of Prescription Opioid Dependence[18]
  - Utilized a modified Bernese method

Day	Buprenorphine Dose and Frequency	Full Agonist
1	0.5 mg daily	No change
2	0.5 mg BID	No change
3	1 mg BID	No change
4	2 mg BID	No change
5	2 mg TID	No change
6	4 mg TID	No change
7 and beyond	Per provider discretion	Taper by 25% weekly

  - Case summary

Age	Sex	Full Agonist at Time of Induction	MEDD	Substance Use Disorder	Pain Generator	Maintenance SL Bup Dose at 30 days
53	F	Fentanyl 100 mcg/hr patch	240	No	RA	4/8/8 mg
67	M	Hydrocodone/APAP 10/325mg – 8 tablets daily	80	No	Shoulder, knee, cervical, lumbar OA	N/a, unable to tolerate d/t sedation
69	M	Oxycodone 30mg 5x daily	225	Benzodiazepine use disorder, mild	Failed back surgery syndrome	8mg TID, continues on oxycodone 15mg TID on slow taper
62	F	Oxycodone 10mg 5x daily	75	Alcohol use disorder, mod	Chronic pancreatitis, chronic abdominal pain	N/a, unable to tolerate d/t nausea
63	F	Methadone 10mg BID; hydromorphone 2mg 4x daily	92	Opioid use disorder, mild	Fibromyalgia, knee OA	4mg four times daily
67	M	Hydromorphone 4mg five times daily; morphine SA 15mg daily	95	Opioid use disorder, mild	Multiple orthopedic surgeries; Parkinson's	8mg three times daily
70	F	Morphine SA 30mg twice daily; morphine IR 15mg 3x daily	105	No	Neuropathy, fibromyalgia, knee OA	8mg three times daily
53	M	Oxycodone 10mg seven times daily	105	No	Chronic leg wounds, lumbar OA2	8mg twice daily

  - Review of outcomes
    - 5 of 8 participants transitioned to buprenorphine and were able to stop their full agonist
    - 2 were unable to tolerate buprenorphine
    - 1 was still working on tapering their full agonist
    - No formal documentation of ADRs mentioned; however, authors do mention that withdrawal was not precipitated.
  - Strengths
    - Allowed longer taper period
    - Provides some more structured guidance
    - Includes patients with wide variety of pain syndromes
    - Includes patients with history of SUD
    - Includes patient on many different types of full agonists
  - Limitations
    - Only eight cases

        - No formal documentation of ADRs or withdrawal symptoms
        - Patients were all older
- Switching from High-Dose, Long-Term Opioids to Buprenorphine[19]
    - Overview
        - Case series of 6 patients
        - Utilized a protocol
        - Used sublingual buprenorphine-naloxone
    - Protocol utilized
        - See table for buprenorphine doses
        - Discontinues use of full agonist on day 5
        - Unclear on exact plan/dosing for full agonist on days 1-4 but did taper dosage slightly for one patient prior to stopping

Day	Buprenorphine Dose and Frequency
1	0.5 mg BID
2	1 mg BID
3	2 mg BID
4	2 mg TID
5	4 mg TID
6 and beyond	Adjust dose to symptoms

    - Case summary

Age	Sex	Full Agonist at Time of Induction	MEDD	Bup Dose when Full Agonist was Stopped	Bup Dose at 1 Month	Patient Summative Impression of Change at 1 month
62	M	Oxycodone CR 80 mg 3x daily	360	4 mg 3x daily	4 mg 4x daily	Equivalent pain intensity, improved pain interference, decreased ADRs
67	M	Morphine SA 30 mg 4x daily	120	4 mg 3x daily	4 mg 3x daily	Improved pain intensity, improved pain interference, decreased ADRs
58	F	Morphine SA 30 mg 2x daily Oxycodone IR 10 mg 3x daily	105	2 mg 3x daily	NA, switched back to oxycodone 10 mg 4x daily	Inadequately effective for pain
72	M	Oxycodone CR 60 mg 3x daily Oxycodone IR 40 mg 2x daily	390	2 mg 3x daily	4 mg 3x daily	Equivalent pain intensity, improved pain interference, improved mood, decreased ADRs
73	M	Morphine SA 30 mg 2x daily Oxycodone IR 10mg 4x daily	120	2 mg 3x daily	2 mg 3x daily	Equivalent pain intensity, improved pain interference, decreased ADRs
68	M	Methadone 10 mg 3x daily	240	2 mg 3x daily	2 mg 4x daily	Improved pain intensity, improved pain interference, decreased ADRs

    - Review of outcomes
        - 5 out of 6 were successfully transitioned
        - 1 stopped due to the medication being ineffective for her pain after 3 weeks
        - Authors report no symptoms of withdrawal or other adverse effects during transition
        - All patients who remained on buprenorphine
            - experienced no change or improvement in pain intensity
            - experienced improvement in pain interference and decrease in ADRs
    - Strengths
        - Shorter taper
        - Provides some more structured guidance
        - Provided information regarding withdrawal symptoms and patient impression of induction
        - Did not require patients meet 12 mg target dose

- Limitations
  - Only six cases
  - Patients were all older
  - Limited information regarding strategy for full agonist on days 1 to 4 of treatment

Assessment Question 2
Which of the following statements best describes the theory behind why microinduction could be an effective strategy to transition patients over to buprenorphine?

A. More mu receptors become available as the full agonist dose is decreased. When buprenorphine is started, it can occupy those now available receptors.
B. Small doses of buprenorphine displace small amounts of full agonist. Buprenorphine continues to build up with increasing doses, and it slowly displaces full agonist until receptors are being activated primarily by buprenorphine.
C. Mu receptors become available for binding when full agonist doses are held. This puts the patient into withdrawal and once symptoms are significant enough, buprenorphine can take the place of the full agonist and relieve the symptoms and be titrated to the point of analgesia.

Clinical Application and Conclusions

- Strengths of microinduction in chronic pain
  - Potentially improved tolerability
    - May be easier to get patients open to transitioning to buprenorphine and thus increases access to the many benefits of buprenorphine
  - In some ways, is not as complex for both patient and provider
- Limitations of microinduction in chronic pain
  - Limited data, especially in chronic pain
  - Can be difficult for patients to cut tablets
    - Previous regimens studied would require tablet splitting into fourths
  - Cost of medication when being used off label
    - Some insurance plans may not cover use of buprenorphine sublingual tablets if the patient does not have opioid use disorder
  - Some patients have had difficulty with tolerability of buprenorphine, although not common
  - Stigma related to buprenorphine use
- Good candidates for microinduction
  - Any patient taking > 90 MMEs of full mu agonist
  - Patients with significant concern regarding tolerability of induction process
  - A patient who maintains good follow-up
- Comparing rapid micro-induction and standard induction of buprenorphine/naloxone for treatment of opioid use disorder by Wong et al. [20]
  - Upcoming study
  - Randomized, open labeled, two-armed, superiority study
  - Primary outcome: Completion of induction with low levels of withdrawal

Assessment Question 3

Although limited to case studies at this time, all studies presented in this presentation showed which of the following?

A. Decreased dose in total daily dose of opioids with transition to buprenorphine
B. Improvement in pain scores with transition to buprenorphine
C. Minimal to no withdrawal symptoms with microinduction
D. Excellent tolerability of buprenorphine

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Venous Thromboembolism: Use of Direct Oral Anticoagulants in Obesity

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November 15th, 2022

Learning Objectives:

1. Identify risk factors for developing venous thromboembolism
2. Discuss current literature on the use of direct oral anticoagulants as VTE treatment in obesity

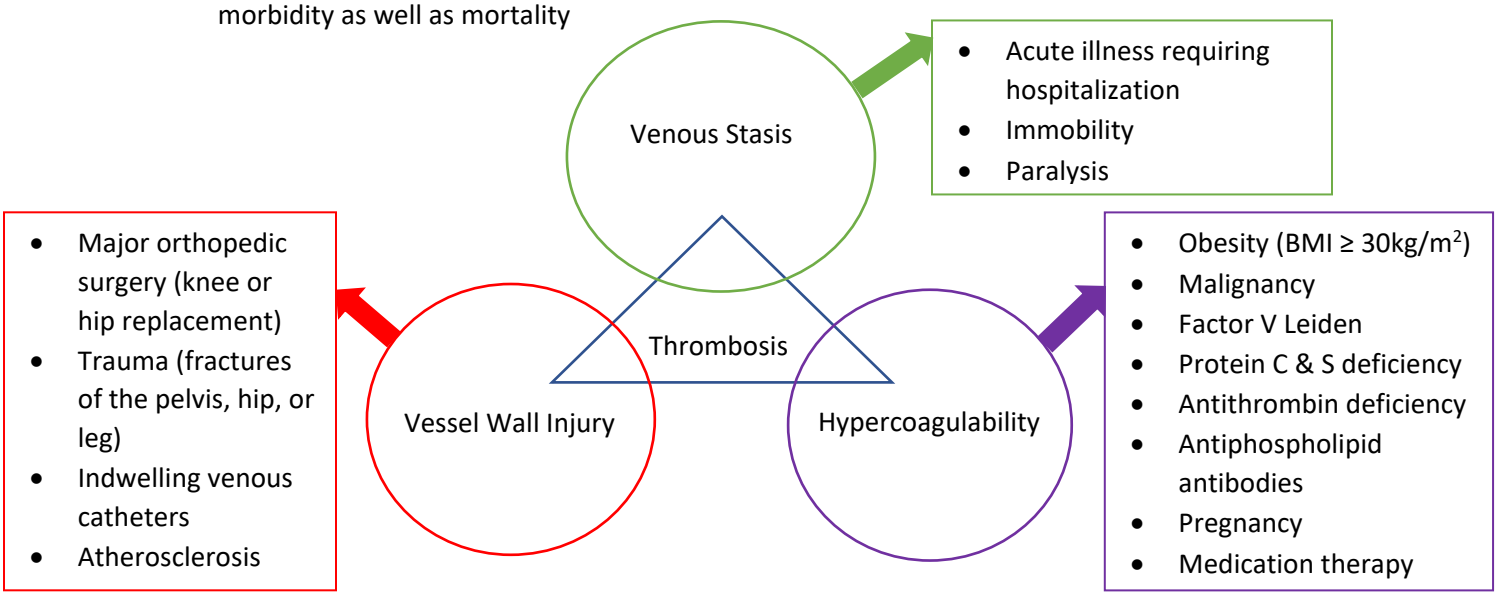
Background

Epidemiology[1]

- VTE ranked 3rd most common cardiovascular disorder
- Estimated 900,000 people affected annually
    - 60,000 – 100,000 deaths due to deep vein thrombosis (DVT) or pulmonary embolism (PE)
    - 33% will have recurrence within 1 year
- Healthcare burden
    - Estimated 2 billion – 10 billion dollars annually

Pathophysiology of VTE[2-6]

- Common complication in hospitalized patients that can lead to longer stays and increase morbidity as well as mortality



- Virchow's triad is a model that represents the physiologies which may lead to thrombus formation
    - Hypercoagulability
        - Increased tendency of blood to thrombose, where there is a pathologic state of exaggerated coagulation due to overactivity of pro-coagulant factors or a deficiency in anti-coagulants
    - Vessel wall injury
        - Endothelial dysfunction due to increased oxidative stress and decreased bioavailability of nitric oxide, resulting in atherosclerosis
        - Endothelial damage due to exposure of tissue factor and collagen, increasing platelet binding which promotes thrombus formation

- Venous stasis
    - Prolonged stasis causes lowered oxygen tension, resulting in oxidative stress and activation of pro-inflammatory cells. This will further trigger the extrinsic and intrinsic coagulation pathway, resulting in thrombus formation

Thrombosis in Obesity[7-9]

- According to the CDC, in 2016 more than 1.9 billion adults were overweight (body mass index (BMI) 25-29 kg/m^2) and over 650 million were obese (BMI ≥ 30 kg/m^2)
- Retrospective analyses
    - US population based-study suggested 10-point increase in BMI found to increase risk of VTE recurrence by 24%
- Prospective cohort analyses
    - Nurses' Health Study on 87,000 women
    - Relative risk of unprovoked PE not associated with prior surgery, trauma or cancer raised by 8% per 1 kg/m^2 increase in BMI
    - Nearly sixfold greater risk in those with a BMI ≥ 35 kg/m^2

Prothrombotic Pathways in Obesity[10-11]

- Promotion of chronic inflammation
    - Triggered by release of inflammatory cytokines from adipocytes, bringing macrophages to the adipose tissue
    - Activation of prothrombotic signaling in vascular cells
- Impaired fibrinolysis
    - Rate of fibrin clot degradation is affected
    - Increased plasminogen activator inhibitor-1 expression which inhibits fibrinolysis, leading to thrombus formation
- Increased presence of coagulation factors including fibrinogen, von Willebrand factor, and factor VIII, which are likely secondary to inflammatory cytokine release

Assessment Question #1

According to the Virchow's triad model, obesity is an example of which component?

A. Venous stasis
B. Vessel wall injury
C. Hypercoagulability
D. All the above

Guideline Recommendations on Use of DOACs in the General Population[12]

American College of Chest Physicians (CHEST 2021)

- VTE treatment
    - DVT or PE and no cancer
        - DOACs (dabigatran, rivaroxaban, apixaban or edoxaban) over vitamin K antagonist (VKA) (Grade 2B)
        - If not on DOACs, suggest VKA over low molecular weight heparin (LMWH) (Grade 2C)
    - Duration of therapy:
        - Proximal DVT provoked by surgery = 3 months (Grade 1B)
        - Proximal DVT provoked by non-surgical transient factor = 3 months (Grade 1B)

        - Distal DVT provoked by surgery or non-surgical transient factor = 3 months (Grade 2C)
        - Unprovoked DVT (distal or proximal) = 3 months (Grade 1B)
- Limitations: No weight-specific recommendations

Guideline Recommendations on Use of DOACs in Obesity[13]

International Society on Thrombosis and Hemostasis (ISTH 2021)

- For patients with BMI up to 40kg/m^2 or 120kg
    - Use of any DOAC is appropriate
- For patients with BMI > 40kg/m^2 or weight > 120kg
    - For VTE treatment
        - Rivaroxaban or apixaban at standard doses
        - Dabigatran and edoxaban **not** recommended
- **Note:** Limited analyses exist for dabigatran and edoxaban in VTE treatment with obese patients, therefore the remainder of this presentation will primarily focus on the place in therapy of rivaroxaban and apixaban

Oral Therapy for VTE Treatment[14-19]

Drug	Dose	Drug Interactions
Apixaban	10mg PO BID x 7 days, then 5mg PO BID	CYP 3A4/PGP inducers • Phenytoin, carbamazepine, St. John's Wort CYP 3A4/PGP inhibitors • Azole antifungals, ritonavir, clarithromycin, dronedarone, cobicistat, cyclosporine, tacrolimus
Rivaroxaban	15mg PO BID with meals x 21 days, then 20mg PO with evening meal	
Warfarin	Bridged with parenteral anticoagulant for 5 days and 2 consecutive INRs in therapeutic range Goal INR: 2 – 3	Decreased INR • Carbamazepine, phenobarbital, phenytoin, St. John's Wort Increased INR • Amiodarone, azole antifungals, metronidazole, sulfamethoxazole-trimethoprim, doxycyline, fluoroquinolones, diltiazem, fenofibrate

Obesity and Kinetics

General Population[14-15, 20]

Drug	Absorption	Distribution	Metabolism	Excretion/Elimination
Apixaban	• Bioavailability ~ 50% • Unaffected by food	• 87% protein binding • Vd ~ 27L	• Major: CYP 3A4, PGP • Minor: CYP 1A2, 2C8, 2C9, 2C19, 2J2	• Renal and fecal excretion • Half-life ~ 12 hours
Rivaroxaban	• Bioavailability ~ 66% • Food increases bioavailability of doses ≥ 15mg	• 92-95% protein binding • Vd ~ 50L	• Major: CYP3A4, PGP • Minor: CYP 2J2	• Renal excretion • Half-life ~ 11-13 hours

Kinetics in obesity: [13, 21]

- Obese patients have an imbalance in larger body mass vs. lean body mass compared to the general population which may alter distribution of drugs due to the impact on volume of distribution
- Sparse pharmacokinetic data and influence of extreme body weight
    - Some studies for both apixaban and rivaroxaban, suggest body weight may not play a factor in DOAC exposure as opposed to other clinical factors such as renal clearance
- Limitations with monitoring anti-Xa levels
    - Therapeutic drug targets for DOACs are unknown
    - Current available reference levels represent "on-therapy" ranges
    - Limited studies available correlating levels with risks of clinical outcomes
    - Insufficient data to utilize anti-Xa levels in clinical decision making

VTE Treatment: DOACs in the General Population[22-24]

Study	Structure and Methods	Outcomes
Wang Y, et al. (EINSTEIN – DVT) Rivaroxaban vs. enoxaparin-VKA (warfarin)	• Open-label, randomized, event-driven, non-inferiority trial • Rivaroxaban (N=1731) vs. Enoxaparin-VKA (N=1718) • Included patients with acute symptomatic objectively confirmed proximal DVT without symptomatic PE • Primary efficacy outcome: symptomatic, recurrent VTE (composite of DVT, nonfatal PE, or fatal PE) • Primary safety outcome: clinically relevant bleeding (composite of first major or clinically relevant nonmajor bleeding)	• Efficacy: 2.1% vs. 3.0%; HR 0.68, CI 0.44-1.04, P<0.001 o Majority = nonfatal PE and recurrent DVT, both less with rivaroxaban • Safety: 8.1% in both groups; HR 0.97, CI 0.76-1.22, P=0.77 o Majority of major bleeding events was associated with fall in hgb of ≤ 2g/dL, transfusion of ≥ 2 units, or both • Weight > 100kg: 14%
Büller H, et al. (EINSTEIN – PE)	• Open-label, randomized, event-driven, non-inferiority trial • Rivaroxaban (N=2419) vs. Enoxaparin-VKA (N=2413)	• Efficacy: 2.1% vs. 1.8%; HR 1.12, CI 0.75-1.68 o Majority = nonfatal PE and recurrent DVT

Rivaroxaban vs. enoxaparin-VKA (warfarin)	• Included patients with acute, symptomatic PE with objective confirmation, with or without symptomatic DVT • Primary efficacy outcome: symptomatic recurrent VTE (composite of fatal or nonfatal PE, or DVT) • Primary safety outcome: clinically relevant bleeding (composite of major or clinically relevant nonmajor bleeding)	• Safety: 10.3% vs. 11.4%; HR 0.49, CI 0.31-0.79 o Majority of major bleeding events was associated with fall in hgb of ≤ 2g/dL, transfusion of ≥ 2 units, or both • Weight > 100kg: 14%
Agnelli G, et al. (AMPLIFY) Apixaban vs. enoxaparin-VKA (warfarin)	• Randomized, double-blind trial • Apixaban (N=2691) vs. enoxaparin-VKA (N=2704) • Included patients with objectively confirmed symptomatic proximal DVT or PE (with or without DVT) • Primary efficacy outcome: incidence of the adjudicated composite of recurrent symptomatic VTE or death related to VTE • Primary safety outcome: adjudicated major bleeding	• Efficacy: 2.3% vs. 2.7%; HR 0.84, CI 0.60-1.18, P<0.001) o Majority = nonfatal PE with or without DVT • Safety: 0.6% vs. 1.8%, HR 0.31, CI 0.17-0.55, P<0.001 o Majority = intracranial, lower with apixaban • Weight > 100kg: 19%

DOACs in Obesity[25-27]

Coons, JC, et al. Effectiveness and Safety of Direct Oral Anticoagulants versus Warfarin in Obese Patients with Acute Venous Thromboembolism. Pharmacotherapy. 2010 Mar; 40(3):204-210.	
Purpose	To evaluate the effectiveness and safety of DOACs versus warfarin for the treatment of VTE in obese patients
Design	Retrospective matched cohort study University of Pittsburgh Medical Center January 1, 2011 – October 2015
Patient Selection	Patients identified through electronic medical record (EMR) Inclusion criteria • 18+ years old identified by international classification of diseases, Ninth Revision, Clinical Modification (ICD-9M) codes for acute VTE as admitting diagnosis • Medication charge code for DOAC (apixaban, dabigatran, or rivaroxaban) or warfarin during index emergency department (ED), observation, or hospital visit • Documented actual body weight > 100kg and < 300kg during index visit Exclusion criteria • Diagnosis of atrial fibrillation or atrial flutter
Outcomes	Primary outcome • Recurrence of VTE within 12 months of index admission date Secondary outcome • Occurrence of PE and DVT events separately within study timeframe • Bleeding defined as any readmission with a primary admission ICD-9-CM or ICD-10-CM code for bleeding within 12 months

<table>
<tr><td>Statistical Analysis</td><td>Baseline demographic and clinical characteristics
• Chi-squared for categorical data and Mann-Whitney U test for continuous data
• Propensity score matching in a 2:1 ratio using caliper of 0.2 standard deviations
Clinical outcomes
• Chi-squared for 1-year incidences
• Time-to-event (TTE) curves using Kaplan Meier and log-rank test
• Univariable cox regression to calculate hazard ratios (HRs)</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Participants</td><td>DOAC
• 2102 patients with an admission of acute VTE and received a DOAC
o 632 met inclusion criteria
▪ Rivaroxaban accounted for most cases (580 patients, 91.8%)
▪ Apixaban in 33 patients (5.2%)
▪ Dabigatran in 19 patients (3%)
Warfarin
• 14,620 warfarin-treated patients with an admission diagnosis of VTE and received warfarin
o 1208 met inclusion and exclusion criteria

576 DOAC treated patients matched to 2 warfarin-treated controls and 56 were matched to 1 warfarin-treated control

<table>
<tr><th>Baseline Characteristics</th><th>DOAC (N=632)</th><th>Warfarin (N=1208)</th><th>P value</th></tr>
<tr><td>Age, yrs</td><td>55 (46-65)</td><td>55(45-65)</td><td>0.64</td></tr>
<tr><td>Female</td><td>216 (34.2)</td><td>434 (34.9)</td><td>0.46</td></tr>
<tr><td>Weight</td><td></td><td></td><td></td></tr>
<tr><td>• > 120 kg</td><td>264 (41.8)</td><td>497 (41.1)</td><td>0.79</td></tr>
<tr><td>• > 200 kg and < 300 kg</td><td>7 (1.1)</td><td>25 (2.1)</td><td>0.13</td></tr>
<tr><td>BMI, kg/m^2</td><td>38.8 (34.0-44.5)</td><td>39.2 (34.4-45.3)</td><td>0.44</td></tr>
<tr><td>• 30.1 – 35 kg/m^2</td><td>98 (23.3)</td><td>179 (23.7)</td><td></td></tr>
<tr><td>• 35.1 – 39 kg/m^2</td><td>113 (26.9)</td><td>197 (26.1)</td><td></td></tr>
<tr><td>• > 40 kg/m^2</td><td>183 (43.6)</td><td>342 (45.3)</td><td></td></tr>
<tr><td>History of VTE</td><td>132 (20.9)</td><td>237 (19.6)</td><td>0.52</td></tr>
<tr><td>History of Cancer</td><td>45 (7.1)</td><td>40 (3.3)</td><td><0.001</td></tr>
<tr><td>Home anticoagulant</td><td>120 (19)</td><td>152 (12.6)</td><td><0.001</td></tr>
</table>
• Data listed as median (interquartile range) or no. (%) of patients
• Home anticoagulant included either DOAC or warfarin
o Median weight 115kg (101-299kg)
o BMI only available for 755 patients in warfarin group and 420 patients in DOAC group</td></tr>
<tr><td>Outcomes
DOAC vs. Warfarin</td><td>Primary outcome
• No difference in VTE recurrence within 12 months of index admission between groups
o 41 patients (6.5%) vs. 77 patients (6.4%), P=0.93
Secondary outcome
• No difference observed in occurrence of PE or DVT within study timeframe
o PE: 3.7% vs. 3.8%, P=0.94
o DVT: 3.0% vs. 3.5%, P=0.56</td></tr>
</table>

	• Bleeding within 12 months of index admission date in 11 patients (1.7%) vs. 14 patients (1.2%), P=0.31 o Majority = GI bleed which was higher in the warfarin group (7 vs. 4) and genitourinary which was higher in the DOAC group (5 vs. 2) o Other types included epistaxis, intracranial, and injury which only occurred in the warfarin group, and hemoptysis was similar between both groups
Authors' Conclusion	DOACs (rivaroxaban, apixaban, and dabigatran) may be considered as alternatives to warfarin in patients with obesity for acute VTE treatment
Strengths & Limitations	Strengths • Propensity score matching to account for potential confounding factors • Appropriate statistical tests were used • Included patients that had anticoagulation before index visit and those who received new anticoagulant therapy for acute VTE Limitations • No assessment of anticoagulant therapy prior to enrollment • Retrospective: relies on accurate EMR documentation of ICD-9 codes in defining VTE and bleeding events • Majority of the patients received rivaroxaban, therefore unable to extrapolate results to individual DOAC • Only 40-45% of patients with weight > 120kg and BMI > 40kg/m^2 • Did not assess adherence or duration of anticoagulation, only focused on inpatient medication use • Did not assess INR for warfarin group to evaluate TTR • Unable to discern whether VTE events were provoked due to trauma or surgery or unprovoked which could influence the appropriateness of duration of therapy related to VTE recurrence • Unable to determine if patients switched anticoagulant therapy during follow-up period • No assessment of appropriate dosing or duration of therapy
Key Take Away	There were no differences observed in VTE recurrence or bleeding within 12 months of index admission date, although it is important to note that this study only had 40-45% with a weight ≥ 120kg and BMI ≥ 40kg/m^2 therefore severe obesity (weight ≥ 120kg or BMI ≥ 40kg/m^2) still underrepresented

Weaver P, et al. Management of Venous Thromboembolism in Morbid Obesity with Rivaroxaban or Warfarin. Annals of Pharmacotherapy. 2022 May;6(11):1166-75.

Purpose	To evaluate the rates of thrombosis and bleeding in morbidly obese patients receiving rivaroxaban or warfarin for VTE
Design	Multicenter, retrospective cohort study 7 healthcare systems in the US within Ascension Health network
Patient Selection	Inclusion criteria • ≥18 years • BMI ≥ 40kg/m^2 or weight ≥ 120kg • ICD-9-CM and ICD-10-CM codes for acute VTE • Receiving warfarin or rivaroxaban Exclusion criteria • Valvular atrial fibrillation defined as presence of mechanical heart valve • Pregnancy • Severe liver disease defined as Child Pugh C, presence of liver cirrhosis, or hepatorenal syndrome • Concomitant medications with significant drug interactions (itraconazole, ketoconazole, ritonavir, rifampin, carbamazepine, phenytoin, St. John's Wort)
Outcomes	Primary efficacy outcome • Hazard of recurrence of VTE within 12 months from index visit or physician documentation of new or worsened DVT or PE Primary safety outcome • Hazard of major bleeding at 12 months based on ICD-9-CM or ICD-10-CM codes or physician documentation o Major bleeding defined in accordance with ISTH definition of major bleeding in non-surgical patients: fatal bleeding, and/or bleeding at critical are or organ, and/or bleeding caused by hemoglobin decrease of ≥ 2g/dL in a 24-hour period leading to transfusion of ≥ 2 units of blood Secondary outcomes • Incidence of clinically relevant non-major bleeding (CRNMB) defined as clinically overt bleeding leading to hospitalization, medical or surgical intervention, or change in anticoagulation management but did not meet the definition of major bleeding • Incidence of CRNMB and major bleeding • All-cause mortality • Number of total hospital encounters • Length of stay of initial encounter • Incidence of switch in anticoagulant defined as switch from index medication to different anticoagulant based on orders for alternative
Statistical Analysis	• Sample size based on Costa et al showing lower rates of recurrent VTE in those with a BMI ≥ 40kg/m^2 who received rivaroxaban vs. warfarin (2.89% vs. 5.66%; HR 0.51, CI 0.36-0.72) • Estimated 1751 patients needed to detect a difference in the hazard of recurrent VTE within 12 months (1167 = warfarin and 584 = rivaroxaban) • 80% power, alpha = 0.05 • Univariable analysis using chi-square test for nominal data and student t test for continuous data • Kaplan Meier curve and log rank test used to assess time to VTE recurrence and time to major bleeding in 12 months

	• Multivariable analysis using cox proportional hazards model
	• Two models used to assess confounding variables
	  o First model included all potential confounding variables
	  o Second model was backwards elimination, removing P = 0.1
	• Logistic regression used to analyze propensity matching score performed in 1:1 ratio
	• Subgroup analysis of BMI ≥ 50kg/m^2 and/or ≥ 140kg for primary and relevant secondary outcomes

Participants	1,272 participants • 785 patients in warfarin group and 487 patients in rivaroxaban group

Baseline Characteristics	**Rivaroxaban (N=487)**	**Warfarin (N=785)**	**P value**
Age, years	56.6± 14.7	57.7 ± 14.7	0.22
Weight, kg	134.1 ± 23.2	139.2 ± 30.2	**<0.01**
Male	256 (52.1)	345 (43.7)	**<0.01**
Past medical history			
Active cancer	36 (7.3)	42 (5.3)	0.14
Atrial fibrillation	42 (8.6)	98 (12.4)	**0.03**
Diabetes	172 (35)	366 (46.3)	**<0.01**
Liver Disease	18 (3.7)	36 (4.6)	0.44
CKD	56 (11.4)	147 (18.6)	**<0.01**
Hypercoagulable state	34 (16.9	82 (10.4)	**0.04**
History of stroke	17 (3.5)	32 (4.1)	0.59
History of VTE	195 (39.7)	305 (8.6)	0.69
History of bleeding	13 (2.6)	24 (3.0)	0.69
Trauma within 6 months	12 (2.4)	18 (2.3)	0.85
Surgery within 6 months	18 (3.7	29 (3.7)	0.99
Concomitant medications			
NSAID	21 (4.3)	57 (7.2)	**0.03**
Aspirin	96 (19.6)	252 (31.9)	**0.01**
Clopidogrel	21 (4.3)	39 (4.9)	0.59
Prasugrel	0	0	--
Ticagrelor	1 (0.2)	1 (0.1)	0.73
Estrogen	7 (1.4	6 (0.8)	0.25
Cilostazol	2 (0.4)	4 (0.5)	0.8
SSRI	67 (13.6)	148 (18.7)	**0.02**
Admission laboratory values			
Discharge SCr, mg/dl	0.99 (0.59)	1.27 (1.3)	**<0.01**
Lowest hemoglobin, mg/dl	11.8 (2.5)	10.7 (2.3	**<0.01**
Lowest platelet, K/cm	204 (78)	198 (77)	0.28
Initial INR	1.17 (0.54)	1.38 (0.85)	**<0.01**
Highest INR	1.31 (0.66)	2.35 (1.32)	**<0.01**

- Mean weight was 136.4 ± 27.2kg, and mean BMI was 45.9 ± 9.2kg/m^2
- 93% of patients on rivaroxaban dosing per prescribing information

Outcomes	Primary efficacy outcome

Rivaroxaban vs. warfarin	• Rivaroxaban use not associated with increased hazard of VTE events compared to warfarin with adjusted analyses (HR 0.69, 95%CI: 0.42-1.08, P=0.12) Primary safety outcome • No significant difference found in development of major bleeding within 12 months for patients on rivaroxaban compared to warfarin in the unadjusted analysis (P=0.82) • No significant differences in major bleeding events with rivaroxaban and warfarin patients (HR 1.21, CI 0.62-2.34, P=0.58) in adjusted analysis o No difference observed after backward elimination (HR 1.29, CI 0.66-2.30, P=0.52) • Time to major bleeding was similar between groups with propensity matching (P=0.54) Secondary outcomes • Statistically significant difference in VTE (5.3% vs. 8.7%, P=0.03), initial length of stay in days (4.1 ± 4.7 vs. 8.5 ± 8.7, P < 0.01), and total number of hospital encounters (2.97 ± 4.9 vs. 6.57 ± 9.1, P < 0.01) • No significant differences in incidence of major bleeding or CRNMB in 12 months in rivaroxaban vs. warfarin (3.1% vs. 3.3%, P=0.87 and 1.8% vs. 3.1%, P=0.21) • No significant differences in all-cause mortality (1.2% vs. 2.3%, P=0.21) • No significant differences in incidence of switch in anticoagulation (9.9% vs. 8.2%, P=0.33) Subgroup Analysis: BMI > 50kg/m^2 and/or weight > 140kg • Rivaroxaban (N=159), warfarin (N=335) • Mean weight = 170kg and mean BMI = 53.4kg/m^2 • No significant differences in VTE recurrence, major bleeding, CRNMB, or all-cause mortality
Authors' Conclusions	No difference observed in hazard of VTE recurrence or major bleeding between rivaroxaban and warfarin treatment in severe obesity (body weight >120kg and/or BMI > 40kg/m^2), therefore either agent is appropriate for VTE treatment
Strengths & Limitations	Strengths • Performed unadjusted and adjusted analyses of the primary outcome to account for potential confounding factors • Propensity matched scoring also to account for confounding factors • Evaluated concomitant medications that may have impacted the safety and effectiveness of anticoagulant therapy • High percentage of follow-up (95.9%) Limitations • Retrospective • Identification of VTE by diagnostic codes may lead to misidentification of the patient population • Did not meet power to detect a difference o Needed 1167 patients in warfarin group and 584 patients on rivaroxaban o Study included 785 patients in warfarin and 487 patients on rivaroxaban • Warfarin arm had higher percentage of patients with history of atrial fibrillation and hypercoagulable states increases risk of VTE recurrence • No collection of anticoagulation therapy changes during follow-up period • Follow-up was conducted via phone to gather information related to primary and secondary outcomes, if unsuccessful after 3 attempts, patient was noted as not having either VTE nor bleeding event • No assessment of adherence

	• Unable to capture INR or TTR • No assessment of appropriate dosing or duration of therapy
Key Take Away	No difference observed in hazard of VTE recurrence of major bleeding with rivaroxaban compared to warfarin, but the study was underpowered to detect a difference.

Crouch A, et al. Multi-center retrospective study evaluating the efficacy and safety of apixaban versus warfarin for treatment of venous thromboembolism in patients with severe obesity. Pharmacotherapy. 2022 Feb;42(2):119-133

Purpose	To evaluate the efficacy and safety of apixaban for venous thromboembolism (VTE) in patients with body mass index (BMI) ≥ 40kg/m^2 or weight ≥ 120kg
Design & Patient Selection	• See above study
Outcomes	• Time to recurrent VTE at 12 months • Time to major bleeding at 12 months
Statistical Analysis	1754 patients needed to detect a difference • Power 80%, alpha = 0.05 • Chi-square and t test used to compare baseline characteristics between groups • Kaplan Meier curve and log rank test used to assess time to VTE recurrence and time to major bleeding within 12 months • Cox-proportional regression used for multivariable analysis • Logistic regression used for propensity analysis performed in a 1:1 ratio • Subgroup analyses for relevant primary and secondary outcomes in BMI > 50kg/m^2 or weight > 140kg
Participants	4803 patients with VTE/ AF on DOAC or warfarin • Excluded those with liver disease (N=76), who were pregnant (N=25), taking concomitant medications (N=107), valvular atrial fibrillation (N=295), and those within the rivaroxaban or AF study (N=487) • 1099 patients with VTE receiving apixaban or warfarin

Baseline Characteristics	**Apixaban (N = 314)**	**Warfarin (N=785)**	**P value**
Age, years	59.3 ± 13.9	57.7 ± 14.0	0.15
Weight, kg	131.3 ± 22.9	139.5 ± 30.1	**<0.01**
BMI, kg/m^2	44.1 ± 6.8	47.1 ± 10.4	**<0.01**
Male	164 (52.2)	345 (43.9)	**<0.01**
Past medical history			
Alcohol use disorder	20 (6.4)	26 (3.3)	**0.03**
Active smoker	55 (15.75)	171 (21.8)	0.12
Active cancer	27 (8.6)	42 (5.4)	0.05
CKD	57 (18.2)	147 (18.7)	0.86
Diabetes mellitus	74 (23.6)	363 (46.2)	**<0.01**
Coagulation disorder	22 (7.0)	80 (10.2)	0.11
Atrial fibrillation	49 (15.6)	97 (12.4)	0.17
History of stroke	21 (6.7)	32 (4.1)	0.09
History of VTE	70 (22.3)	305 (38.9)	**<0.01**

	History of bleeding	7 (2.2)	24 (3.1)	0.55
	History of trauma in prior 6 months	4 (1.3)	18 (2.3)	0.35
	History of surgery in prior 6 months	21 (6.7)	29 (3.7)	**0.04**
	Liver disease	13 (4.1)	35 (4.5)	0.87
	Concomitant medications			
	NSAID	21 (6.7)	57 (7.3)	0.80
	Aspirin	99 (31.5)	251 (32.0)	0.94
	Clopidogrel	25 (8.0)	40 (5.1)	0.09
	Prasugrel	0	0	--
	Ticagrelor	1 (0.3)	1 (0.1)	0.49
	Estrogen	1 (0.3)	6 (0.8)	0.68
	Cilostazol	1 (0.3)	5 (0.6)	0.68
	SSRI/SNRI	48 (15.3)	148 (18.9)	0.19
	Admission laboratory values			
	Discharge SCr, mg/dl	1.40 ± 1.55	1.27 ± 1.31	0.05
	Lowest hemoglobin, mg/dl	10.9 ± 2.6	10.7 ± 2.3	**0.03**
	Lowest platelet, K/cmm	198 ± 77	199 ± 77	0.91
	Length of initial hospital stay			
	Days	6.5 ± 7.2	8.5 ± 8.8	0.09

Apixaban
- Higher percentage of males (52.2% vs. 43.9%)
- Lower mean weight (131kg ± 22.9 vs. 139.5 ± 30.1)
- Lower BMI (44.1 ± 6.8 vs. 47.1 ± 10.4)

Comorbid conditions were similar between groups, but higher incidence of alcohol use and surgery within 6 months prior to admission in apixaban patients. Patients in the warfarin arm had higher incidence of diabetes and history of VTE, but lower recorded hemoglobin lab value compared to apixaban arm.

Outcomes
Apixaban vs. warfarin

Primary efficacy outcome

Unadjusted analyses
- Time to recurrent VTE at 12 months was longer in the apixaban arm compared to warfarin (P=0.018)

Primary safety outcome
- No difference in time to major bleeding at 12 months between apixaban and warfarin (3.8% vs. 3.3%, P=0.715)

Secondary outcome
- No significant difference in incidence of CRNMB or all-cause mortality between groups
- Significantly reduced incidence of recurrent VTE in 12 months (4.5% vs. 8.7%, P=0.02)
- Significantly fewer hospital encounters in 12 months (2.92 ± 4.3 vs. 6.56 ± 9.2, P<0.01)

Subgroup analyses

Outcomes, no (%)	Apixaban (N=93)	Warfarin (N=335)	P value
Recurrent VTE	3 (3.2)	33 (9.9)	0.06
Major bleeding	4 (4.3)	10 (3.0)	0.52

	CRNMB	1 (1.1)	9 (2.7)	0.70
	All-cause mortality	4 (4.3)	8 (2.4)	0.30
Authors' conclusions	Apixaban was associated with longer time to VTE recurrence and reduced rates of VTE recurrence compared to warfarin within 12 months in patients with severe obesity with no differences in rates of bleeding			
Strengths & Limitations	Strengths • Studied a patient population that is generally underrepresented (severe obesity, BMI ≥ 40kg/m^2 or weight ≥ 120kg) • Median weight and BMI were appropriate with definition of severe obesity • Evaluated concomitant medications that may have impacted the safety and effectiveness of anticoagulant therapy • High percentage of follow-up patients at 12 months (97.1%) Limitations • Retrospective • Higher patient population with history of VTE in warfarin arm, already at an increased risk of recurrent VTE at baseline • Unable to assess adherence • Did not assess INR TTR for warfarin arm • Follow-up was conducted via phone to gather information related to primary and secondary outcomes, if unsuccessful after 3 attempts, patient was noted as not having either VTE nor bleeding event			
Key Take Away	Time to recurrent VTE was longer and incidence of VTE was also reduced in patients with severe obesity (BMI ≥ 40kg/m^2 or weight ≥ 120kg) receiving apixaban compared to warfarin with no significant differences in bleeding compared to warfarin, therefore apixaban can be an appropriate alternative for VTE treatment in those with severe obesity			

Bariatric Surgery[13, 28]

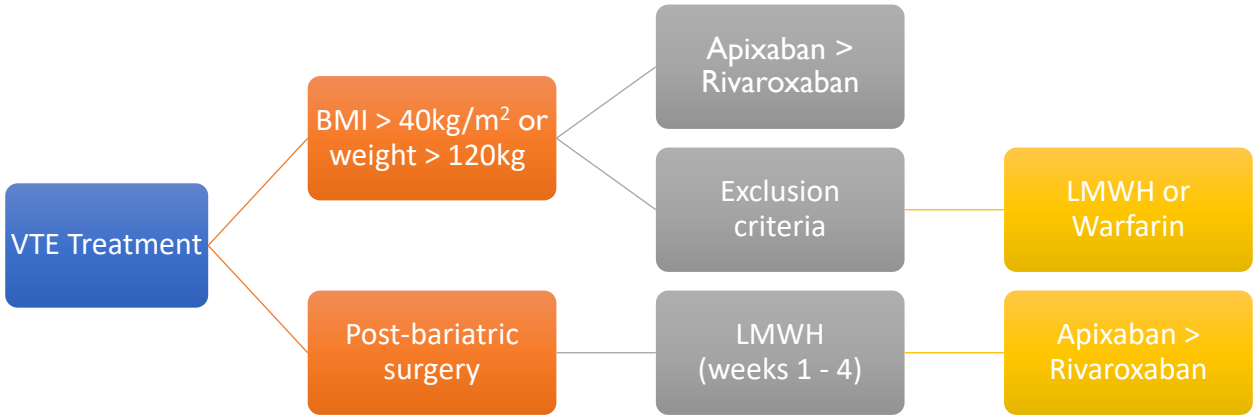
- ISTH Guidelines
  - DOACs are **not** recommended in post-bariatric surgery in the acute setting
    - Decreased absorption
    - Initiate parenteral anticoagulation in early postsurgical phase and switch to VKA or DOAC after at least 4 weeks of parenteral therapy
- Potentially reduces drug absorption in patients undergoing gastrointestinal tract resections which may reduce efficacy
- Rivaroxaban
  - Readily absorbed in the stomach after oral administration
  - Requires passage through the stomach and dependent on site of release in the GI tract
  - Unclear on absorption difference in patients undergoing partial vs. sleeve gastrectomy
- Apixaban
  - pH-independent absorption in the upper GI tract
  - Unaffected by administration with meal intake
  - Theoretically safer in post-bariatric surgery as it would be unaffected by change in meal sizes after surgery

DOAC	Site of absorption	Type of surgery		
		Gastric Banding	Partial/Sleeve Gastrectomy	Roux-en-Y Gastric Bypass (RYGB)

Apixaban	Mainly in the upper GI tract	Unlikely affected	Unlikely affected	Possibly reduced
Rivaroxaban	Mainly in the stomach	Possibly reduced	Possibly reduced	Possibly reduced

- Majority of studies on apixaban and rivaroxaban in bariatric surgery are limited to small sample sizes
- Study investigating DOAC levels in 18 patients on chronic anticoagulation who underwent bariatric surgery showed:
    - Median peak level for rivaroxaban was lower than the control group (159ng/mL vs. 249ng/mL, P=0.02)
    - Median peak level for apixaban was within expected range
- Reduced caloric intake in the acute setting post-bariatric surgery may affect absorption of rivaroxaban

Conclusion and Recommendations for use



Exclusion criteria:

- Severe liver disease (Child Pugh C, presence of liver cirrhosis, or hepatorenal syndrome)
- Pregnancy (LMWH only)
- Valvular atrial fibrillation (presence of mechanical heart valve)
- Renal dysfunction (CrCl < 30 ml/min)
- BMI > 50kg/m^2 and/or weight > 140kg

Assessment Question #2

According to the ASCEND-HIGHER studies, which of the following would be the most appropriate recommendation for a patient with a BMI > 40kg/m^2?

A. apixaban 10mg PO BID x 7 days, then 5mg PO BID

B. rivaroxaban 15mg PO BID with meals x 21 days, then 20mg PO with evening meal

C. dabigatran 150mg PO BID

D. warfarin bridged to target INR goal of 2 – 3

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