CRITICAL REVIEW FORM:
THERAPY ARTICLES

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Citation: Faselis C, et al., Loop Diuretic Prescription and 30-Day Outcomes in Older Patients With Heart Failure. J Am Coll Cardiol. 2020 Aug 11;76(6):669-679.

Study Objective: Determine relationship between loop diuretics and clinical outcomes in pts w/ HFrEF and HFpEF

Study Methodology:

- Retrospective study of the OPTIMIZE-HF (Organization Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure)
  - Web-based registry of 48,612 HF hospitalizations from 259 hospitals from 48 states between 3/1/03-12/31/04
  - The study group included 7,936 patients hospitalized with HF who were not on diuretics prior to hospitalization
  - The cohort was divided into patients discharged on loop diuretics versus not.
  - To account for characteristics influencing discharge on a loop diuretic, the two groups were propensity matched
  - Outcomes of interest included HF and all-cause readmission and all-cause mortality at 30 and 60 days from discharge.

GUIDE	COMMENTS
I. Are the results valid?	
A. Did experimental and control groups begin the study with a similar prognosis	
1. Were patients randomized?	- No, retrospective analysis of a HF database that sought to identify impact of discharge diuretics to patients admitted for HF who were not previously on diuretics. - Conditional probability (0-100%) AKA propensity score is a study design tool: influenced by measured and unmeasured baseline characteristics rather than RCT (50%) - Similar to RCT: Propensity score-matched cohort is outcome blinded - Unlike RCT: NOT balanced using baseline characteristics - **Using a greedy matching algorithm 2191 pts matched receiving a prescription for loop w/ 2191 not receiving prescription**
2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to	- No randomization - Pts would have known whether they are taking loops prior to admission and whether they got a

ensure that a patient would be "randomized" to a particular group?	prescription afterwards - Clinicians not told to prescribe or not prescribe loops
3. Were patients analyzed in the groups to which they were randomized?	Pts weren't randomized to groups but were analyzed in the group they fit into (loop prescription vs not)
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Matched propensity scoring was utilized in order to minimize measurable confounders. Authors identified: 74 baseline characteristics and were able to propensity match 2191 patients (Table 1) who received or did not receive loop diuretic prescription at the time of discharge. Examples included: - Age, gender, African American separated - PMH (HF, HTN, COPD, AF, MI, DM etc) - Admission s/s, admission labs, admission VS - In hospital medical interventions - d/c meds, instructions, length of stay Authors **used a greedy matching algorithm of 2191 pts propensity matched receiving a prescription for loop w/ 2191 not receiving prescription**
5. Were patients aware of group allocation?	N/A
6. Were clinicians aware of group allocation?	N/A. Clinicians used their own clinical judgment in prescribing loops at discharge.
7. Were outcome assessors aware of group allocation?	Yes? There was no mention that data analysis was blinded.
8. Was follow-up complete?	Uncertain. Authors report on database derived 30 and 60 day follow-up but do not report on any missing follow-up data which likely occurred. - 30d readmission - 30d all-cause mortality - 30d combined endpoints
What are the results ?	- Started w/ ~26,376 pts, of whom 25,345 were d/c'd alive (~4% mortality) (Figure 1) Excluded: - 15,479 who were on loop diuretics prior. - 1,083 hemodialysis patients - 847 d/c'd on thiazide) Included: - 5568/7936 (70%) prescribed loop diuretics at dc - 2,368/7936 (30%) not prescribed LD's at dc Propensity Matched: - (4,382) 2,191 in each group were included and had no statistically significant difference in 74 matched

	baseline characteristics - Among the 4,382 matched patients, those receiving and not receiving a prescription for loop diuretics had the same 67% probability of receiving those drugs (mean propensity score +/- SD, 0.67 +/- 0.13 Primary Outcomes Propensity Matched: 30 Days (Table 2) 1. All-cause mortality 144 (6.6%) No loop diuretic at dc vs. 107 (4.9%) loop diuretic at dc HR 0.73 (0.57–0.94) p=0.016 2. Heart failure readmission† 168 (7.7%) no loop at dc vs 135 (6.2%) loop at dc HR 0.79 (0.63–0.99) p= 0.037 • HFrEF: All cause mortality 5.7% vs 6.6% (HR .78; CI .56-1.09) ← not statistically significant • HFpEF: all cause mortality 4.1% vs 5.9% (HR .68; CI .46-.99) ← barely , p.043 - **NOT different associations when EF used as continuous variable** - Readmissions o 6.2% vs 7.7% (HR .79, .63-.99) o HFrEF: 6.4% vs 8.2% (H .76, CI .56-1.04) o HFpEF 6.0% vs 7.2% (HR .81, CI .59-1.12) - All cause mortality and readmission o General: 11% vs 14% (.76, CI .64-.91), No statistical significance at 60d o HFrEF: 11.6% vs 15.1% (.76, CI .6-.95) o HFpEF 9.7% vs 12.3% (.77, .6-.99) - No diff in all-cause mortality or non-HF related readmissions - No dif in HF readmission or all-cause readmission during 60d f/u - Important subgroup result o Association of prescriptions for loops + 30d HF readmission or all cause mortality was stronger in subgroups w/ admission rales and LE edema ▪ Pulm edema .62, CI .5-.77 ▪ No pulm edema 1.08 (.81-1.43) No associations statistically significant during 60d f/u
1. How large was the treatment effect?	Quite small, all CI were very close to 1.
2. How precise was the estimate of the treatment effect? (CI's?)	Pretty precise, CI rather narrow. Large sample size used Usually w/in .3-.4 (e.g. .63-99, .56-1.04, .64-.91)
III **How can I apply the results to patient care?**	

1. Were the study patients similar to my patient?	- Yes, lots of HF pts here, lots of admissions for it. - Ages similar - Only 11% African American - Though we don't have lots not already on diuretics, lot of non-compliance so somewhat similar to them not being on diuretics - Limited f/u so difficult as titration and f/u seem to be large components of best effect for diuretics
2. Were all clinically important outcomes considered?	I think so. Mortality and readmission are both very patient-centered outcomes. No harms assessment of diuretics and no economic analysis included.
3. Are the likely treatment benefits worth the potential harm and costs?	- Overall, yes (harms e.g. electrolyte abnormalities, hypotension, dehydration) - Issues with f/u in our population so can have some concerns with the risks - We would think everyone is on loops, but lots of pts they researched weren't, some previously hadn't been given prescriptions as some ppl think they're only needed for continued sx improvement - HF = leading cause of 30d hospital readmission for older adults - Role of mineralocorticoid receptor antagonist which has Class A ACC/AHA Reccs in 2022 Guideline is new evidence since publication and not addressed here.

Limitations:

- Confounders (though they measured on 74 characteristics) there may be others.
- While the authors did propensity match for admission creatinine, discharge creatinine was not adjusted for which could be a reason for withholding diuretics in that group
- Sensitivity analyses suggest study may be sensitive to unmeasured confounder regarding the 30d associations
    - Possibly thought to be something unmeasured regarding dyspnea on exertion that wasn't adjusted for with the propensity scoring? (table 1)
    - Possible it doesn't exist though, and it'd have to match the association and be completely unlike the other 74 characteristics
- Didn't have access to start/restart/d/c after hospital discharge doses
    - Important b/c frequent adjustments and may be more about the route, frequency, dose titration rather than just their use to get the effects
    - Just fee-for-service Medicare, limits generalizability

Clinical Bottom Line:

- Loop prescription at discharge -> significant (but pretty small) reduction in 30d HF readmission in older pts hospitalized for HF who aren't taking diuretic prior
- Loops -> appear to lower 30d all cause mortality
- Found in both pEF and rEF
- NO statistical significance of any sort noted at 60d and is unclear why.
    - Conclusion that there may be some additional benefits rather than just sx control
- From small RCTs with short f/u (4 papers), loops improve s/s of fluid retention therefore may explain some of why the subgroup of edema and congestion had lower 30d readmission for HF because they're having less LE edema or SOB
- Not exactly sure why the 30d mortality is lower, maybe because better sx and therefore less readmission (higher risk of death in pts w/ continued congestion and hospitalization after d/c)
- Findings underestimating true associations ?

- Pt in loop diuretic group prior to admission had higher burden of congestion before admission (prior to propensity scoring, dyspnea on exertion 57% w/ NO prescription, 63% w/ prescription, afterwards 58%, 57% (table 1)) so if continued confounding maybe there still was a difference there
    - Residual confounding and unmeasured confonouding?
- IP use of diuretics in all (likely attenuated between-group differences in congestive sx and signs prior to dc), post-d/c resumption of loops in no-diuretic group and pos residual/unmeasured confounder of higher disease/sx burden of loop group -> actual association at 30d may be greater than the study suggests

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