



CASE STUDY

TZDs in Heart Failure

TZDs in Heart Failure: The Good, the Bad, and the Ugly

Bobbi Herron MS, APRN, BC-CNS
Heart Failure Clinical Nurse Specialist
St. Mary Medical Center
Hobart, IN

Susanne Heinzman BS, RN
Masters Candidate, Purdue University
Staff Development Coordinator
Saint. Anthony
Crown Point, IN.

Introduction:

Type 2 Diabetes Mellitus (DM) has quickly become a worldwide epidemic with no evidence of eradication in the near future. Its effect on the vasculature often leads to cardiovascular disease with subsequent morbidity and mortality. Type 2 DM is a complex disease that requires meticulous attention from healthcare providers and patients. Heart failure nurses must be responsible for the assessment and monitoring of risk factors associated with diabetes in patients with heart failure. (Chorzempa, 2006).

Thiazolidinediones (TZDs) are oral hypoglycemic medications that are frequently used to treat Type 2 Diabetes Mellitus. Thiazolidinediones are peroxisome proliferators-activated receptor agonists that counter insulin resistance and increase insulin sensitivity. By decreasing insulin resistance, TZDs improve cardiovascular and metabolic health by improving glucose homeostasis, decreasing plasma insulin levels, improving endothelial function, decreasing vascular inflammation and C-reactive protein levels and correct lipid abnormalities. The ability of TZDs to counter metabolic syndrome has led to widespread use of these drugs in patients with insulin resistance and diabetes. However, TZDs can cause weight gain and fluid retention in some patients. In large clinic trials with rosiglitazone (Avandia) and pioglitazone (Actos), the frequency of edema was 3 to 4 times higher than in placebo-treated patients. (Hollenberg, 2003). Advanced Practice Nurses (APNs) who manage complex conditions such as heart failure with multiple comorbid conditions must understand the repertoire of options and strategies available for optimal patient outcomes. Inquiring minds need to know if and when TZDs can be safely used for patients with heart failure.

Case Presentation:

Background Information:

HISTORY OF PRESENT ILLNESS:

69-year-old woman presented to the Heart Failure Treatment Center July 18, 2006. Claims incremental ongoing weight gain, decrease in physical strength and endurance, fatigue, abdominal bloating, severe peripheral edema. C/O severe dyspnea on exertion, paroxysmal nocturnal dyspnea with CPAP, non-productive cough, using portable O₂ at 3L/min via NC, Can no longer attend church or go to the grocery store. She uses a motorized scooter to get around in the house.

PAST MEDICAL HISTORY:

Patient reports she experienced gestational diabetes during her second pregnancy. At birth the baby weighed 10 lb 10 oz and patient states she was very overweight. The doctor told her she would never have a normal blood sugar as long as she was overweight, so she did not seek any further treatment. She thought this was “normal” for her. Decades later, during a hospitalization for kidney stones, she was assigned a different attending physician. She began following him and his nurse practitioner who were the first to treat her for diabetes. Once she started on Actos, the blood sugars were better controlled. Due to an irregular heart beat, she was referred to a cardiologist. She was told she had suffered a series of silent myocardial infarctions, was diagnosed with CAD and underwent a CABG. Over time she developed congestive heart failure (CHF). From 2001-2004 she was sent for outpatient infusions of Nesiritide (Natrecor) due to decompensating CHF. She was sustained this way until 2004 when the hospital no longer offered intermittent outpatient infusion therapy. Patient reports frequent hospitalizations with some recurring within 30 days.

ALLERGIES: Morphine, Ambien- both cause severe confusion

MEDICATIONS:

Furosemide 40 mg po bid, Coumadin 4 mg po HS, Lipitor 40mg po HS, Actos 30 mg po QD, Norvasc 5 mg po QD, Nesiritide (Natrecor) infusions as observation patient PRN, home O2, 3L per NC, using CPAP at night (Note: patient failed prior ACEI trial due to recurrent renal failure and an elevated potassium, and was not able to use Betablocker due to low heart rate in past).

DIETARY RESTRICTIONS:

1800 ml fluid restriction, 2 Gm sodium restriction, low fat, 2000 calorie American Diabetic Association

SOCIAL HISTORY:

Retired widow, who lives alone, has social support from family and church friends. Son and daughter-in-law live next door, daughter lives in neighboring town. Has 3 dogs that she adores and loves to play with but cannot presently, due to severe dyspnea and fatigue. Quit smoking over 20 years ago, and does not drink alcohol.

FAMILY HISTORY: Father died from heart attack, mother died from cancer.

DIAGNOSTICS:**Laboratory Results:**

WBC 8.2, RBC 3.91, Hgb 12.0, Hct 28; PT 25.2, INR 2.5; BUN 43, Creat 1.9, Na 141, K+ 4.0, CO2 33; Albumin 2.9; BNP 844; Hgb A1C 8.5

Echocardiogram: EF 29%, moderate mitral insufficiency, mild aortic insufficiency, moderate pulmonary hypertension

PHYSICAL EXAM:

Height 5' 0," Weight 260

Vital signs: BP: 188/78, HR: 70, R: 22, SaO2 92% using portable O2

Appearance: Ill appearing obese, white, female, alert and oriented x 3, with blunted affect

Neck: Short and wide, with JVD 6 cm, positive HJR, no carotid bruits noted

Heart: S1, S2, no S3, or S4, loud systolic murmur over apex radiating to the axilla, loud murmur over aorta

Chest: Bibasilar coarse crackles which extends up to left posterior mid lung, clear anteriorly

Abdomen: Round, firm with abdominal wall edema, decreased bowel sounds to lower quads, with tympanic percussion to all fields

Extremities: Significant periorbital edema, 3+ edema to upper extremities, 4+ pitting edema noted to bilateral lower extremities with weeping areas to bilateral shins, very tender to palpation

DIFFERENTIAL DIAGNOSIS:

Acute on Chronic combined Systolic and Diastolic Heart Failure; NYHA Class IV, Stage D

Uncontrolled Diabetes Mellitus

Pulmonary Hypertension

Uncontrolled Hypertension

COPD

Renal Insufficiency

Anemia

Status Post Chemotherapy and Radiation for Colon Cancer

Course of Treatment

Initial HF Clinic Visit:

At first visit patient was assessed and then given a CHF questionnaire to complete. The document was reviewed with the patient. Topics reinforced for clarity include: how to measure and calculate a 2000 mg sodium diet, how to conduct a 1800cc fluid restriction, the proper way to weigh daily and report to the telemanagement system (My HealthCall, Inc.©), and the importance of staying active as tolerated. It was suggested that she perform chair exercises while watching TV and walk for 5 minute intervals in her house. The CNS also reviewed the signs and symptoms of worsening heart failure, diabetic emergencies, when to call 911, when to call the health professionals, and taught energy conservation strategies. Medications were reviewed at each visit. The SF-36™ Health Survey was completed which indicated an overall poor functional score. The Becks Depression Score showed significant depression. These surveys are preset by the hospital and were not chosen by the APN. The patient's cardiologist was informed of all results. Physician referral was made for complaints of depression. Cymbalta was subsequently started. The APN was concerned that some of the patient's edema may have been caused by Actos, a TZD which was used for glycemic control. Within 2 weeks, Actos was discontinued. Patient then returned to the clinic weekly for evaluation and management of HF symptoms.

1 Month Visit:

Labs: BUN, CR, and fasting glucometer readings lower

Vital signs: SBP still elevated 150/72, pulse 72

Within the first month, this lady lost 30 lbs, which brought her current weight to 230 pounds. The pioglitazone (Actos) was discontinued on second visit. Although the blood sugar readings were lower, it was believed to be due to a change in diet habits. Patient started using Meals on Wheels. Lisinopril was started and the patient was monitored closely. Low dose of ACEI was started after much discussion with the cardiologist who was hesitant due to this patient's past reaction to ACEI as evidenced by high potassium and renal insufficiency. The diuretics were adjusted as needed. The patient was referred to an endocrinologist for better glucose control. He added Humulin insulin on a sliding scale. Since some improvement was evident, the patient was then asked to return to the clinic for evaluation and management monthly.

After 3 months:

Weight: down to 222 pounds

Vital signs: BP 130/42, HR 72, RR 20, O2 sat 95% on 3L via NC

Fasting home glucometer readings improved but still unstable. Meals on Wheels continued, however this patient did not like the food and started skipping meals. The diabetes educator was consulted for meal planning and medication reinforcement. The endocrinologist changed her Humulin to Novolog with sliding scale and a Lantus standard bedtime dose was added. Since carvedilol, a non-cardioselective betablocker (BB) was ordered by her physician at last MD visit, and the patient still complained of shortness of breath with wheezing, the APN changed the BB to metoprolol (Toprol XL). The patient was asked to return to the clinic in 2 weeks for medication up titration.

APN appointment 2 weeks later:

Patient still complained of fatigue but less dyspnea and wheezing. BB up titration was planned to take place slowly once the ACEI was optimized. Caution was taken due to the renal history and past problem with high potassium. Clinic appointments were made every two weeks for medication optimization. Patient now taking lisinopril 40mg po dly, metoprolol 50mg po daily, furosemide 40mg po bid, Norvasc 10 mg po daily, Coumadin 5 mg po at HS, Lipitor 40 mg po dly.

After 6 months

Vital signs: SBP 126/70, pulse 68, SaO2 92%

Weight loss; current weight 216 lb

Labs: Hgb 13.6, HCT 30, K+ 4.0, BNP 299, Bun 29, Creat 1.2. Fasting home glucometer readings average in 90s-130s with rare hypoglycemic reactions. Patient is consistent with fasting glucometer checks, but still varies with her before meals and bedtime readings. She does not eat lunch and does not see the need to check a reading if she does not eat. More diabetic teaching and reinforcement is needed. The patient is now ambulating with a walker and with minimal dyspnea. Lung fields diminished with fine left posterior basilar crackles. She now reports improved quality of life as seen by an increase in physical activity and ability to now go to church and occasionally go shopping with the use of her motorized scooter. The ACEI was up titrated slowly over 6 months and Atacand 8 mg was added to the regimen due to the systolic blood pressure indicating prehypertension according to the JNC 7 guidelines. Extra Lasix 80 mg IVP was administered in clinic twice, however no

further Nesiritide infusions were ordered. There were no repeat hospitalizations for 6 months for ADHF.

Since the blood sugars were still erratic, a home health nurse was referred for in home diabetic teaching and reinforcement. Insulin sliding scale adjustments were made. An in-home assessment was also made for physical therapy for strengthening and endurance and occupational therapy since 2 home falls were reported. Telemanagement and Heart Failure Clinic Follow-ups continued monthly. More frequent visits were scheduled as patient reported escalating symptoms via call-in telemanagement program. Eventually, Bidil was needed to assist with cardiac stability and hypertension. Clinic visits continued monthly.

After 9 months

Labs: Bun 29, Creat 1.3; BNP 180; K⁺ 4.2; Hgb 13, Hct 29; PT 27.5, INR 2.7

Fasting home glucometers fluctuate between 60 and 200 with occasional hypo/hyperglycemic episodes.

Novolog and Lantus insulin is adjusted per endocrinologist.

Weight loss continues and patient now weighs 199 lbs. She was hospitalized once in nine months due to uncontrolled pain related to an old cervical spine injury/arthritis, however no hospitalizations for acutely decompensated Heart Failure. The BB and ACEI optimized to maximal tolerable doses while the diuretics were significantly decreased. The lisinopril is given at 40mg po dly, the Atacand is 32 mg po dly, Metoprolol is 200mg po dly, Bidil 37.5/20 po tid, the furosemide is 40 mg po dly. The patient is using a wheeled walker and driving herself to all appointments, church and shopping. She only uses her scooter for shopping trips. The CNS is collaborating with endocrinologist for tighter glucose control.

After 1 year:

Patient reports, "I feel like I experienced a miracle; my quality of life is as good as I think it can get, I can go to church, shop, and play with my dogs again. And best of all, I feel as good as I think I can feel." A repeat SF 36™ showed an improved perceived functional status, health and sense of well-being. The Becks Depression Scale greatly improved with a score below 15. The patient was able to walk a total of 267 feet with only one rest using her wheeled walker. At her last cardiologist appointment, she was told she has no overt CHF or any problem with it. A repeat echocardiogram showed an improved EF of 59%.

After 18 months:

Vital signs: SBP 160/80, pulse 74, SaO₂ 97%

Weight loss: total 73 lbs, current weight 187lbs

Her blood pressures continue to be monitored closely. Patient often forgets to take glucometer readings 4 x daily and report to endocrinologist. The APN has contracted with the patient to call the prior day's glucometer checks into telemanagement. Each Monday once the readings are collected by the APN, the results will be faxed to the endocrinologist in an attempt to tightly control glycemic goals.

SUMMARY:

This study is an excellent example of the complexity of the heart failure patient. Since most heart failure patients come to clinic with multiple co-morbidities, it is imperative that APNs

gird themselves with an ever expanding arsenal of knowledge of the latest evidence based practices. Heart failure patients are prescribed a minimum of 9 to 12 medications so the understanding of medication interactions, side effects and contraindications is key to achieving optimal patient outcomes.

The mechanism of fluid retention resulting in pulmonary and peripheral edema is unknown. According to the prescribing information, TZDs increase the intravascular plasma volume, which also results in reduction of hemoglobin concentration. These agents are well known to cause idiosyncratic hepatotoxicity and fluid retention, however, only a few patients have been reported to have developed congestive heart failure and pulmonary edema. Evidence suggests that TZDs may have positive effects on cardiac function including diminished vascular resistance, improved cardiac metabolism, positive inotropic effect, coronary vasodilation, increased natriuretic peptide production, improved endothelial function, and attenuation of cytokines. These effects may prevent heart failure in patients with diabetes, especially if TZDs are used before cardiac dysfunction develops. However, they can cause pulmonary edema and exacerbate the congestive heart failure state. Thus, TZDs should be used with caution or avoided in patients with left ventricular dysfunction or chronic renal insufficiency. Heart failure patients particularly, should be monitored for possible complications with their use. Current data suggest that TZDs may be used cautiously in patients with type 2 DM who are at risk for heart failure or who have NYHA Class I or II heart failure (Granberry, 2007). Patients with NYHA class III or IV HF are at risk for fluid retention and should not take this medication. (Nesto, R., Bell, D., Bonow, R., Fonseca V., Grundy, S., Horton, E., 2003).

Once Actos was discontinued, this patient lost 30 pounds in one month for a total of 73 pounds over 18 months. Proper assessment, medication management, follow-up, and compliance resulted in a stable cardiac state, which in turn improved quality of life. Although TZDs play a crucial role in treating insulin resistance, when prescribing these medications, the APN must keep in mind the possible deleterious effects for the heart failure patient.

References:

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