Literature Review: Hospital Medicine Pt 1

SEPTEMBER 19, 2024

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Conflicts of interest

- Nothing to disclose

Literature Selection

- Published 2023-2024
- Focus on commonly encountered inpatient situations
- Practice-changing or practice-confirming

Agenda

- Prevalence of DVT/PE in patients with COPD exacerbation
- Cardiovascular and renal outcomes of combination GLP-1 RA and SGLT-2i therapy in patients with diabetes
- Hospital-based protocol for rapid initiation of methadone
- Edoxaban monotherapy for patients with AF and stable CAD

Case 1

- 75 yo man with COPD on ICS/LABA combination, CAD on ASA 81 mg, CKD III presenting with dyspnea and wheezing for the past 2-3 days
- CXR with hyperinflated clear lungs, WBC wnl, requiring 3-4L O2 by NC
- You order sputum culture and swab for flu/COVID, start prednisone, azithromycin and scheduled nebulizer treatments

Q1: How common is VTE in COPD exacerbations?

International Journal of Chronic Obstructive Pulmonary Disease

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CLINICAL TRIAL REPORT

Prevalence, Risk Factor and Clinical Characteristics of Venous Thrombus Embolism in Patients with Acute Exacerbation of COPD: A Prospective Multicenter Study

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VTE in AECOPD

Design:

- Multicenter, prospective cohort study Jan 2017- Jan 2021
- 11 hospitals in China

Patient selection:

- Inclusion: Age > 40, prior diagnosis of COPD, admitted for COPD exacerbation (dyspnea, cough, sputum production)
- Excluded for: contraindication to CTPA, active malignancy, already on treatment with anticoagulation
- 1580 patients enrolled, all of whom underwent CTPA, 12-lead EKG, bilateral LE venous duplex ultrasound and TTE within 48 hours

Results

- Any VTE in 387 of 1580 (24.5%)
- 180 had PE *without* DVT
- 86 with both PE and DVT
- 121 with DVT only
- Amongst the 266 with PE (+/- DVT):
  - 49 in a main PA
  - 117 in a lobar artery
  - 100 in segmental/subsegmental

Takeaways

- We are potentially missing PEs in patients with COPD exacerbation
- Should be scanning more patients admitted with COPD exacerbation, especially if the history doesn't contain a clear etiology
- Step-wise imaging protocols such as LE ultrasound prior to deciding on CTPA could miss a significant number of patients with PE but not DVT

Case 2

- 64 yo woman with CAD on aspirin, HFrEF on propranolol, hydralazine and furosemide, T2DM on metformin and liraglutide, OSA on CPAP has been admitted to your service for 2 days with fluid volume overload
- You adjusted her heart failure medication regimen on admission, and will plan to do so again at discharge, to better align with current evidence-based guidelines
- What about other classes of medications?

Q2: Does addition of GLP-1 agonist to SGLT-2 (or vice versa) improve cardiovascular and renal outcomes?

Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study

Nikita Simms-Williams,[1] Nir Treves,[2] Hui Yin,[1] Sally Lu,[3] Oriana Yu,[3,4] Richeek Pradhan,[5] Christel Renoux,[3,6,7] Samy Suissa,[3,6] Laurent Azoulay[3,6,8]

Combination therapy: GLP-1 RA and SGLT-2i

Design:

- Population-based cohort study
- Prevalent new-user design, which emulates an RCT

Brief aside on the design:

- Records pulled from UK-based primary care database containing 60 million patients between 2013-2020
- Created 2 cohorts of patients with T2DM:
  - Patients previously prescribed GLP-1 RA who later added SGLT-2i
  - Patients previously prescribed SGLT-2i who later added GLP-1 RA
- Cohorts were then matched 1:1 to patients on the same base drug who continued monotherapy
- 46 factors used for propensity score matching (e.g. age, sex, smoking status, duration of DM dx, medical comorbidities, and duration of exposure to the drugs)
- Limitations: "on treatment analysis" tracks prescription records from primary care only, without adherence data or prescriptions from specialists

Table 1 | Characteristics of GLP-1 receptor agonist-SGLT-2 inhibitor combination users and GLP-1 receptor agonist users after matching. Values are numbers (percentages) unless stated otherwise

Characteristics	GLP-1 receptor agonist-SGLT-2 inhibitor combination users (n=6696)	GLP-1 receptor agonist users (n=6696)	Absolute standardised difference
Mean (SD) age, years	56.7 (10.4)	57.3 (10.4)	0.05
Male sex	3652 (54.5)	3643 (54.4)	0.00
Body mass index:			
30	837 (12.5)	840 (12.5)	0.00
≥30	5782 (86.4)	5790 (86.5)	0.00
Unknown	77 (1.1)	66 (1.0)	0.02
Smoking status:			
Ever	5384 (80.4)	5434 (81.2)	0.02
Never	1302 (19.4)	1251 (18.7)	0.02
Unknown	10 (0.1)	11 (0.2)	0.00
Alcohol related disorders	566 (8.5)	567 (8.5)	0.00
Mean (SD) duration of GLP-1 receptor agonist use, years	1.6 (1.4)	1.6 (1.4)	0.00
Mean (SD) duration of diabetes, years	11.0 (6.1)	11.2 (6.3)	0.03
Haemoglobin A_{1c}:			
≤7.0%	323 (4.8)	281 (4.2)	0.03
7.1-8.0%	983 (14.7)	994 (14.8)	0.00
>8.0%	5374 (80.3)	5409 (80.8)	0.01
Unknown	16 (0.2)	12 (0.2)	0.01
Type of antihyperglycaemic drugs:			
Metformin	6048 (90.3)	6035 (90.1)	0.01
Thiazolidinediones	469 (7.0)	467 (7.0)	0.00
Meglitinides	26 (0.4)	21 (0.3)	0.01
α glucosidase inhibitors	7 (0.1)	4 (0.1)	0.02
Sulfonylureas	3411 (50.9)	3386 (50.6)	0.01
DPP-4 inhibitors	1705 (25.5)	1695 (25.3)	0.00
Insulin	1705 (25.5)	1701 (25.4)	0.00
Peripheral vascular disease	652 (9.7)	689 (10.3)	0.02
Ischaemic stroke	240 (3.6)	252 (3.8)	0.01
Myocardial infarction	438 (6.5)	444 (6.6)	0.00
Coronary artery disease	1088 (16.2)	1131 (16.9)	0.02
Coronary revascularisation	472 (7.0)	485 (7.2)	0.01

Combination therapy: GLP-1 RA and SGLT-2i

Patient selection:

- Cohort 1: GLP-1 RA base therapy with add-on SGLT-2i: 6696 patients
- Cohort 2: SGLT-2i base therapy with add-on GLP-1 RA: 8942 patients

Statistically Significant Results:

- Cohort 1 (GLP-1 RA base therapy): median follow-up 9 months
  - 30% lower risk of MACE
  - 57% lower risk of serious renal events (defined as AKI or progression to CKD)
  - 65% lower risk of cardiovascular mortality
  - 43% lower risk of heart failure
- Cohort 2 (SGLT-2i base therapy): median follow-up 9 months
  - 29% lower risk of MACE
  - No difference in serious renal events

Takeaways

- Adding SGLT-2 to GLP-1 reduced CV mortality and heart failure, which was not seen in the reverse situation, consistent with previous studies such as DAPA HF, EMPEROR reduced and EMPEROR preserved demonstrating cardiovascular benefit from SGLT-2 monotherapy
- Combination therapy confers additional benefit to monotherapy, but perhaps skewed in favor of SGLT-2i
- Made me much more likely to start SGLT-2 inhibitors for inpatients, especially if they have comorbid cardiac disease
- Still working on my pitch to patients about starting a GLP-1 agonist, but I will include in discharge summaries sent to PCP

Case 3

- 23 yo man with fentanyl use disorder admitted with sepsis and deep lower extremity abscess, s/p fluid resuscitation and initiation of broad spectrum antibiotics
- He reports high opioid tolerance and extreme fear of withdrawal while awaiting surgical I&D
- You start short-acting opioids at 5x the dose you ordinarily would for an opioid-naïve patient
- 3 hours later, you receive a bedside stat page
- When you arrive, the patient is hitting his head against the floor and is being actively restrained

Q3: How quickly can methadone be titrated to treat fentanyl use disorder?

ORIGINAL RESEARCH

EARN CREDIT

Piloting a Hospital-Based Rapid Methadone Initiation Protocol for Fentanyl

Patricia Liu, MD, Brian Chan, MD, Eleasa Sokolski, MD, Alisa Patten, MA, and Honora Englander, MD

Rapid initiation of methadone

Design:

- Retrospective chart review of all patients who underwent a new inpatient protocol for methadone initiation in OUD in the first 9 months

Patient selection:

- Inclusion criteria: inpatients with OUD who report routine fentanyl use and who are being followed by addiction medicine consult team
- Exclusion criteria: Age > 65, end organ failure, ventricular arrhythmias, QTc > 500 ms, concurrent use of benzos or EtOH, use of medications known to have drug-drug interactions with methadone

The Rapid Protocol in Question

Day	Traditional Protocol dosing	Maximum total daily dose of methadone	Recommended dosing
1	40	60	30 or 40 mg x1, followed by 10 mg Q3H PRN x2 or 3 doses
2	50	70	50 mg x1, followed by 10 mg Q3H PRN x2
3	60	80	60 mg x1, followed by 10 mg Q3H PRN x2
4-7	60	100	70 mg (or average of previous days TDD) x1, followed by 10 mg Q3H PRN x3

Results

- No adverse events associated with methadone therapy reported
  - Held dose due to concern for sedation or respiratory depression
  - Administration of naloxone
  - Transfer to higher level of care

TABLE 3. Average TDD of Methadone and MME of Other Full Opioid Agonists Received

Day of IMPACT Consult	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Average TDD methadone (mg) ± standard deviation	39.1 ± 14.5	53.0 ± 12.9	69.2 ± 11.2	75.4 ± 14.5	79.5 ± 15.6	87.1 ± 13.6	87.1 ± 13.6	96.6 ± 16.6
Number of patients who received methadone	11	25	25	23	21	17	16	16
Number (%) of patients who received other full opioid agonists	11 (100%)	21 (84%)	20 (80%)	18 (78%)	17 (80%)	13 (76%)	10 (63%)	11 (68%)
Median MME of other full opioid agonists (interquartile range)	43 (24–105)	92 (45–160)	128 (81–169)	158 (73–233)	120 (48–240)	120 (75–210)	169 (109–198)	120 (51–161)

IMPACT, Improving Addiction Care Team, the inpatient addiction medicine consult service; TDD, total daily dose; and MME, morphine milligram equivalents.

Takeaways

- All hospitalists should become familiar with inpatient management of opioid withdrawal, especially in the fentanyl era
- Careful patient selection is key: exclusion criteria were specifically selected to help minimize risk of adverse events
- Ideally initiation of methadone will lead to follow-up in outpatient treatment, but even if patients only participate during their admission for other medical conditions, I call that a win

Case 4

- Let's bring back the woman from case 2:
- "64 yo woman with CAD on aspirin, HFrEF on propranolol, hydralazine and furosemide, T2DM on metformin and liraglutide, OSA on CPAP has been admitted to your service for 2 days with fluid volume overload"
- Now let's also give her atrial fibrillation (CHA2DS2VASc 5) on apixaban

Q4: Does my patient with AF and stable CAD need dual therapy?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease

M.S. Cho, D.-Y. Kang, J.-M. Ahn, S.-C. Yun, Y.-S. Oh, C.H. Lee, E.-K. Choi, J.H. Lee, C.H. Kwon, G.-M. Park, H.O. Choi, K.-H. Park, K.-M. Park, J. Hwang, K.-D. Yoo, Y.-R. Cho, J.H. Kim, K.W. Hwang, E.-S. Jin, O. Kwon, K.-H. Kim, S.-J. Park, D.-W. Park, and G.-B. Nam, for the EPIC-CAD Investigators*

AC monotherapy vs dual therapy in AF with stable CAD

- Design
  - Multi-center, open-label randomized trial
  - 18 clinical sites in South Korea
  - Follow-up at 6 and 12 months, with data validated against National Health Insurance database
- Patient selection
  - Inclusion criteria:
    - Dx of AF with CHA2DS2VASc score >= 2
    - Stable CAD
  - Exclusion criteria
    - Contraindication to antithrombotic drugs
    - Intracranial hemorrhage
    - Prosthetic heart valve
    - Moderate-severe mitral stenosis
    - Severe liver or kidney dysfunction

Results

- Primary outcome was a composite of the following:
  - Death from any cause
  - MI
  - Stroke
  - Unplanned urgent revascularization
  - Bleeding
- Secondary outcomes:
  - Individual outcomes from the composite above
  - Stent thrombosis
  - Composite of major ischemic events (MI, stroke, urgent revasc)

Results (cont.)

- At 12 months:
  - Primary outcome event in 6.8% of the monotherapy vs 16.2% of the dual-therapy group
  - Within secondary outcomes, major ischemic events were similar in both groups, with significant reduction in bleeding events in the monotherapy group (4.7%) vs dual therapy (14.2%)

Takeaways

- In addition to AFIRE (rivaroxaban monotherapy vs dual therapy), we have more evidence to support anticoagulation monotherapy in patients with AF and stable CAD
- Similar protection against major ischemic events, with decreased bleeding on monotherapy with edoxaban

Bibliography

- Liu X, Jiao X, Gong X, et al. Prevalence, Risk Factor and Clinical Characteristics of Venous Thrombus Embolism in Patients with Acute Exacerbation of COPD: A Prospective Multicenter Study. International journal of chronic obstructive pulmonary disease. 2023;18:907-917. doi:10.2147/COPD.S410954
- Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study. BMJ (Online). 2024;385:q1237-. doi:10.1136/bmj.q1237
- Liu P, Chan B, Sokolski E, Patten A, Englander H. Piloting a Hospital-Based Rapid Methadone Initiation Protocol for Fentanyl. Journal of addiction medicine. 2024;18(4):458-462. doi:10.1097/ADM.0000000000001324
- Cho MS, Kang DY, Ahn JM, et al. Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease. The New England journal of medicine. Published online 2024. doi:10.1056/NEJMoa2407362