GDMT use in LVAD patients
Not A Be All, End All

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Introduction

- Durable LVAD is a definitive therapy for Stage D HF
- LVAD is preload dependent and afterload sensitive
- Maintaining a balanced afterload is important with LVAD flow
- Afterload balance can be made with specific combination therapy such as GDMT combo vs. other antihypertensive/s

LVAD medical therapy

- Other than the need for anticoagulation the evidence behind medical therapy is limited post dLVAD

- Consensus has shifted between use of antihypertensives vs. the use of GDMT

- What are GDMT?

  - ARB/ACEi/ARNi
  - Beta blockers
  - SGLT-2 inhibitors (e.g. Jardiance)
  - Mineralocorticoid receptor antagonists (e.g. Eplerenone)

LVAD medical therapy-Other

- Other modes of medical therapy that can be used also inlcude

  - Digoxin
  - Amiodarone
  - Calcium channel blockers e.g. Amlodipine
  - Hydralazine
  - ACEi/ARB
  - Phosphodiesterase inhibitors e.g. Sildenafil

Arguments against GDMT

- Main side effect of GDMT is hypotension leading to readmissions
- AHFT referrals (VAD/Tx) due to inability to **tolerate GDMT**
- Hence GDMT may still not be tolerated following VAD implant leading to hospital admissions/renal impairment etc (Rawlley et al, 2023)
- Tolerance to GDMT may be a marker for survival as reported in some observational studies (McCullagh et al 2019, Rawlley et al 2023)
- No RCTs to evaluate

Study 1

- Propensity match observational study
- 651 with GDMT and 651 without
- GDMT gp had lower mortality
- GDMT gp higher risk of hypotension and renal injury
- GDMT gp higher risk of decompensation
- Pros → high volume study
- Cons → non RCT, Selection bias as patients who can not tolerate (rather than by choice) GDMT hence are not on it

on Guideline Directed Medical Therapy: A Propensity Score Matched Analysis

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Abstract

Introduction: We investigate the benefit of Guideline Directed Medical Therapy [GDMT] in patients with Left Ventricular Assist Device (LVAD) using an insurance claims database.

Methods: We queried Trinetx US collaborative network for patients with LVAD and created two groups; those who received ≥2 prescriptions of any GDMT medication and who did not receive any GDMT after implantation. These were matched by Propensity Score Matching (PSM) for age, race, sex, BMI, LVEF, SBP, DBP, ischemic heart disease, hypertension, disorder of pulmonary circulation, chronic kidney disease (CKD) and acute kidney injury (AKI). All diagnosis were identified using ICD codes. Patient demographics, LVEF, BMI, SBP and DBP were recorded as reported by TriNetX. We looked at primary and secondary outcome measures starting 90 days until 10 years post implantation, primary being all cause mortality and secondary being risk of decompensated heart failure, hypotension, AKI, odds of receiving heart transplant and LVAD explant.

Results: We had 4514 patients with LVAD on GDMT and 687 without GDMT. After PSM, we had 651 patients in each group. Both were matched by PSM with Standardized mean difference (SMD) < 0.1 for all variables. Those with LVAD on GDMT had lower risk of all-cause mortality [233 (37.28%)] compared to those not on GDMT [157 (56.29%)] (hazard ratio [HR] 0.30, 95% confidence interval [CI] 0.24-0.37, P < 0.0001) [Figure 1] but at a higher risk of decompensation (RR 2.74, 95% CI 2.19-3.42), hypotension (RR 3.58, 95% CI 2.73 - 4.69) and AKI (RR 2.64, 95% CI 2.23-3.18). Patients receiving heart transplant and LVAD explant had higher odds of being on GDMT [Odds Ratio [OR], 95% CI: 2.86, 1.87 - 4.37; 4.29, 2.13 - 8.63, respectively).

Conclusions: LVAD patients on GDMT have lower all-cause mortality, higher odds of receiving heart transplant and LVAD explant starting 90 days post implant. However, for reasons not clear to us, they are also at higher risk of decompensation, hypotension and AKI.

Study 2

- Large volume INTERMACS registry study
- 12,144 VAD patients 85.8% received GDMT
- Survival and QoL benefit with GDMT
- Pros: large volume study, long term F/U
- Cons: Overwhelming majority got GDMT, the ones that didn't probably couldn't tolerate and were frailer (hence mortality rate higher)

Neurohormonal Blockade and Clinical Outcomes in Patients With Heart Failure Supported by Left Ventricular Assist Device

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IMPORTANCE Left ventricular assist devices (LVADs) improve outcomes in patients with advanced heart failure, but little is known about the role of neurohormonal blockade (NHB) in treating these patients.

OBJECTIVE To analyze the association between NHB blockade and outcomes in patients with LVADs.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort analysis of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) included patients from more than 170 centers across the United States and Canada with continuous flow LVADs from 2008 to 2016 who were alive with the device in place at 6 months after implant. The data were analyzed between February and November 2019.

EXPOSURES Patients were stratified based on exposure to NHB and represented all permutations of the following drug classes: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and mineralocorticoid antagonists.

MAIN OUTCOMES AND MEASURES The outcomes of interest were survival at 4 years and quality of life at 2 years based on Kansas City Cardiomyopathy Questionnaire scores and a 6-minute walk test.

RESULTS A total of 12 144 patients in INTERMACS met inclusion criteria, of whom 2526 (20.8%) were women, 8088 (66.6%) were white, 3024 (24.9%) were African American, and 753 (6.2%) were Hispanic; the mean (SD) age was 56.8 (12.9) years. Of these, 10 419 (85.8%) were receiving NHB. Those receiving any NHB medication at 6 months had a better survival rate at 4 years compared with patients not receiving NHB (56.0%; 95% CI, 54.5%-57.5% vs 43.9%; 95% CI, 40.5%-47.7%). After sensitivity analyses with an adjusted model, this trend persisted with patients receiving triple therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, and mineralocorticoid antagonist having the lowest hazard of death compared with patients in the other groups (hazard ratio, 0.34; 95% CI, 0.28-0.41). Compared with patients not receiving NHB, use of NHB was associated with a higher Kansas City Cardiomyopathy Questionnaire score (66.6; bootstrapped 95% CI, 65.8-67.3 vs 63.0; bootstrapped 95% CI, 60.1-65.8; $P = .02$) and a 6-minute walk test (1103 ft; bootstrapped 95% CI, 1084-1123 ft vs 987 ft; bootstrapped 95% CI, 913-1060 ft; $P < .001$).

CONCLUSIONS AND RELEVANCE Among patients with LVADs who tolerated NHB therapy, continued treatment was associated with improved survival and quality of life. The optimal heart failure regimen for patients after LVAD implant may be the initiation and continuation

Study 3

- Intermediate volume observational study
- 144 VAD patients received NHB
- Reduction in HF recurrence in LVADs
- Pros: Well run study with follow up
- Cons: Selection bias, non RCT, no control arm

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Neurohormonal Blockade During Left Ventricular Assist Device Support

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Neurohormonal blockade (NHB) is the mainstay of therapy for patients with systolic heart failure (HF). However, the efficacy in patients with left ventricular assist devices (LVADs) remains unknown. Of all, 114 LVAD patients (57 [48, 65] years old and 78% male) were enrolled and followed during the early period (6 months after index discharge), and 98 were followed during the late period (6–12 months following index discharge). Of them, 46% were on beta-blocker (BB), 49% on angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin II receptor blocker (ARB), and 51% on aldosterone antagonist at baseline. Prevalence of BB and ACEi/ARB use increased during the study period. During the early period, similar event rates were found irrespective of the NHB uses. During the late period, BB was associated with reduced HF readmission, and ACEi/ARB was associated with reduced HF readmission and gastrointestinal bleeding ($p < 0.05$ for all). In conclusion, BB and ACEi/ARB use during the late period was associated with a reduction in HF recurrence in LVAD patients. Further prospective randomized control trials are warranted to clarify the utility of NHB therapy in LVAD patients. *ASAIO Journal* 2020; 66:881–885.

Key Words: beta-blocker, angiotensin-converting enzyme inhibitor, heart failure, hemodynamics

(ACEi), angiotensin II receptor blocker (ARB),[5,6] and aldosterone antagonist (AA).[7,8] However, for patients with end-stage HFrEF, the benefits of NHB often cannot overcome progression to heart replacement therapies including left ventricular assist devices (LVADs) and heart transplantation.

Since inception, there have been substantial improvements in LVAD technology. In the MOMENTUM 3 trial, 2-year survival was nearly equivalent to heart transplantation.[9] Despite this, our team recently demonstrated that approximately 50% of clinically stable LVAD outpatients still had abnormal hemodynamics,[10] which were associated with increased adverse events, *i.e.*, HF and hemocompatibility-related adverse events (HRAEs) including LVAD-related bleeding or thromboembolic events.[11]

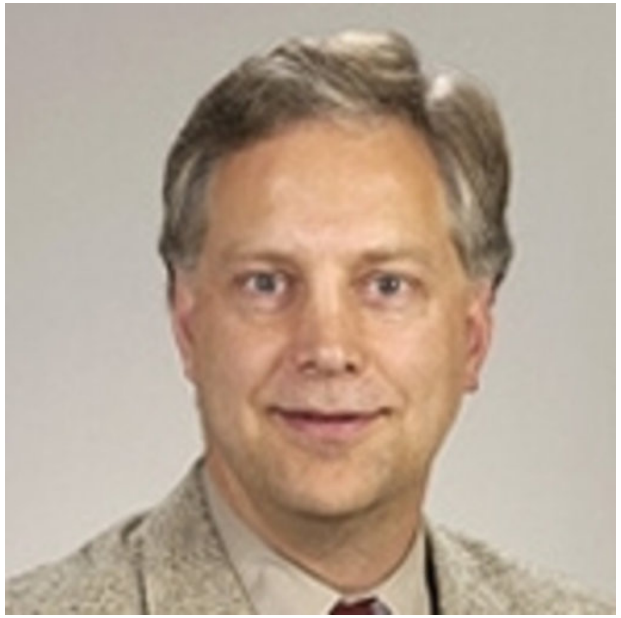
In the current LVAD guidelines, NHB during LVAD support has a Class I recommendation with the level of evidence C (no data are available to support benefit).[12] Given the strong evidence of NHB in patients with HFrEF, our hypothesis is that NHB might have the potential to improve hemodynamics and other neurohormonal abnormalities, reducing adverse events during LVAD support. The aim of this study was to assess the association between the NHB therapy and adverse event during LVAD support.

Conclusions

- GDMT is corner stone of medical therapy for heart failure
- GDMT is often not well tolerated prompting referral for VAD/Tx
- GDMT is not tolerated in all VAD patients
- The evidence supporting its use for LVADs is based on retrospective observational studies
- Selection bias is a factor in these studies
- RCT is needed for more objective analysis

I agree with Dr. LEVY

I AGREE WITH DR. LEVY!!



But…

- GDMT is established in conventional HFrEF
- However, LVADs are by convention, non-conventional HF

- LVADs support a BIONIC heart
- The LV is supported mechanically
- The RV is critical for longer term prognosis – quality of life / survival

Also ....

- Like the LVAD, the RV is PRELOAD dependent and afterload sensitive

- % of LVADs with RV dysfunction
- Timing of initiation is a factor also!
  - Early post-implant, RV dysfunction may limit BB use
  - Early post-implant, renal dysfunction may limit ARNi
  - RV dysfunction may challenge SGLT2i that promote an osmotic diuresis which could exacerbate preload sensitivity

Long-term

- GDMT may be beneficial but ultimately, unlike traditional HF, the prognosis in an LVAD patient may in fact be the health of the pump itself

- Device complications – DLI, strokes, GI bleeding and ultimately progressive RVF

You may think

Wait Maz Knows a lot about GDMT and heart failure management …

Acknowledging my secret weapon for this talk

Dr. Sunu Thomas