THERAPEUTICS POTPOURRI

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Jan 21-23, 2025
Big Sky, MT

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OBJECTIVES

- Discuss pharmacotherapeutic principles from case-based presentation.
- Review clinically relevant therapeutic information from the medical literature and updated clinical guidelines.
- Summarize up-to-date therapeutic concepts in the management of common primary care diseases.

2

CASE – MS

- 29 y/o WF admitted on **9/6** with fever, shaking chills, rash , back pain, blurred vision, severe abd pain
- PMH – epilepsy; suicide attempt 2y; med assistant at childrens' home
  - TMP/SMX; Ditropan; Mysoline; Pb; Valium; Ovral
- BP 130/80; RR 18; HR 95; T 38.6; wt 45 kg
  - Bilateral adnexal tenderness
  - Neg w/u, probably hysterical personality
  - Consider PID – ampicillin and gentamicin
- Continued to complain and demanded meperidine frequently

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CASE – MS

- Observed to regulate IV & taking own meds
- 9/18 team started reducing meperidine despite patient demands
  - Requests transfer to another hosp on 9/19
- 9/19 at 0900 unresponsive
  - BP 102/64; HR 114; RR 10 & shallow
  - PG obtained and D50W administered
  - Transfer to ICU

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CASE - MS - HOSP COURSE

- Tylenol tabs found in bed
  - Acetaminophen level ordered - **not stat**
- PG < 10, started D10W
- ABGs on RA
  - pO2 105; pCO2 25; **pH 7.21; HCO3 10**
  - NaHCO3 administered

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CASE - MS - HOSP COURSE

- History from boyfriend
  - Brought in bottle of Tylenol 100 tabs evening of 9/18 per pts request
  - Stated she was not getting enough pain meds
  - She told him she could take up to 2000 tabs before being harmful
  - He believed her because of her job as a MA
  - She took about 50 tabs at about 1900 on 9/18

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CASE - MS - HOSP COURSE

- Tab count produced 37 tabs left with unknown number in bed
- Dose about 16 g (about 355 mg/kg)
- Acetaminophen level of 61 mcg/mL about 14 h post ingestion
- NAC po started about 1800 on 9/19

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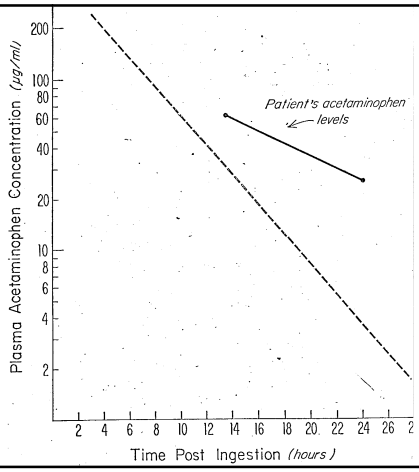

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	9/11	9/19	9/20 0830	9/21	9/23
Wt	46.4	45.2		54.7	
Cr	0.8	1.2	0.9	3.4	5.8
Bili	0.5	**1.7**	**3.7**	4.6	5.6
LDH	205	**595**	**11,200**		3407
AST	30	**371**	**9760**		18
ALT			**2340**	5800	4680
Lactate	13		**18.9**	11.9	26.1
PT	10.8		**49**	32	25.3
PTT	31.8		**55.1**	65.5	
PCO2			**17**	29	49
HCO3			**7**	16	19
pH			**7.22**	7.37	7.19

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CASE - MS - HOSP COURSE

- 9/20 at 1100 BP 80/40; HR 120
  - Started dopamine
  - Abnl coags, ABGs, renal function, LFTs,
  - Decreased mental function – lactulose
- 9/21
  - Pulmonary edema – intubated
- 9/22
  - Anasarca, hemodialysis,
  - Failed to assist vent, tachy arr
- 9/23
  - Hypotension despite fluid, levophed & dopamine
  - 0635 asystole

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PATH REPORT

- Widespread hepatic necrosis
  - Severe hepatocellular fatty metamorphosis
  - Parenchymal widespread hemorrhage in centrilobular areas
  - Massive necrosis of hepatocellular elements
- CNS – severe cerebral edema
- Pulm – bilateral congestion & severe edema

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CASE

- 12/15/22 64 y/o male
  - **Jaundice since 11/30/22**
  - 15 mon prior Melanoma on face with > 20 lymph nodes on PET scan – treated with chemo
  - 12 mon prior PET scan unchanged
    - **Immune check point inhibitor therapy started Pembrolizumab (Keytruda)**
  - c/o difficulty with swallowing and dry mouth for 3 months – AE? – also has multiple system atrophy
  - PET scan July clear
    - **d/c Keytruda 5 mon prior**
  - Increased LFTs

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- 12/17 onset encephalopathy
- Dx – **Autoimmune drug-induced hepatitis**
  - 12/15 Bx 50% necrosis, **12/19 bx 90% necrosis**
  - **INR 6, TBili 26**
  - High dose steroids, plasma exchange X 2, NAC
- **Died 12/25/22**

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DRUG-INDUCE LIVER INJURY (DILI) CATEGORIES

- Intrinsic or Idiosyncratic
- **Intrinsic (direct) hepatotoxins**
  - **Predictable and reproducible**
  - **Dose-dependent** hepatocellular necrosis
  - Onset within hours-days
  - Drug or metabolites cause hepatotoxicity
    - Induce mitochondrial dysfunction & affect bile acid hemeostatis
  - **Acetaminophen**, Amanita phalloides mushroom (amatoxin), FeSO4, EtOH, phosphorus

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CATEGORIES OF DILI

- **Idiosyncratic hepatotoxicity**
  - **Unpredictable –** Not related to dose for occurrence or severity
  - Risk factors
    - Smoking, EtOH, drug-related factors, **host factors** (i.e., genetic, age, gender, immune,)
  - Mediated by **adaptive immune activation**
    - **Response of drug or metabolite (drug-altered peptide, hapten) that binds to hepatocyte proteins triggering immune response with tissue damage**
  - **Latency wks to ≥ 1 year**
    - **May occur after the drug has been stopped**

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CATEGORIES OF DILI

- Idiosyncratic hepatotoxicity (continued)
  - **Hypersensitivity – immune-mediated**
    - Positive with rechallenge of drug
    - Phenytoin, **amoxicillin-clavulanate**, erythromycin, sulfonamides, diclofenac, carbamazepine, sulindac, **immune checkpoint inhibitors**
  - **Metabolic injury – from reactive metabolites**
    - Genetic polymorphism leading to formation of a toxic metabolite
    - INH, ketoconazole, disulfiram, valproate, amiodarone

Dis Mon 08;54:457-85 Clin Liver Dis 09;13:277-94 Clin Liver Dis 20;24:75–87
Int J Mol Sci 21;22:2954 ACG Guideline. Am J Gastroenterol 21;116:878-98
Ther Adv Gastroenterol 23;16:1-13 J Clin Transl Hepatol 23;11:1239-45
Sem Liver Dis 24;44:239-57 Toxics 24:12:421

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CASE

- 79 y/o male on 10/22
  - Bilat maxillary sinus tenderness > 7 d
  - Influenza 2 wks ago
- PMH: CAD, gout, HTN, LDL, OA, Sz
  - Few crackles at L base
- CBC WNL, CXR neg
- Acute sinusitis post influenza
  - Secondary bacterial RTI after influenza
  - **Amoxicillin/Clavulanate** 875 mg 2xd X 10d
  - RTC 1 wk

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1 Week Later 10/30

- Neg for postnasal drainage, lungs clear
- Abd slightly tender to palpation, without masses
- CBC, CMP, UA, Lipase, abd xray, CT abd/pelvis
- Finish Augmentin
- Omeprazole 20 mg/d

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	5/28	**2/20**	**10/30**	**11/12**	11/20
Cr	1.2	1.2	1.3	1	2.2
Alb	4.1	4.1	3.7	3.9	4.1
Alk Phos	70	**71**	**331**	**165**	**122**
TBili	0.9	**0.8**	**1.7**	**0.9**	**1.1**
AST	19	**19**	**71**	**19**	**21**
ALT	15	**14**	**89**	**16**	**26**

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Amox/clav

- Most common cause of non-APAP DILI
- **8.6-43/100,000 Rx's – commonly used**
- **Immunoallergic & Idiosyncratic**
  - May see fever, rash, arthralgias, and eosinophilia but usually not prominent
  - Considered to be primarily due to **clavulanic acid** from rechallenge cases

J Antimicrob Chemother 11;66:1431-46
Gastroenterol Clin N Am 46 (2017) 273-296
Clin Liver Dis 21 (2017) 35-54
https://livertox.nlm.nih.gov//AmoxicillinClavulanate.htm
Prim Care Clin Office Pract 23;50:363-76 Sem Liver Dis 24;44:239-57

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Amox/clav DILI

- **Usually cholestatic** – increased AP, Bili, GGT
- Some cases hepatocellular or mixed pattern
- **Often missed** since s/s often mild with delayed onset
  - Fatigue, low grade fever, nausea & abdominal pain, pruritus, jaundice
  - Onset few d to 8 wks (avg ~3 wks)
- **Rechallenge with amox/clav should be avoided**
  - **Amox is usually safe** except if due to PCN allergy

Gastroenterol Clin N Am 17;46:273-296 Clin Liver Dis 17;21:35-54
https://livertox.nlm.nih.gov//AmoxicillinClavulanate.htm Clin Liver Dis 20;24:37-48
Sem Liver Dis 24;44:239-57

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ACUTE LIVER FAILURE (ALF)

- INR > 2, ALT > 10xULN, Tbili > 3xUNL
- **> 50% due to drugs (DILI)**
  - Primary cause in US
- **75% APAP** – most common cause of ALF
  - **<u>> 50% unintentional</u>** – e.g. narcotic/APAP
- Non-APAP drug cases
  - Antibiotics most common
  - < 5/100,000 but many receive antibiotics

Hepatology 06;43:618-31 Cochrane Reviews 2006, Issue 2. NEJM 06;354:731-9
J Antimicrob Chemother 11;66:1431-46 NEJM 13;369:2525-34
Annu Rev Pathol Mech Dis 24;19:453-78

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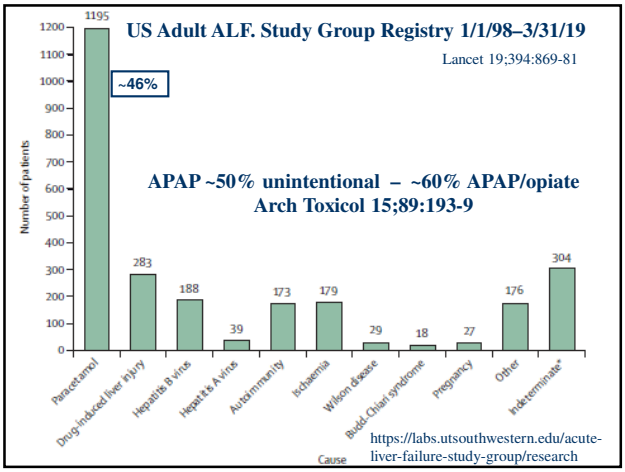

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ACETAMINOPHEN

- N-acetyl-p-aminophenol (APAP)
- One of the most **commonly used drugs**
  - Ingredient in many OTCs and Rx products
  - Safe in recommended doses
- **Liver injury from:**
  - **Acute single dose OD**
  - **Repetitive excess dosing**
    - > 4 g/d of APAP

Toxicol Res 19;8:489-98 Am J Gastroenterol 23;118:1128-53

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APAP LIVER INJURY

- **Classic predictable hepatotoxin (intrinsic)**
- **CYP450** 2E1 metabolism to a **highly reactive metabolite** N-acetyl-p-benzoquinone imine (NAPQI)
  - NAPQI detoxified by glutathione reactions to nontoxic metabolites
- Large doses deplete glutathione
  - NAPQI binds to hepatocytes – hepatotoxicity

Crit Care Clin 21;37:543-61 Biomed & Biotechnol 22 23:265-85
Am J Gastroenterol 23;118:1128-53 Exp Biol Med 23;248:412-24
Annu Rev Pathol Mech Dis 24;19:453-78

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RISK OF TOXICITY

- Single dose >150-200 mg/kg or >7.5-10 g
  - Unreliable due to inaccurate history
  - Lower doses may be toxic in alcohol users or malnourished with low glutathione reserves
- Assess with APAP level > 4 h after ingestion
  - Rumack-Matthew nomogram – **ONLY USEFUL IN ACUTE OD**
  - **Toxic range treat with N-acetylcysteine**
  - Predicts ALT, AST and PT (INR) elevation
    - Does not predict survival or death

NEJM 97;337:1112-7 Hepatol. 2017 Dec; 67(6): 1324-31
Crit Care Clin 21;37:543-61 Am J Gastroenterol 23;118:1128-53

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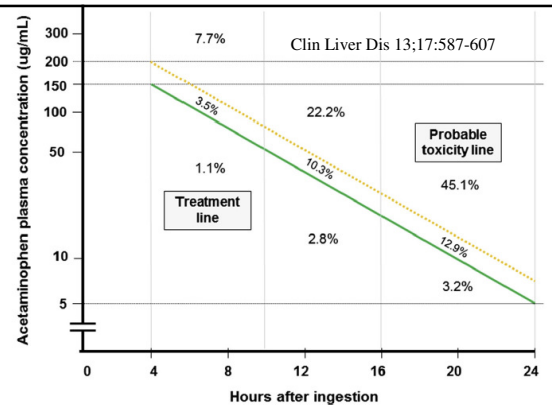

ig. 2. Rumack-Matthew nomogram and outcome of treatment. Percentages are the num-er of cases with AST greater than 1000 IU/L at any time during their course taken from data rom the US nationwide NAC study. (*Adapted from* Rumack BH. Acetaminophen misconcep-

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Supratherapeutic Repeated Ingestions

- **Chronic toxicity**
  - No data on specific threshold – **Nomogram no help**
  - **>4 g/d; eg, 6-10 gm/d over several days**
  - Easy to exceed this dose with multiple APAP containing OTC and Rx (opioid combinations)
- Delay in onset & non-specific liver symptoms
  - May lead to poor outcomes

NEJM 97;337:1112-7 Hepatol. 2017 Dec; 67(6): 1324-31
Crit Care Clin 21;37:543-61 Am J Gastroenterol 23;118:1128-53

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APAP OD POSSIBLE INTERVENTIONS

- Inhibit absorption
  - **Activated charcoal if given < 4 h post ingestion**
- **Detoxify NAPQI or prevent toxic effects**
  - **N-acetylcysteine (NAC)**
  - NAC > survival with fulminant hepatic failure
- **ALF ~28% mortality**
  - **Up to 33% require liver transplant**
  - **Challenge is identifying those who will not survive**

Cochrane Database of Systematic Reviews 2006, Issue 2.
Arch Toxicol 15;89:193-9 Clin Liver Dis 20;24:121-9 CrIt Care Clin 21;37:543-61
Am J Gastroenterol 23;118:1128-53

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NAC

- Oral (Mucomyst) or IV (Acetadote)
  - 72 h oral vs. **21 h IV** – Or longer based on condition and lab values
- "no clear difference [efficacy] between oral and IV NAC administration or different intravenous protocols."
- **Administer as soon as possible for significant acute ingestion – preferably ≤ 8-10 h**
  - Within 10 h – 76/1153 (7%) hepatotoxicity
  - > 10 h – 392/1435 (27%) hepatotoxicity

Cochrane Database of Systematic Reviews 2006, Issue 2. CrIt Care Clin 21;37:543-61
Annu Rev Pathol Mech Dis 24;19:453-78

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CASE

- 36 y/o African American male
  - SOB, DOE, malaise, fatigue, bilateral LE edema
- PMH: HTN
- Meds: Lisinopril 20 mg/d – not taking, Meloxicam – not taking
- Biventricular HF with EF 25-30%
- Acute on CKD
- Start Carvedilol, Lisinopril, consistent with **GDMT** in setting of HFrEF
  - Can use nitrates and hydralazine if necessary

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HF Guideline Directed Medical Therapy (GDMT)

- GDMT with the **highest expected benefit should be prioritized**
  - ↓ symptoms, hospitalizations, & mortality
- **1st-line meds**
  - ARNIs, ACEIs, ARBs, ßBs, MRA, and **SGLT2i (Dapa, Empa, Sota)**
- **< 20% get GDMT "quad therapy"**
- **Improve HFrEF & CKD outcomes regardless of DM**

2024 ACC HFrEF J Am Coll Cardiol 24;83:1444-88
2024 ACC Consensus Hospitalized JACC 8/8/24 Pharmacist's Letter. September 2024

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GDMT

- **Use all 4 key med classes**
- **Initiate early and as rapid** as possible after diagnosis
  - May be able to start all 4 at same time at low doses
- Those **hospitalized initiate before discharge** and titrate to target doses outpatient
- **Reach target or max tolerated** doses ≤ 3 mon

2024 ACC HFrEF J Am Coll Cardiol 24;83:1444-88
2024 ACC Consensus Hospitalized JACC. Aug 08, 2024. Epublished DOI: 10.1016/j.jacc.2024.06.002

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NEWER T2DM THERAPY

- **Positive CV & renal outcome studies with GLP-1RA and SGLT2i**
- **Therapy not ONLY for glucose control anymore**
  - Shift from **glycemic control alone to simultaneous improvement of CV & renal outcomes**
- Guidelines now recommend **adding to metformin a SGLT2i or GLP-1RA for benefit in CVD, kidney disease, and HF**

Ann Intern Med 24;177:658-66 ADA 2024 Guideline

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Na-glucose cotransporter-2 inhibitors (SGLT2i)

- Bexagliflozin (Brenzavvy)
- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)
- Sotagliflozin (Inpefa) – dual SGLT1 & 2 inhibitor
- **COST ~$55 (Bexagliflozin) ~$600/mon**

Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023
Med Lett Drugs Ther 23;65:130-2

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SGLT2i CV EFFECTS

- **Weight loss** of ~2-4.7 kg
- **Reduces pre-load and afterload – HF effects**
- **Osmotic diuresis – HF effects**
- **Reduces angiotensinogen – CV & HF**
- **Reduces total body Na – HF and BP lowering**
- **Decreases SBP ~2-10 mmHg & DBP ~1.3-1**
- **Reduces arterial stiffness – CV**
- **Improves endothelial dysfunction, inflammation**
- **Improves mitochondrial efficiency**
- **CV and Renal benefits**

JACC 18;72:1845-55 Diabetologia 18;61:2134–9 Med Clin N Am 21;105:955-66
ADA Guidelines 2024 AACE 2023
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023
2024 ACC HFrEF J Am Coll Cardiol 24;83:1444-88 Prim Care Clin Office Pract 24;51:171-8

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SGLT2i CARDIAC EFFECTS

- Benefits in HFrEF are attained **regardless** of DM, MRAs and/or ARNIs

Butler J, Zannad F, Filippatos G, Anker SD, Packer M. opinion. ESC on line 9/15/20

- Reduce CV mortality and HF hospitalizations regardless of LVEF

J Am Coll Cardiol 24;84:1089-90

- Lower risk vs. second-line therapy for CVD, CVA, AF, MI, HF

Mayo Clin Proc 23;98:985-96

- Significant reduction in composite CV death or hospitalization for HF

Am J Cardiol 24;218:24-31

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SGLT2i RENAL EFFECTS

- Reversible decrease in eGFR during first 4 wks
- **Nephroprotective**
- **Reduces progressive decline of eGFR** with long-term use in CKD
- **Delay in micro- and macroalbuminuria**
- **Reduces albuminuria**
- **Reduces CV risk in CKD**

Lancet Diabetes Endocrinol 17;5:610-21 Circulation 18;137:119-29
Clin J Am Soc Nephrol 18;13:318-20
JACC 18;72:1845-55
Med Lett Drugs Ther 2020 Nov 16;62(1611):e184-8
Prim Care Clin Office Pract 22;49:315-26

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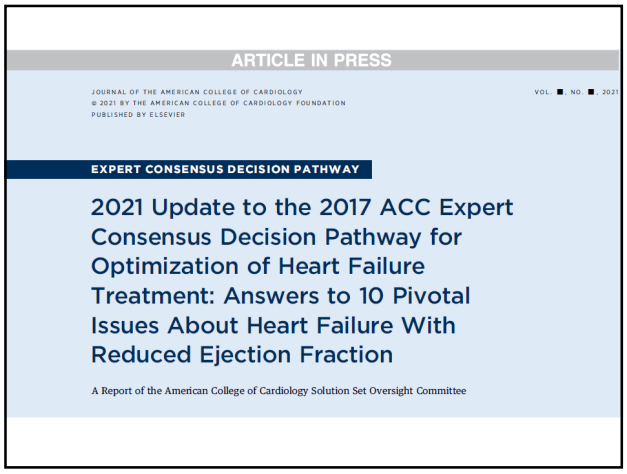

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AHA 2021 Stage C HFrEF Recommendations – Class I

- ARNI or ACEI or ARB
  - ARNI preferred
  - ACEI or ARB considered only if contraindications, intolerance or inaccessibility to ARNI
- Evidence-based ßB
- MRA in NYHA II-IV if no contraindications
- SGLT2i if no contraindications

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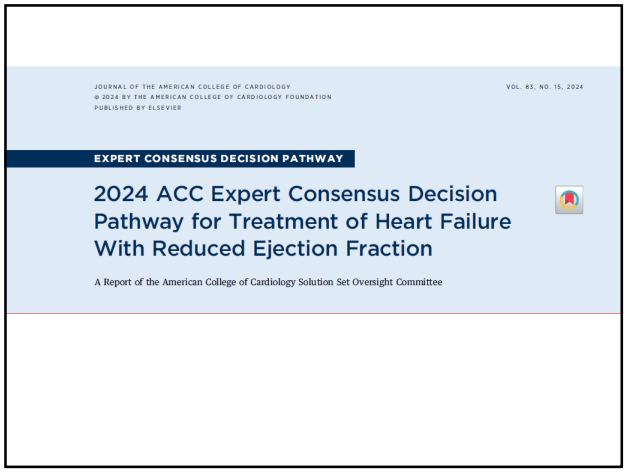

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2024 ACC HFrEF STAGE C TREATMENT

- **All patients** with current or prior HF, irrespective of EF, should be considered for guideline-directed medical therapy (**GDMT**).
- **Class I recommendation**
  - **Initiate ARNI + ßB + MRA + SGLT2i**
  - ARNI contraindications, intolerant or inaccessibility then consider **ACEIs or ARBs**
  - Persistent volume overload add **diuretic**
  - African-American symptomatic on GDMT add **hydralazine/isosorbide dinitrate**

2024 ACC HFrEF J Am Coll Cardiol 24;83:1444-88

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GLP-1 Receptor Agonists (GLP-1RA)

- SC dosing except oral semaglutide
- Dulaglutide (Trulicity)
- Exenatide (Byetta), Exenatide ER (Bydureon BCise)
- Liraglutide (Victoza), (Saxenda for weight loss)
- Semaglutide (Ozempic), Oral (Rybelsus), (Wegovy SC for weight loss)
- Tirzepatide (Mounjaro) **GIP & GLP-1 receptor agonist,** (Zepbound for weight loss)
- **Costly** > $800-1,300/month, weight loss ~$1,300/mon, compounding due to shortage <$

Med Lett Drugs Ther 24;66:e1-3
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2024

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CV & Renal Benefits

- **CV benefit**
  - **Dulaglutide, liraglutide, semaglutide injection**
  - Reduce first occurrence CV death, nonfatal MI or CVA

NEJM 16;375:311-22 NEJM 16;375:1834-44 Lancet 18;392:1519-29
Cleve Clin J Med 22;890:457-64 NEJM 23;389:2221-32
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2024

- **Modify risk factors for CKD progression and DM nephropathy**
  - Promote diuresis and natriuresis
  - **SGLT2 inhibitors are more effective**

NEJM 17;377:839-48 Cleve Clin J Med 22;890:457-64 AACE 2023 ADA 2023
Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights. August 2023
Expert Opin Drug Saf 24;23:797-810 NEJM 24;39:109-21

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Semaglutide Eligibility Across All Current Indications for US Adults

- Semaglutide #1 in 2023 US $13.8B
- Estimated 137M adults eligible
  - > 50% of all adults
  - Weight loss 129M
  - DM 35M
  - Secondary CV prevention 9M
- Potential transformative impact on population health
- >50% state difficult to afford

JAMA Cardiol. Research Letter. Published online November 18, 2024. doi:10.1001/jamacardio.2024.4657

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ADA 2025 T2DM PHARMACOLOGIC THERAPY

- **Shared decision-making**
- **Without** obesity, CV or renal risk
  - **Metformin** or other therapies to reach goal
- **Overweight or obesity**
  - **Preferred should be GLP-1RA or GIP/GLP-1 agonists (i.e., semaglutide or tirzepatide)**
- **ASCVD or high CVD risk, CKD, or HF**
  - **Should include SGLT2i &/or GLP-1 receptor agonist** with demonstrated CVD benefit recommended **irrespective of A1C**

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ADA 2025 T2DM PHARMACOLOGIC THERAPY

- **HFrEF or HFpEF**
  - **SGLT2i recommended for prevention of HF hospitalizations irrespective of A1C**
- **Symptomatic HFpEF and obesity**
  - **GLP-1 RA is recommended with demonstrated reduction of HF related symptoms irrespective of A1C**

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ADA 2025 T2DM PHARMACOLOGIC THERAPY

- **CKD (eGFR 20-60 and/or albuminuria)**
  - **Should use SGLT2i or GLP-1 RA to reduce CKD progression and CV events irrespective of A1C**
- **CKD (eGFR <30)**
  - **GLP-1RA preferred due to lower risk of hypoglycemia and decrease CV events**

Diabetes Care 25;48(Suppl 1):S181-206 |

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ACP NEWER TREATMENTS IN T2DM GUIDELINE

- Recommend adding **SGLT-2i inhibitor or GLP-1RA to metformin** and lifestyle with **inadequate control** (strong recommendation; high-certainty evidence).
  - SGLT-2 inhibitor to reduce risk for all-cause mortality, MACE, progression of CKD, and HF hospitalization
  - GLP-1RA to reduce risk for all-cause mortality, MACE, and stroke

Ann Intern Med 24;177:658-66

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- **FDA-APPROVED INDICATIONS SGLT2i**
- Bexagliflozin (Brenzavvy)
  - Adjunct to diet and exercise to improve **glycemic control** in adults with T2DM
- Canagliflozin (Invokana)
  - Adjunct to diet and exercise to improve **glycemic control** in adults with T2DM
  - **Reduce risk of MACE in adults with T2DM and established CVD**
  - **Reduce risk of ESKD, doubling of SCr, CV death, and hospitalization for HF in adults with T2DM and diabetic nephropathy** with albuminuria > 300 mg/d

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- Dapagliflozin (Farxiga)
  - Adjunct to diet and exercise to improve **glycemic control** in adults with T2DM
  - **Reduce risk of hospitalization for HF in adults with T2DM and either established CVD or multiple CV risk factors**
  - **Reduce risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF**
  - **Reduce risk of sustained eGFR decline, ESKD, CV death, and hospitalization for HF in adults with CKD at risk of progression**

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- Empagliflozin (Jardiance)
  - **Reduce risk of CV death and hospitalization for HF in adults with HF**
  - **Reduce risk of sustained decline in eGFR, ESKD, CV death, and hospitalization in adults with CKD at risk of progression**
  - **Reduce risk of CV death in adults with T2DM and established CVD**
  - Adjunct to diet and exercise to improve **glycemic control** in ≥10 y with T2DM
- Ertugliflozin (Steglatro)
  - Adjunct to diet and exercise to improve **glycemic control** in adults with T2DM

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- Sotagliflozin (Inpefa)
  - **No T2DM glycemic control indication**
  - **Reduce risk of CV death, hospitalization for HF, and urgent HF visit** in adults **with:**
    - **HF**

    OR
    - **T2DM, CKD, and other CV risk factors**

FDA Prescribing Information

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Rx Patterns for SGLT2i in US Health Systems

- US Rx rates for Class 1 recommendations regardless of DM from 2022-23
  - DM 63.4% had class 1 recommendation – **11.9% taking SGLT2i**
  - Without DM 6.2% had class 1 recommendation – **3.1% taking SGLT2i**
- **"SGLT2i Rx … with a Class 1a recommendation is low. Interventions are needed to increase uptake of guideline-recommended SGLT2i use."**

J Am Coll Cardiol 24:84:683-93

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SGLT2i

- Effects on multiple organs and multiple diseases (e.g. DM, renal injury, HF, nonalcoholic fatty liver disease, inflammatory bowel disease, cognitive disorder)
  - Nonalcoholic fatty liver disease (NAFLD): AACE recommends as adjunctive therapy in patients with type 2 DM and NAFLD

JAMA Intern Med 24;184:375-83

- PAD
- May slow aging, prevent disease and improve life expectancy

Progress Cardiovascular Diseases 23;81:2-9

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SGLT2i

- **HTN with co-morbidities, eg, HFrEF and T2DM**

Endocr Pract 24;30:481-9

- Potential **anti-arrhythmic activity**
  - SGLT2i effect on Ca and Na and myocardial energy metabolism

Cardiovascular Diabetology 24;23:252

- **Reduce risk of gout in T2DM**
  - May not be from a decrease in uric acid (uricosuric property) – **may be from metabolic and anti-inflammatory effects**

Diabetes Obes Metab. 2023;25:2697–2703

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SGLT2i

- **SGLT2i vs non-SGLT2i**
  - **Alzheimer's disease 19% reduced risk**
  - **Vascular dementia 31%**
  - **All-cause dementia 21%**
  - **Parkinson's disease 20%**

Medscape Medical News. 9/13/24. Europ Assoc Study of Diabetes 2024 Annual Meeting

- **SGLT2i lower risk of sight-threatening retinopathy** vs. DPP-4i, pioglitazone and sulfonylureas

JAMA Network Open 23;6:e2348431

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- **<u>FDA-APPROVED INDICATIONS</u>** GLP-1RA
- Dulaglutide (Trulicity)
  - Adjunct to diet and exercise to improve **glycemic control** in ≥ 10 y with T2DM
  - **Reduce risk of MACE** (CV death, nonfatal MI, or nonfatal stroke) in adults **<u>with T2DM</u> who have established CVD or multiple CV risk factors**.
- Exenatide
  - Byetta
    - Adjunct to diet and exercise to improve **glycemic control** in adults with T2DM
  - Bydureon BCise (exenatide ER)
    - Adjunct to diet and exercise to improve **glycemic control** in > 10 y with T2DM

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- Liraglutide
  - Victoza
    - Adjunct to diet and exercise to improve **glycemic control** in > 10 y with T2DM
    - **Reduce the risks of MACE in adults <u>with T2DM</u> and established CVD**
  - Saxenda – adjunct to a reduced-calorie diet and increased physical activity for **chronic weight management** in:
    - Adults with initial BMI of ≥ 30 kg/m2 or ≥ 27 kg/m2 in presence of ≥ 1 weight-related comorbid condition (eg, HTN, T2DM, or dyslipidemia)
    - ≥ 12 y with body weight above 60 kg (132 lbs) and initial BMI corresponding to ≥ 30 kg/m2 for adults (obese)

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- Semaglutide
  - Ozempic
    - Adjunct to diet and exercise to **improve glycemic control** in adults with T2DM
    - **Reduce risk of MACE in adults <u>with T2DM</u> and established CVD**
  - Wegovy – combination with a reduced calorie diet and increased physical activity:
    - **Reduce risk of MACE in adults <u>with established CVD and either obesity or overweight</u>** NEJM 23;389:2221-32
    - Reduce excess body weight and maintain **weight reduction** long term:
      - ≥ 12y with obesity
      - Adults overweight in presence of ≥1 weight-related comorbidity
  - Rybelsus
    - Adjunct to diet and exercise to improve **glycemic control** in adults with T2DM

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TIRZEPATIDE INDICATIONS

- Mounjaro
  - Adjunct to improve glycemic control in adults with T2DM
- Zepbound
  - Reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition
  - Treat moderate to severe OSA in adults with obesity – FDA-approved Dec 20, 2024

Lilly Prescribing information. Dec 2024

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GLP-1RA UNDERUSE

- "Despite the recommendations of international guidelines, the **use of GLP-1RAs remains rather low in clinical practice and surprisingly even lower in patients with T2DM and ASCVD**."
- "Bridging the gap between evidence-based CV protection and real-life GLP-1RA underuse in patients with T2DM at high CV risk is crucial from a public health viewpoint."

Expert Opin Drug Saf 24;23:797-810

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GLP-1RA USES

- **GLP-1 receptors** are expressed in CNS associated with food intake and chemical-related reward
  - Hypothalamus and brain stem
  - Mesolimbic dopamine system
  - Ventral tegmental area and nucleus accumbens
- **Current studies in process**
  - **Alcohol use disorder, Cocaine use disorder**
  - **Smoking cessation without weight gain**

Medical News & Perspectives. Could GLP-1RA Like Semaglutide Treat Addiction, Alzheimer Disease, and Other Conditions? JAMA 24;331:1519-21
Ann Intern Med. Online July 30, 2024 Ann Intern Med 24;177:1016-27

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GLP-1RA USES

- Anti-inflammatory properties
  - Decrease cytokines e.g., IL-17, TNF-a, NFkB.3, VEGF
- Depression
- Alzheimer disease
- Parkinson disease
- Asthma, COPD
- PCOS
- Psoriasis
- (MASH) Metabolic dysfunction-associated steatohepatitis
- Neuro-ophthalmic
  - Diabetic retinopathy, glaucoma, & idiopathic intracranial HTN

Explor Drug Sci 23;1:221-38
Medical News & Perspectives. Could GLP-1RA Like Semaglutide Treat Addiction, Alzheimer Disease, and Other Conditions? JAMA 24;331:1519-21
Ann Med 24;56:2357737

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Compounding when Drugs are on FDA's Drug Shortages List 12/18/24

- Outsourcing facilities are restricted from making essentially a copy of FDA-approved drug
- Limitation is not applicable for identical or nearly identical copies of FDA-approved drug that is on the FDA's drug shortages list
- When a drug is on FDA's drug shortages list, an outsourcing facility can use a bulk drug substance, also known as an active pharmaceutical ingredient, to make that drug

https://www.fda.gov/drugs/human-drug-compounding/compounding-when-drugs-are-fdas-drug-shortages-list

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Resolution of Shortages of Tirzepatide Injection Products (Mounjaro and Zepbound)

- Added to shortage list Dec 15, 2022
- FDA removed from list Oct 2, 2024
- FDA revoked and replaced order Dec 19, 2024
- Shortage is resolved – Lilly's supply is meeting or exceeding demand with adequate reserves
- Some may still be currently encountering challenges in obtaining Lilly's product
  - May be explained by dynamics of supply chain

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Resolution of Shortages of Tirzepatide Injection Products (Mounjaro and Zepbound)

- "significant compounding of tirzepatide injection products is occurring, and that some number of patients currently receiving those products can be expected to seek Lilly's approved products at a future point when compounding is curtailed."

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Resolution of Shortages of Tirzepatide Injection Products (Mounjaro and Zepbound)

- "FDA does not intend to take action against compounders for violations … from … tirzepatide injection products' inclusion on the FDA drug shortage list for the following time periods from date of this order"
  - State-licensed pharmacists/physicians compounding – 60 calendar days until Feb 18, 2025
  - Outsourcing facilities – 90 calendar d until Mar 19, 2025

FDA Declaratory Order Dec 19, 2024 https://www.fda.gov/drugs/drug-safety-and-availability/fda-clarifies-policies-compounders-national-glp-1-supply-begins-stabilize

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