TREATMENT OF ADVANCED HEART FAILURE

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November 1, 2009

TOPICS FOR DISCUSSION

- ACE inhibitors & Beta-blockers
- Diuretics
- Cardiac resynchronization
- Cardiac transplantation

ACE INHIBITORS

- Standard therapy for heart failure
- Best randomized trial data for captopril, lisinopril, and enalapril
  - All are now generic and cheap!
- Start low dose and titrate upwards to goal
  - Enalapril: 2.5 mg qd-bid to 10-20 mg bid
  - Lisinopril: 2.5 mg qd to 20-40 mg qd
- ARB can be used if ACEi intolerant

BETA BLOCKERS

- Standard therapy for heart failure
- Best randomized trial data for metoprolol succinate (Toprol XL) and carvedilol (Coreg)
  - Both are now generic
  - Start low dose and titrate upwards to goal
  - Toprol XL: 25 mg qd to 200 mg qd
  - Carvedilol: 3.125 mg bid to 25 mg bid
- COMET trial suggested better outcomes with carvedilol than with metoprolol (although metoprolol tartrate was used)

ACE INHIBITORS AND BETA-BLOCKERS

- ACE inhibitors are commonly instituted first
  - Beneficial effects of BB were found after use of ACE inhibitors was standard-care
  - BB contraindicated if patients are significantly volume overloaded
- Is this titration scheme necessary?
ACE INHIBITORS AND BETA-BLOCKERS

Sliwa et al. (2004) evaluated initiation of therapy with carvedilol either before (n=38) or after (n=40) perindopril therapy in newly diagnosed NYHA II-III HF patients.

Alternative agent was added at 6 months (target doses: carvedilol 25 mg bid, perindopril 8 mg qd).

Endpoint: LVEF and functional class at 1 year.

Carvedilol first group:
- Better improvement in NYHA class
- Better improvement in LVEF
- Lower dose of furosemide
- Higher dose of carvedilol (43 mg vs. 33 mg)

ACE INHIBITORS AND BETA-BLOCKERS

CIBIS III study randomized 1010 patients with class II-III systolic HF to monotherapy with bisoprolol (target dose 10 mg qd) or enalapril (target dose 10 mg bid) for 6 months, followed by their combination for 6-24 months.

Primary end-point: mortality or hospitalization.

Trend towards better survival in bisoprolol first group
Trend towards more HF hospitalization in bisoprolol first group
Safe and efficacious to initiate CHF treatment with beta-blockers

ACE INHIBITORS AND BETA-BLOCKERS

Not necessary that ACE inhibitors be used before beta-blockers
Titration of both drugs can be accomplished at the same time
Volume status needs to be managed before beta-blockers are aggressively titrated

IS THE DOSE IMPORTANT?

ATLAS study randomized 3164 NYHA II-IV systolic HF patients to low dose lisinopril (2.5 to 5.0 mg qd) or high dose (32.5 to 35 mg qd)

LVEF < 30%
No BB use (trial published in 1999)
**ACE INHIBITORS**

**IS THE DOSE IMPORTANT?**

- High-dose group had a nonsignificant 8% lower risk of death ($p = 0.13$)
- Significant 12% lower risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF in high dose group

Packer et al. Circ 1999;100:2312-2318

**BETA BLOCKERS**

**IS THE DOSE IMPORTANT?**

- McAlister et al. (2009) performed a meta-analysis on 23 BB trials in systolic HF to determine if the survival benefits were associated with BB dose or the magnitude of heart rate reduction
- Medications: metoprolol (5), carvedilol (9), bisoprolol (3), bucindolol (3), atenolol (1), and nebivolol (2)


**MY OPINION**

- If limited by BP, it is better to get a patient on small doses of both classes of medications, as opposed to a moderate dose of one
- Achieving maximal dose of BB is likely more important than achieving maximal dose of ACE inhibitor
- If tolerated, discharge patients with both medications, even if low dose
**DIURETICS**

- Aldosterone antagonist (spironolactone)
- Loop diuretics

**SPIRONOLACTONE**

- RALES randomized 1663 systolic heart failure patients (LVEF < 35%; NYHA class III/IV) to spironolactone or placebo
- Serum Cr < 2.5, K < 5.0
- Initial dose 25 mg qd, increased to 50 mg qd if no benefit, no side effects
- 94% on ACEi, 10% on BB

**SPIRONOLACTONE IN THE “REAL WORLD”**

- Retrospective studies have identified inappropriate use of spironolactone in patients with renal insufficiency as well as less than ideal follow-up
- Bozkurt et al. in a retrospective review of 104 pts reported 10% rate of serious hyperkalemia (K+ > 6)

**LOOP DIURETICS**

- Loop diuretics (IV) are a mainstay of therapy for AHFS – 75-80% in ADHERE received IV diuretics
- Reduce left ventricular filling pressures
- Reduce central venous pressure
- 40 mg furosemide = 20 mg torsemide = 1 mg bumetanide

**PROBLEMS WITH DIURETICS**

- Adverse neurohormonal activation
  - Increased plasma renin, aldosterone, norepinephrine
- In SOLVD trial, use of long-term diuretics was associated with a 1.33 fold increase in risk of arrhythmic death after correcting for other mortality risk factors
- Postdiuretic sodium rebound as a result of poor dietary compliance
  - Given short half-life of diuretics, there is a significant amount of time where the tubular concentration of the diuretic is subtherapeutic.

**CARDIO-RENAL SYNDROME**

Low cardiac output is not necessary and many patients have preserved LVEF (diastolic HF) and/or elevated MAP

Registry of 1098 patients admitted with CHF found worsening renal function during hospitalization (Cr rise > 0.3 mg/dl in 27%), which was statistically associated with hospital deaths and LOS > 10 days
Animal studies have demonstrated that temporary elevation of CVP can lead to worsened renal function via congestion of the renal veins.

Mullens et al. (JACC 2009) recently showed in 145 patients with AHFS that patients who developed worsening renal function had greater CVP upon admission as well as greater CVP following medical therapy. Renal function did not correlate with other hemodynamic variables.

Addition of thiazide diuretic to a loop diuretic results in greater diuresis and natriuresis than increasing dose of loop diuretic alone.

Dormans et al. (JACC 1996) randomized 20 CHF patients on high doses of oral lasix (> 250 mg/day) to intravenous bolus therapy versus the same dose given as a continuous infusion for 1 day. Urinary volume and urinary excretion of sodium were both significantly greater at 8 hours and 24 hours in the continuous infusion group (mean daily dose of 690 mg). Less peak concentration with continuous infusion may lessen risk of ototoxicity.

Oral torsemide may be better and more reliably absorbed than either furosemide or bumetanide, with more consistent bioavailability.

Furosemide in particular has variable absorption.

Response to intravenous doses likely to be similar.

Use lowest dose possible to achieve effective diuresis.

Loop + thiazide combination and consideration of continuous infusion are options for those difficult to diurese.

Worsening renal function is not a contraindication to diuretic therapy.
CARDIAC RESYNCHRONIZATION THERAPY (CRT)

- Biventricular pacemaker / ICD
- Left ventricular dyssynchrony prevalent in systolic HF
- Indicated in:
  - Chronic systolic HF on optimal medical Rx
  - NYHA class III/IV
  - QRS duration > 120 seconds

CRT

- Can CRT be utilized in patients with less severe heart failure?
- Previous studies have suggested that CRT can lead to positive remodeling including improvement in left ventricular end-systolic volumes
- MADIT-CRT was designed to determine if CRT could improve outcomes in NYHA I-II HF patients with QRS duration > 130 ms

CARDIAC TRANSPLANTATION

- Treatment option for systolic heart failure refractory to maximal medical therapy
- Limited by supply of donor organs
  - 3000-4000 heart transplants / year in US
- Extensive patient evaluation required
  - Medical, psychosocial, insurance, etc.
**WHEN TO REFER**

- Symptoms limiting quality of life
- Recurrent heart failure admissions despite maximal therapy
- Worsening end-organ function (renal, hepatic) – Before they become irreversible
- Refractory ventricular arrhythmias
- For younger patients, may be useful to be “plugged” into the system

**ADULT HEART TRANSPLANTATION**


- Survival (%)
- Years

**ADULT HEART RECIPIENTS**

Functional Status of Surviving Recipients (Follow-up: 1995 - June 2006)

- No Activity Limitations
- Performs with Some Assistance
- Requires Total Assistance

**CONTRAINDICATIONS**

- Active substance abuse
- Lack of social support
- Severe peripheral vascular disease
- Severe lung disease
- Active viral hepatitis / HIV
- Recent malignancy

**VAD**

- Option for patients with end-stage HF and who are not candidates for transplantation, or who cannot wait for transplant
- Requires major cardiothoracic surgery with similar contraindications as transplant
- Devices are getting smaller and safer
REMATCH (2001) DESTINATION L-VAD

- 129 patients with end-stage CHF, 80% requiring IV inotropic therapy, randomized to medical therapy versus HeartMate I LVAD (pulsatile device)
- Patients were not transplant candidates
- Cause of death in LVAD group was predominantly sepsis, LVAD failure, and CVA

HEARTMATE II

- Continuous flow rotary pump
- External drive line still needed
- Smaller size allows for use in smaller patients, females
- Recent studies have shown lower adverse events (stroke, bleeding, infection) compared to older, larger devices

HEARTMATE II

- HM II device appears to be safe for bridge to transplant and an improvement over older pulsatile devices
- No randomized study versus transplant
- Learning curve is present
- Outcomes not assessed after transplant – does VAD prior to transplant constitute a risk factor for poor outcome?

WHAT ABOUT THE COST?

  - Primary device group (n = 1476)
  - Post cardiotomy (n = 1467)
- 1 year survival was 51.6% in the primary device group and 30.8% in post-cardiotomy group
- Mean 1-year Medicare payments for inpatient care was $178,714 in the primary device group and $111,769 in the post-cardiotomy group

CONCLUSION

- Advanced heart failure is a severe, debilitating illness that requires a multidisciplinary approach
- Evidence based therapy is still underutilized
- Referral for transplantation should be considered in acceptable candidates

QUESTIONS?

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For each of the following medications used in chronic HF, specify if they improve mortality, worsen mortality, or are neutral.

A. Enalapril  IMPROVE
B. Digoxin  NEUTRAL
C. Amlodipine  NEUTRAL
D. Dobutamine  WORSEN
E. Nesiritide  ????????

ACE INHIBITORS AND BETA-BLOCKERS

Which of the following statements is true about management of chronic HF?

A. ACE inhibitors should be started before beta blockers
B. Carvedilol is the only FDA approved beta-blocker for heart failure
C. ACE inhibitors are contraindicated in HF patients with serum creatinine > 2.0
D. Despite benefits seen with hydralazine / nitrates in African Americans, African Americans with HF should still be started on ACE inhibitors first
E. If a HF patient develops cough from ACE inhibitor, it is advisable not to switch to an angiotensin receptor blocker (ARB) given the lack of data using ARBs in heart failure

DIURETICS IN HEART FAILURE

Which of the following has proven mortality benefit in patients with systolic heart failure?

A. Furosemide
B. Spironolactone
C. Torsemide
D. Chlortalidone
E. None of the above

DEVICE THERAPY

Patient is referred to Electrophysiology. What device is recommended by the current heart failure guidelines?

A. No device
B. Dual chamber pacemaker
C. Biventricular pacemaker / ICD (i.e CRT)
D. Dual chamber ICD

CARDIAC TRANSPLANTATION

All of the following statements are true, except:

A. Following cardiac transplantation, 5 year survival is 75% and 10 year survival is 50%
B. History of drug abuse including smoking is a contraindication for cardiac transplantation
C. For patients who unable to receive a heart transplant in time, left ventricular assist devices (VAD) can be utilized as a “bridge” to transplantation
D. Referral for heart transplantation should be considered if a patient remains significantly limited despite optimal medical therapy