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Beta-blocker target dosing and tolerability in a dedicated Heart Failure Clinic Charlotte Maxeke Johannesburg Academic Hospital

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Beta-blocker target dosing and tolerability

in a dedicated Heart Failure Clinic

Charlotte Maxeke Johannesburg Academic Hospital

2000-2014

Jonathan Graham Bolon

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in Internal Medicine.

Johannesburg, 2017.

DECLARATION

I, Jonathan Graham Bolon, declare that this research report is my own work, and is being submitted for the degree Master of Medicine (in the submissable format with my protocol and extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university

Signature.....

Date :

DEDICATION:

To C., A., and as yet unnamed bb, evermore.

ACKNOWLEDGEMENTS

A big thank you to Professor Manga and Dr Keir McCutcheon, Division of Cardiology, CMJAH & University of the Witwatersrand, Johannesburg for all the guidance and support in this endeavor.

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ABSTRACT

Beta-blocker target dosing and tolerability in a dedicated heart failure clinic: Charlotte Maxeke Academic Hospital- 2000-2014.

BACKGROUND: The benefit of Beta-blockers in chronic heart failure with left ventricular dysfunction is well established. However, actual use in “real world” heart failure patients has been relatively poor. Beta-blockers have generally been underused and under-dosed, largely due to perceptions about intolerability. Ivabradine, a pure heart rate lowering agent has recently been advocated for heart failure patients with elevated heart rates who could not tolerate target doses of beta-blockers.

AIMS: The aim of this study was to document beta-blocker target dosing and tolerability in a dedicated heart failure clinic at Charlotte Maxeke Johannesburg Academic Hospital and assess the proportion of patients who may require Ivabradine therapy.

METHODS: The records of all patients attending the heart failure clinic between 2000-2014 were reviewed. Demographic, clinical and outcome data was recorded for 500 patients.

RESULTS: At their last clinic visit, 489 out of 500 (97.80%) patients were taking a beta-blocker. Patients were stratified into categories according to guideline target doses, with 59.8% (n=299) achieving ‘target dose’, 28.0% (n=140) a ‘moderate’ dose, 5.4% (n=50) receiving ‘low dose’ of beta-blocker and 11 patients (2.2%) no dose. Beta-blocker “intolerant” patients numbered 61(7.6%). Conventional reasons for beta-blocker caution

(bronchospasm/breathlessness, syncope, cardiac decompensation, hypotension) were found to be rare. Bradycardia was the commonest cause of inadequate uptitration. Only 53 patients (10.6%) were deemed to be “Ivabradine suitable”.

CONCLUSIONS: Beta-blockers are well tolerated with perceptions around intolerability and concerns about safety largely unsupported by our experience. As a consequence, the role for Ivabradine therapy in patients with chronic heart failure is limited.

Key words: Beta-blockers, Heart Failure, Ivabradine

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LIST OF ABBREVIATIONS

CMJAH, Charlotte Maxeke Johannesburg Academic Hospital

ESC, European Society of Cardiology

AHA, American Heart Association

ACC, American College of Cardiology

SHIFT, Systolic Heart Failure Treatment with If Inhibitor Ivabradine Trial

IHD, ischaemic heart disease

HT, hypertension

PPCMO, peripartum cardiomyopathy

HIV, human immunodeficiency virus

NYHA, New York Heart Association classification

eGFR, estimated glomerular filtration rate

SBP, systolic blood pressure

HR, heart rate

BPM, beats per minute

ACEi, angiotensin converting enzyme inhibitor

MRA, mineralocorticoid receptor antagonist

ISMO, isosorbide mononitrate

CCB, calcium channel blocker

LVEF, left ventricular ejection fraction

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

Beta-blocker Target Dosing and Tolerability in a dedicated Heart Failure Clinic – Charlotte Maxeke Johannesburg Academic Hospital: 2000-2014

The benefit of beta-blockers in heart failure is well established (1). Major clinical trials have consistently shown reduced morbidity and mortality in patients with chronic heart failure with left ventricular dysfunction of all causes when beta-blockers are used (2, 3). These large trials are supported by meta–analyses of smaller studies (3, 4). Significant mortality benefit has been demonstrated, with some variation of degree within the drug class. In addition to prolonging survival, reduction in the need for hospital admission, prevention of dysrhythmia's, improvement in symptoms of heart failure, and control of ventricular rate has been repeatedly demonstrated (4).

As a result, beta-blockers have become an established first line, best practice treatment in the management of heart failure with reduced left ventricular function. This is reflected in the guidelines of major national and international cardiology organizations such as the European Society of Cardiology (ESC) and American Heart Association (AHA) /American College of Cardiology (ACC) (5). The Heart Failure Society of South Africa, a special interest group of the South African Heart Association has adopted the ESC guidelines with minor modifications for local circumstances (6). Three key trials have influenced the practice guidelines. These are the CIBIS II (Cardiac Insuffiency Bisoprolol Study II), COPERNICUS (Carvedilol

Prospective Randomised Cumulative Survival) and MERIT – HF (Metoprolol CR / XL Randomised Intervention Trial in Heart Failure) trials (7-9).

The introduction of beta-blockers in these large trials was in addition to conventional heart failure treatment, including an angiotensin converting enzyme inhibitor (ACEi) / Angiotensin II Receptor Blocker (ARB) in over 90% of patients in the trials(10).

In CIBIS II, bisoprolol, a beta-1 selective blocker was assessed.
In 2647 patients, mainly in Class III failure, bisoprolol or placebo was added to current optimized therapy. Early termination of the trial was mandated due to a clear and significant reduction in mortality (34%), reduction in sudden death (44%) and in heart failure hospitalization (20%) in the beta blocker group(7).

Metoprolol, a beta-1 selective blocker was tested in MERIT-HF. Metoprolol (slow release formulation) or placebo was administered to 3991 patients, mostly with Class III failure. Early termination resulted from a major mortality reduction (34%) and decreased rate of sudden cardiac death (44%) in the Metoprolol group (8).

Carvedilol was compared to placebo in the COPERNICUS trial of 2289 patients. These patients were significantly clinically worse than studied in the other large beta blocker trials with Class III/IV heart failure / ejection fraction less than 25% enrollment criteria. (9). This was in addition to optimized standard guideline treatment for heart failure. COPERNICUS was terminated early due to the large

effect of the carvedilol arm on reducing the all cause mortality end point. A 35% reduction in total mortality was noted for carvedilol compared to placebo. Notably, the annual mortality of the placebo group in COPERNICUS (18.6%) was significantly higher than that of either the study placebo groups in MERIT-HF (11.0%) or CIBIS II (13.2%). This was due to the more advanced stage of disease enrollment criteria. Consequently, although the relative risk reduction was similar in the large studies, the sicker nature of the patients in COPERNICUS meant there was greater absolute mortality advantage and therefore a lesser number needed to treat(9).

These large trials (nearly 9000 patients in total), have clearly shown a decrease in mortality (average of 34% in each trial), decrease in heart failure related hospitalization (28-34% relative risk reduction) within one year of introduction of treatment(4).

Additional evidentiary support for the use of beta-blockers is gained by SENIORS (Study of effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) and USCS (the United States Carvedilol Study), and meta-analyses of smaller beta-blocker trials, all of which showed similar clinical outcomes of varying degree's (5).

Within the drug class, the major head to head beta-blocker comparison trials include the COMET (Carvedilol or Metoprolol European Trial). Treatment with Carvedilol was associated with decreased rate of all-cause mortality (primary

endpoint) but was not associated with difference in co-primary endpoint of all-cause mortality or all-cause hospitalization in patients with congestive heart failure (2)

The use of beta-blockers has unequivocally shown benefit in chronic heart failure with reduced left ventricular function across multiple clinically relevant endpoints, including sudden death, pump failure, hospital readmission and self-reported patient well being(2, 4, 11-13). The inclusion of beta-blockers in best practice guidelines is accepted and considered a core treatment modality in the management of heart failure with reduced ejection fraction (1).

The full mode of action of beta-blockers in cardiac failure is incompletely understood despite decades of research. The postulated benefit of beta-blockers is via multiple mechanisms. The benefits of beta blockade in heart failure accrue through several pathophysiological mechanisms, all of which are potentially responsive in a dose - dependant fashion (14). The majority of benefit of beta-blocker use is derived from of beta-1 receptor blockade.

The deleterious effect of the high plasma catecholamines and increased sympathetic activity on the heart in severe left ventricular dysfunction has been well described.(14). Possible mechanisms for beta receptor blockade improving survival include reduction in arrhythmia's, anti-ischaemic action, reduction of catecholamine injury, decreased pathological cardiac remodeling, improved heart rate variability and reducing heart rate (15).

It has been suggested that the majority of benefit in the use of beta-blockers is mediated via heart rate reduction (16, 17). As a result the effect on heart rate has been most scrutinized. Heart rate is an important prognostic factor in heart failure. Increased heart rate is a risk factor for cardiovascular mortality and is independent of other accepted risk factors and confounding variables. (18)

There is a defined relationship between increased heart rate and mortality in studied patients with heart failure (19). The recent large studies in heart failure (CIBIS II, COPERNICUS etc.) have sustained this view. The best prognosis in these groups was noted in patients with the lowest baseline heart rate and greatest heart rate reduction on therapy (20, 21).

The relationship between resting heart rate and clinical outcome was studied in the control arm of the BEAUTIFUL trial, in patients with reduced left ventricular function and coronary artery disease (22). There was a clear association of heart rate with progression of heart failure. In the control arm, where patients had heart rates >70 resting heart beats per min (bpm) group had a 34% greater mortality, 53% greater hospitalization rate compared to the <70 bpm cohort. Every 5 bpm above this was associated with an 8% increased risk of cardiovascular death (22).

A recent meta-analysis of heart failure trials, revealed that for every 5 bpm reduction in heart rate with beta blockade, relative risk of death decreased by 18% (17). However magnitude of heart rate reduction was a better explanatory variable than heart rate achieved in this review. In addition, there was no statistical

relationship in this and other studies between beta-blocker dosing achieved and the magnitude of all-cause mortality reduction (17, 20, 23).

Ivabradine, an If channel antagonist, acting at the sinoatrial node to produce heart rate reduction has been the agent that has been extensively investigated in this regard.(22, 23)

The multi-centre, multi-country SHIFT trial (Systolic Heart Failure Treatment with If Inhibitor Ivabradine Trial), tested Ivabradine in patients with chronic heart failure and a Left Ventricular Ejection Fraction <35%. SHIFT randomised 6505 patients with a baseline HR >70, in patients already on optimal guideline directed heart failure therapy. This included beta-blockers at maximally tolerated doses.(24)

The composite end-point of mortality and cardiovascular associated hospitalization was reduced by 18% in the treatment arm (23). However this effect was mostly achieved by decreased hospitalization rather than decrease in mortality. The outcome of sudden cardiac death wasn't affected by ivabradine, which lacks the attenuating electrophysiological properties of beta blockers (24).

Also, the greatest benefit in terms of outcome was achieved in the subgroups with the highest pre-treatment baseline heart rate and those with the greatest heart rate reduction. This finding was in keeping with the meta-analysis of beta-blocker trials showing an association of magnitude of heart rate reduction and outcome (17).

Of note in the SHIFT trial was the lack of achievement of target dosing in the patient population selected. The average doses of beta-blockers were substantially lower than those used in the clinical trials that showed benefit. Only 23% of the patients were at target doses, and less than half (49%) were receiving 50% or more of the target doses at enrollment. The authors of SHIFT argued that low beta-blocker use was because of beta-blocker tolerability and that this was consistent with "real world experience"(23). However, this has been a consistent point of criticism in interpreting the trial outcomes (25, 26).

In the subgroup of patients receiving at least half the recommended maximum dose of a beta-blocker (56% of the patients included in the trial), there was no statistically significant difference between the Ivabradine and placebo arms in terms of either overall mortality or the primary outcome (a non-significant 12% reduction for those on at least 50% but less than 100% of the recommended beta-blocker dose (*P*=0.193)) (24). The implication being that additional heart rate reduction in this specific group did not lead to significantly improved outcome. A conclusion drawn from this was that the pleomorphic effects of beta-blockers were essential to mortality reduction beyond solely the effect on reducing heart rate (26). Importantly, if beta-blockers can be used optimally in patients with heart failure, there may be a very limited role for further heart rate reduction with Ivabradine.

The actual tolerability of beta-blockers has also been extensively investigated, in light of the lack of achievement of the target doses in surveys of "real world" patients (patients in a clinical setting not enrolled in tightly managed clinical

trials)(27, 28). The results of these reviews showed that heart rate reduction was not being achieved in most patients treated with beta-blockers (29). Beta-blockers were underused and under-dosed in these heart failure population groups for various reasons (30).

In these large international surveys, it has been shown that only 20-40% of heart failure patients were taking beta-blockers and the mean dose was half the recommended target dose (28, 31). There appeared to be an exaggerated perception of risk of adverse events of usage in these heart failure populations.

The surveyed physicians appeared to be reluctant to initiate and/or up-titrate the beta-blockers appropriately because of concerns about safety and tolerability. Particular subgroups who were under-dosed or did not have beta-blockers initiated at all were the elderly, and those with concomitant disorders such as diabetes, chronic obstructive pulmonary disease (COPD)(32) and intermittent claudication (31).

In reality there are very few patients with heart failure in whom beta-blockers are absolutely contraindicated (33). These include asthmatics, AV blocks, and patients with beta-blocker intolerance. Only about 3-5% patients in large survey's have been seen to be intolerant, mainly due to hypotension or bradycardia (29).

In certain subgroups of patients with comorbid diseases such as COPD(34), diabetes mellitus and peripheral arterial disease in whom beta-blocker usage by clinicians is

historically poor, the evidence for benefit versus harm is clearly in favour of use (29). This is reflected in the current guidelines(5) .

The elderly also have traditionally been undertreated in terms of initiation and up-titration of beta-blockers (30). Various studies have looked at the issue. The Cola II study stratified heart failure patients into groups above age 70, in 5-year intervals to treatment with carvedilol and assessed patient tolerability. Its findings, subsequently supported by further evidence in the SENIORS trial (looking at patients >70 years old, treated with nebivolol), demonstrated good tolerability (in excess of 80%) across all studied age groups (29) .

CIBIS- ELD (Cardiac Insufficiency Bisoprolol Study in Elderly) looked at two of the most widely used beta-blockers in heart failure, carvedilol and bisoprolol and investigated tolerability in an elderly population as well as reasons for failure to achieve target doses (35). It found 69% of patients did not reach target doses, however 55% of patients achieved at least half of the target doses (35).

In general local data is sparse regarding beta-blocker use and achievement of target doses. In addition reasons for not tolerating beta-blockers in this population has not been assessed.

Conclusions from the SHIFT trial may have been overstated (beta blocker tolerability, benefit of additional heart rate reduction). If heart failure patients can in fact tolerate optimal therapeutic doses of beta-blockers, there may be very little

added morbidity and mortality benefit in adding Ivabradine. It is in this light that I planned to evaluate beta-blocker tolerability in the heart failure population at CMJAH.

1.1 Study Objectives:

The aim of this study is to investigate target dosing and tolerability of beta-blockers in a heart failure population at a tertiary public hospital in Johannesburg.

- To determine beta-blocker tolerability and to compare with the rates of beta-blocker use in the SHIFT trial, to assess whether the conclusions drawn from the SHIFT trial are necessarily applicable to our patient population.
- To ascertain reasons for beta-blocker intolerance
- Assess possible predictive comorbidities / clinical correlates for intolerance
- Determine achievement of target doses of beta-blockers
- Assess achievement of heart rate reduction and target heart rates
- Compare with published cohorts from recent international beta-blocker trials
- To document the demographic and clinical profiles of the patients attending the heart failure clinic at CMJAH.

This study is relevant to our local context for the following reasons:

- Demographics of the studied population are substantially different - there were very few non-caucasian enrollee's in all the large beta-blocker trials.
- Causes of heart failure are very different in our patient population. The majority of patients enrolled in the large trials had ischaemic heart disease as the cause of their heart failure. This is not expected to be replicated in our patient population.

- Comorbidities are expected to be different than previously studied populations
- In general the patient population is expected to be younger than international cohorts
- Socioeconomic status would appear to be substantially different than the large European and North American trials.

It is hypothesized that the patients recruited in the SHIFT trial were on inadequate doses of beta-blockers and the beneficial effect of Ivabradine is exaggerated. The role for Ivabradine may be much narrower than the authors implied. This is relevant to our context because Ivabradine is not currently available in the state sector in South Africa.

The data generated from this study will be compared to the international literature. The local setting of the heart failure population studied may indeed be unique, as the patient profile is substantially different. No current local literature exists assessing beta-blocker tolerability, reasons for intolerabilty and target dose achievement.

1.2 Methods:

- Retrospective analysis of the patient population attending the heart failure clinic at Charlotte Maxeke Johannesburg Academic Hospital.

- Analysis of variables related to demographics, clinical profile, standard treatment, beta-blocker use, tolerability and effect on heart rate.

- Documentation of the clinical records in a standard data collection sheet.

1.3 Study design:

- Retrospective file analysis.
- The files of the current patients with adequate records attending the heart failure clinic at CMJAH will be reviewed.
- Analysis of clinical response to beta-blocker therapy will be compared with published cohorts in various published beta-blocker trials with an emphasis on the recent SHIFT trial.

1.4 Study population and sample

The study population will comprise adult patients attending the heart failure clinic at CMJAH. This is a specialized clinic, accepting patients with a confirmed diagnosis on a referral basis from the ward of the hospital as well as its referral hospital network. Clinic records will be reviewed retrospectively, and will include all patients attending the clinic with complete records.

1.5 Inclusion criteria:

All adult patients attending the heart failure clinic at CMJAH (diagnosed with heart failure previously by a clinician at CMJAH or one of its referral hospitals and referral notes analysed and accepted by Cardiologists at CMJAH prior to acceptance).

1.6 Description of Methods and Techniques Being Used

Retrospective review of files meeting the inclusion criteria, using a standardized data sheet for data collection as attached.

Variables

- Age
- Gender
- Race
- Date of Diagnosis
- Follow up Duration (months)
- Diagnosis (Cause of heart failure)
    - Ischaemic Heart Disease
    - Other
        - Hypertension
        - HIV
        - Peripartum Cardiomyopathy
        - Chemotherapy induced
        - Other
- Beta-blocker
    - Atenolol
    - Carvedilol
    - Other
- Dose of beta-blocker acheived
    - Dose

    - Daily dose
    - % of target dose (per international trial standard)
- Other medication
    - Angiotensin Converting Enzyme (ACE)
    - Mineralocorticoid Receptor Antagonist
    - Digoxin
    - Statin
    - Hydrallazine
    - Isosorbide Mononitrate
    - Thiazide Diuretic
    - Calcium Channel Blocker
- Lasix (Furosemide) daily dose
- Systolic Blood Pressure at baseline
- Systolic Blood Pressure at last visit
- 6-Minute-Walk-Test at baseline
- 6-Minute-Walk-Test at last visit
- New York Heart Association Grading at baseline
- New York Heart Association Grading at last visit
- Heart Rate at baseline
- Heart Rate at last visit
- Heart rate reduction
- Reasons for non achievement of target dose
    - Syncope / pre-syncope
    - Hypotension

    - Bradycardia
    - Bronchospasm
    - Intolerant
    - Logistical
- eGFR (estimated glomerular filtration rate) at baseline
- eGFR l(estimated glomerular filtration rate) at last visit
- Na+ (Sodium) at baseline
- Na+ (Sodium) at last visit
- Ejection Fraction at baseline
- Ejection Fraction a last visit

1.7 Ethics

Application for permission to analyse file records of the Heart Failure was accepted by the Human Research Ethics Committee of the University of the Witwatersrand (Ethics Approval Number: M140611)

Random study numbers will be allocated to the data entries. The data sheet allocation will be kept separate from other materials related to this study. Data entries will not include patient names nor file numbers.

1.8 Funding

Costs associated with the study are funded by the investigator

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Chapter 2:

MANUSCRIPT

(submitted to Cardiovascular Journal of Africa (March 2017)

Beta-blocker target dosing and tolerability in a dedicated Heart Failure Clinic - Charlotte Maxeke Johannesburg Academic Hospital 2000-2014

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Short title: Beta Blocker tolerance and tolerability in systolic heart failure

Conflict of Interest: Nil

Keywords: beta blockers, heart failure, ivabradine, tolerability, target-dosing,

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Abstract: 266

Abstract:

Beta-blocker target dosing and tolerability in a dedicated heart failure clinic.

Background: The benefit of Beta-blockers in chronic heart failure with left ventricular dysfunction is well established. However, actual use in “real world” heart failure patients has been relatively poor. Beta-blockers have generally been underused and under-dosed, largely due to perceptions about intolerability. Ivabradine, a pure heart rate lowering agent has recently been advocated for heart failure patients with elevated heart rates who could not tolerate target doses of beta-blockers.

Aims: The aim of this study was to document beta-blocker target dosing and tolerability in a dedicated heart failure clinic at Charlotte Maxeke Johannesburg Academic Hospital and assess the proportion of patients who may require Ivabradine therapy.

Methods: The records of all patients attending the heart failure clinic between 2000-2014 were reviewed. Demographic, clinical and outcome data was recorded for 500 patients.

Results: At their last clinic visit, 489 out of 500 (97.80%) patients were taking a beta-blocker. Patients were stratified into categories according to guideline target doses, with 59.8% (n=299) achieving ‘target dose’, 28.0% (n=140) a ‘moderate’ dose, 5.4% (n=50) receiving ‘low dose’ of beta-blocker and 11 patients (2.2%) no dose. Beta-blocker “intolerant” patients numbered 61(7.6%). Conventional reasons for beta-blocker caution

(bronchospasm/breathlessness, syncope, cardiac decompensation, hypotension) were found to be rare. Bradycardia was the commonest cause of inadequate uptitration. Ultimately only 53 patients (10.6%) were deemed to be “Ivabradine suitable”.

Conclusions: Beta-blockers are well tolerated with perceptions around intolerability and concerns about safety largely unsupported by our experience. As a consequence, the role for Ivabradine therapy in patients with chronic heart failure is limited.

Beta-blocker target dosing and tolerability in a dedicated Heart Failure Clinic

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Background

The benefit of beta-blockers in heart failure is well established(1, 2).[1] Major clinical trials have consistently shown reduced morbidity and mortality in patients with chronic heart failure with left ventricular dysfunction of all causes when beta-blockers are included in treatment regimens (2).[2] As a result, beta-blockers have become an established first line, best practice treatment in the management of heart failure with left ventricular dysfunction, as reflected in the guidelines of major national and international cardiology organizations such as the American Heart Association (AHA) /American College of Cardiology (ACC) and European Society of Cardiology (ESC) (adopted with minor modification by The Heart Failure Society of South Africa, a special interest group of the South African Heart Association)(3, 4)[3,4]

Despite the documented survival benefit, actual use in "real world" heart failure patient groups has been relatively poor(5).[5] Numerous reviews and surveys have shown that beta-blockers were being underused and under-dosed in these heart failure population groups for various reasons(6),[6] with only 12-40% of heart failure patients tolerating beta-blockers at target doses and the mean doses found to be only half the recommended target dose(5, 7).[5] Patients outside of large protocol-driven clinical trials consistently failed to achieve target dose and or target heart rate (8). The surveyed physicians demonstrated reluctance to initiate or up-titrate

beta-blockers appropriately because of concerns about safety and tolerability (9) (10).[6]

In light of the documented adverse effect on mortality of an elevated heart rate, the demonstration of mortality benefit in heart rate reduction therapy, and the reluctance of physicians to adequately prescribe and up-titrate beta blockers at target dose due to safety concerns, a pure heart rate lowering agent was sought(11)[7]. Ivabradine, a selective I_f current inhibitor, induces dose-dependent heart rate reduction by directly reducing sinoatrial node pacemaker activity. This agent has been studied in the seminal SHIFT trial (Systolic Heart Failure Treatment with If Inhibitor Ivabradine Trial)(12),[8] where 6558 patients with chronic heart failure, left ventricular ejection fraction <35%, and a baseline heart rate (HR) >70 were randomized to receive ivabradine or placebo. Patients were already meant to be on optimal guideline directed heart failure therapy (including beta-blockers at maximally tolerated doses).

The composite end-point of mortality and cardiovascular associated hospitalization was reduced by 18% in the treatment arm, driven mostly by decreased hospitalization for worsening failure (26%, p<0.0001)(13). However, background beta blocker usage was substantially lower in the trial population than recommended by the guidelines. Only 23% of the patients were at target doses, and less than half (49%) were receiving 50% or more of the target doses at enrollment. The authors of the study explained that the low beta blocker was a result of standard clinical practice in their larger study population, however criticism of

applicability followed(14), since under treatment with beta blockers possibly inflated the potential benefit and exaggerated the proposed role of ivabradine as a treatment modality. Despite criticism(14) (15) the results of the SHIFT trial have resulted in ivabradine being given a Class IIa recommendation for the reduction of hospitalization or cardiovascular death in the latest ESC Heart Failure guidelines(3)[4].

In this regard, there remains a paucity of data in South African patients regarding the need for further heart rate reduction therapy in patients with heart failure with reduced left ventricular function. It is our hypothesis that most heart failure patients tolerate guideline-mandated doses of beta-blocker therapy and, if adequately up-titrated, will not need further rate reduction with agents such as ivabradine.

We thus sought to investigate target dosing and tolerability of beta-blockers in a heart failure population at a tertiary public hospital in Johannesburg, South Africa and to assess the potential role for additional heart rate lowering agents (such as ivabradine) in this heart failure population.

Methods

Ethics approval for our study was obtained from the Human Research Ethics Committee, University of the Witwatersrand. Clinical records of all patients attending the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in the period January 2000 to December 2014 were retrospectively reviewed.

All adult patients attending the heart failure clinic at CMJAH during this period were included. These patients were referred to this specialist clinic with a diagnosis of left ventricular systolic heart failure diagnosed by a clinician at CMJAH or a referral hospital and confirmed by echocardiography demonstrating LVEF <50%.

Demographic and clinical data was recorded, including data at entry to the clinic and at the last recorded visit.

Results

Five hundred patients fulfilled the inclusion criteria for the study and were included in this analysis. Patients in the clinic are managed according to local and international best practice and as part of this, beta blockers are routinely used, unless contra-indicated, and judiciously up-titrated to target doses as tolerated. The patients' characteristics are shown in Table 1.

Male patients comprised 52.5% (n=263) and the mean (SD) age of the cohort was 55 (15) years. Black patients (66.4%) constituted the predominant ethnic group of the study. Hypertensive heart disease was the commonest cause of heart failure (32.8%), followed by ischaemic heart disease (22%). Mean (SD) ejection fraction at admission to the clinic was 27.3 (8.4)%.

Median follow up duration (first appointment recorded at clinic to last recorded visit) was 58.7 months (range: 2-179). At enrollment, 87% of patients (n=436) were in sinus rhythm. Mean initial heart rate was 85.9 beats per minute (bpm), with last

achieved mean heart rate 71.7 bpm. The majority of patients were on guideline based heart failure treatments. For example, 95.8% of patients were using ACE inhibitors, and 89.8% of patients were using spironolactone (Table 1). At their last clinic visit, 489 patients (97.8%) were taking a beta blocker. Patients were stratified into categories according to target doses (Table 2), with 59.8% (n=299) achieving target dose, 28.0%(n=140) receiving an intermediate dose and 5.4% (n=50) receiving low doses of beta blockers (Figure 1).

Reasons for intolerance, defined as no or low doses (<50% of target dose), and reasons for not achieving target dose are detailed in Table 3. Conventional reasons for clinician beta blocker caution, such as bronchospasm / breathlessness (n=7; 1.4%), peripheral arterial disease (n=0), syncope (n=3; 0.6%), cardiac decompensation (n=4; 0.8%) and hypotension (n=2; 0.2%) were found to be rare. Approximately 10% of patients did not achieve the target dose for logistical reasons (enrolled in the uptitration phase or poor treatment adherence), and in 5% (n=25), no reason was determined. Bradycardia was the commonest cause of inadequate up-titration. However, analysis of the 201 patients who did not achieve the target dose, demonstrated that 104 (51.7%) ultimately achieved the target heart rates (26/61 (51%) of the nil/low dose group as well as 78/141 (55.3%) of the moderate dose group).

There were no statistically significant correlates for intolerance in terms of ethnicity, cause of heart failure or presence or absence of concurrent treatments. A history of

asthma (p=0.021), and a diagnosis of hypothyroidism (p=0.009) were independently correlated with beta blocker intolerance.

Patients were determined to be ivabadrine "suitable" if they were in sinus rhythm, with an EF<35% and a resting heart rate of greater than or equal to 70 bpm after appropriate up-titration of a beta blocker. Of the 500 initial patients assessed, 137 met this criterion (27.4%). Further excluding patients with New York Heart Association Class I symptoms, only 53 (10.6%) were deemed ivabadrine "suitable" (Figure 2).

The ivabadrine "suitable" subgroup at enrollment had a lower mean ejection fraction compared to the larger clinic cohort (EF: 21.0% vs. EF: 27.3%, p=0.0001), as well as higher resting heart rates (mean 94.2bpm vs. mean 85.9bpm, p=0.006). In addition, this subgroup had a shorter follow up duration (43.3 months vs. 58.7 months, p=0.006).

Diabetes Mellitus as a diagnosis was correlated with ivabadrine "suitable"(p=0.003), with these patients being twice as likely to be suitable (32.7% of suitable subgroup, 16.1% cohort). Unfortunately no data was captured regarding patients' long-term glycemic control, frequency of hypoglycemic episodes or presence or absence of target damage such as autonomic neuropathy. None of patients' gender, cause of heart failure, nor associated treatments were predictive of ivabradine 'suitable' status.

Discussion

Efficacy of beta blockers in heart failure has been widely established but actual use has been unsatisfactory, largely due to perceptions about tolerability and consequent reluctance amongst clinicians to up-titrate doses despite widely accepted guidelines (5) (9).[5] The perceptions of danger and intolerability of beta blockers appear to be over exaggerated to the disadvantage of patients who would fully benefit.

In this study we have demonstrated that in a dedicated heart failure HF clinic in a large public hospital, most (97.8%) heart failure patients can be prescribed a beta blocker. Almost 88% of these patients tolerate up-titration of their beta blockers to target or intermediate doses. Thus in this "real world" population, we have shown that beta blockers were used more often and at much higher doses than those reported in recent multi-centre surveys(6, 8).

Furthermore we have shown that in certain subgroups of patients with comorbid diseases such as chronic obstructive pulmonary disease (COPD)(16), diabetes mellitus and peripheral arterial disease in whom beta-blocker usage by clinicians is historically poor (10), the use of beta-blockers is generally safe with a small minority unable to tolerate intermediate or target doses. This practice is supported in the current guidelines (3, 4).

In the South African context there are no published data regarding beta-blocker use, tolerability and achievement of target doses in heart failure patients. In

addition, reasons for not tolerating beta-blockers in this population has not been assessed previously. Importantly it must be noted that black patients made up 66% of our total cohort. There are no published data reflecting the use and tolerability of beta blockers in black patients with systolic heart failure. In the SHIFT trial (13), the majority of patients were white (89%) with black patients comprising less than 3% (grouped in category of "other").

The socioeconomic status of our clinic patients would appear to be substantially different than that in the large European and North American clinical trials (17). Significantly, despite the major challenges of this relatively economically poor group of patients, the majority of patients were able to be compliant and were up titrated successfully.

Patient factors for predicting intolerance appear to be concurrent asthma (but not COPD) and hypothyroidism. Bronchospastic disorders are a well described cause for traditional clinician reluctance to initiate or uptitrate beta blockers and this subgroup of heart failure patients has been traditionally undertreated(18). Hypothyroidism (as well as hyperthyroidism) has been noted to be associated with an increased risk of mortality in heart failure patients, even after controlling for known mortality predictors, however no risk for beta intolerance has been previously described(19).

It would appear that conclusions from the SHIFT trial are not widely applicable in our setting, with its main conclusions being overstated (beta blocker intolerability / posited role for additional heart rate reducing agent).

The patient populations studied in SHIFT were broadly similar to our cohort (13). However, in our study patients were younger by 5 years (mean age 55.8 vs. 60.1), included more females (47% vs. 24%), and were more ethnically diverse. Ischemic heart disease was the predominant cause of heart failure in SHIFT (68%), compared to 22% in our study (Table 1). Ejection fraction at enrollment was slightly worse in our study patients as compared to SHIFT patients (27% vs 29%). Notably mean estimated glomerular filtration rate (eGFR, mL/min per 1·73 m2) in our study patients was better (85.24 ml/min) compared to SHIFT's cohort (74.6 ml/min). These and possibly other unknown factors may have played a role in the better response and tolerance of our patients to beta blockade.

This study demonstrates that beta blockers are well-tolerated in the treatment of chronic heart failure. The role of ivabradine in the treatment of patients with heart failure remains to be determined. However, our study suggests that it would remain a useful but ultimately limited adjunct to current management. Our results suggest that the number of ivabadrine "suitable" patients in a dedicated Heart Failure clinic in South Africa would be small after deliberate initiation and up-titration of beta blockers according to local and international standards.

Conclusion

In contrast to large international surveys (5) (9),[6] beta blockers were generally well tolerated by patients attending a dedicated heart failure clinic at a large urban public hospital in South Africa. Despite significant socioeconomic challenges for many of these patients, very few were unable to tolerate any dose of beta blocker, and the numbers who were 'intolerant' to beta blocker therapy were relatively small. Compliance was excellent and up-titration to treatment targets was largely successful. Our results demonstrate that in real-life clinical practice, beta blockers can be used more often and at much higher doses than previous physician sentiment suggests. Guideline suggested target doses are largely achievable, and tolerability concerns are not significant at all.

As a consequence, the role for additional rate control therapy beyond beta blockers in systolic heart failure patients is limited to only a small group of selected patients. As the clinical profile of systolic heart failure of our patient cohort is likely to be similar in the rest of South Africa and Africa it is therefore likely that the role for ivabradine in the treatment of chronic heart failure with left ventricular systolic impairment is limited in this region. The posited role for this drug, following from the conclusions of the SHIFT Trial, appears to be exaggerated.

Beta blockers remain the bedrock of standard of care in systolic heart failure and should be actively commenced and up-titrated, with the expectation of achieving moderate to optimum dosage in the vast majority of patients.

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Table 1- Baseline and subgroup patient characteristics

Variable	Baseline Cohort	Beta Blocker Intolerant	Ivabradine Suitable
Number	500	61	53
Age, years	55.28 +-14.94	59.13+-17.29	52.21+-14.74
Male	263 (52.5%)	33(54.1%)	34(64.15%)
Follow-up duration, months	58.70 =-43.80	59.80+-50.9	43.26+-39.08
Causes of HF			

IHD	110 (22%)	17 (27.95%)	14(26.42%)
HT	164(32.8%)	17 (27.95%)	16(30.19%)
PPCMO	61(12.2%)	12(19.7%)	1 (1.89%)
HIV	21(4.2%)	1(1.6%)	4(7.55%)
Chemo	24 (4.8%)	2(3.3%)	5(9.43%)
Alcohol / Toxins	24(4.8%)	1(1.6%)	2(3.77%)
Myocarditis	12(2.4%)	1(1.6%)	0 (0%)
Idiopathic / Unknown	66(13.2%)	11(18.0%)	11(20.75%)
Ethnicity			
Black	332 (66.35%)	37 (60.7%)	33(62.6%)
Indian	32 (6.41%)	6 (9.8%)	6 (11.32%)
White	124 (24.85%)	18(29.5%)	12 (22.64%)
Coloured	12 (2.40%)	0 (0%)	2 (3.77%)
Asian	0 (0%)	0 (0%)	0(0%)
Atrial Fibrillation	64(13.0%)	7(11.5%)	N/A
SBP mmHg			
Initial	120.75+-20.64	116.82+-20.36	118.61+-14.45
Last	116.25+-18.31	109.83+-18.44	111.56+-14.55
NYHA (Initial)			
I	159 (31.8%)	16 (26.2%)	N/A
II	258 (51.6%)	33(54.1%)	37 (69.81%)
III	78 (15.6%)	13(21.3%)	13(24.52%)
IV	5 (1.0%)	1(1.6%)	2 (3.77%)
Weight, initial	78.48 +-17.95	76.37+-19.54	78.05+-16.82
eGFR, ml/min/1.73	85.24 +-34.26	78.36+-24.03	
HR, bpm			
Initial (n=496)	85.90 +-15.13	82.08+-14.95	94.22+-15.66
Last (achieved)(n=480)	71.68 +-11.27	71.92+-14.19	80.17+-8.53
Other Agents			
ACEi	469(93.8%)		
MRA	449(89.8%)		
Cardiac Glycoside	63(12.6%)		
Statin	206(41.2%)		
ISMO	148(29.6%)		
Hydrallazine	72(14.4%)		
Thiazide	73(14.6%)		
CCB	47(9.4%)		

Values are Mean +-SD or n (%)

IHD, ischaemic heart disease; HT, hypertension; PPCMO, peripartum cardiomyopathy; HIV, human Immunodeficiency virus; NYHA, New York Heart Association classification; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; HR, heart rate; BPM, beats per minute; ACEi, angiotensin converting enzyme inhibitor; MRA, mineralocorticoid receptor antagonist; ISMO, isosorbide mononitrate; CCB, calcium channel blocker

Table 2 – Categorisation of Beta Blocker Dose

Total Beta Blocker dose (Daily)			
B-Blocker	**Low Dose Range**	**Moderate Dose Range**	**Target Dose Range**
Bisoprolol	<5mg	5mg to <10mg	10mg
Carvedilol	<25mg	24mg to <50mg	50mg
Metoprolol	<100mg	100mg to <400mg	400mg
Atenolol	<50mg	40mg to <100mg	100mg

Table 3 – Reasons for Not Achieving Beta Blocker Target Dose

Reason for Not at Target	No BB Group	Low Dose Group	Moderate Dose Group	Total	% (n=500)
Syncope	1	2	0	3	0,60%
Hypotension	0	0	1	1	0,20%
Cardiac Decompensation	0	0	4	4	0,80%
Raynauds / PAD	0	0	0	0	0,00%
Bradycardia	6	22	78	106	21,20%
Bronchospasm /Breathlessness	3	2	2	7	1,40%
Fatigue	0	3	2	5	1,00%
Logistical					
Non-Compliance	0	4	12	16	3,20%
Uptitration phase	1	12	21	34	6,80%
Unknown	0	5	20	25	5,00%
Total	11	50	140	201	40,20%

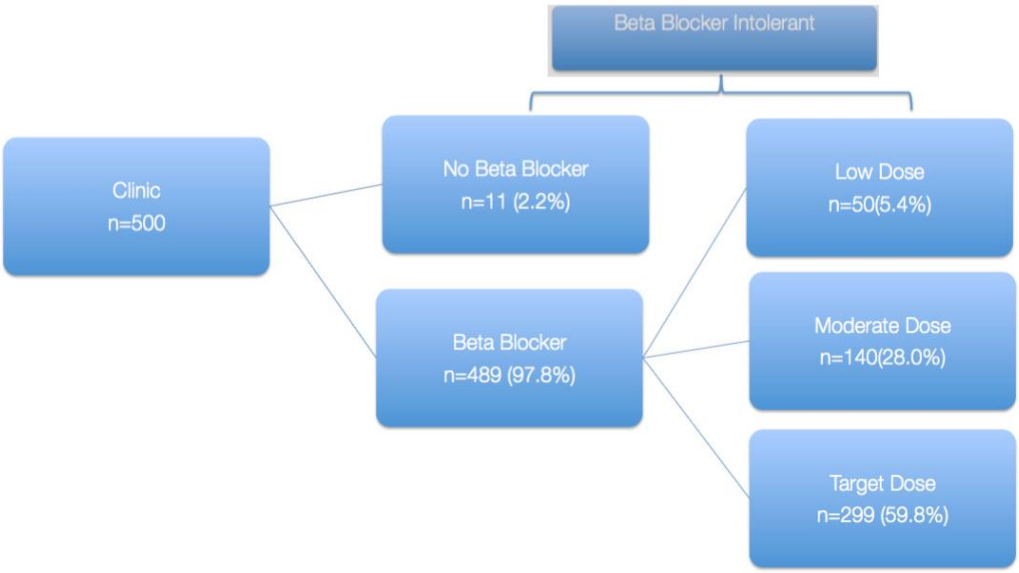


Figure 1 - Beta Blocker Target Dose Stratification

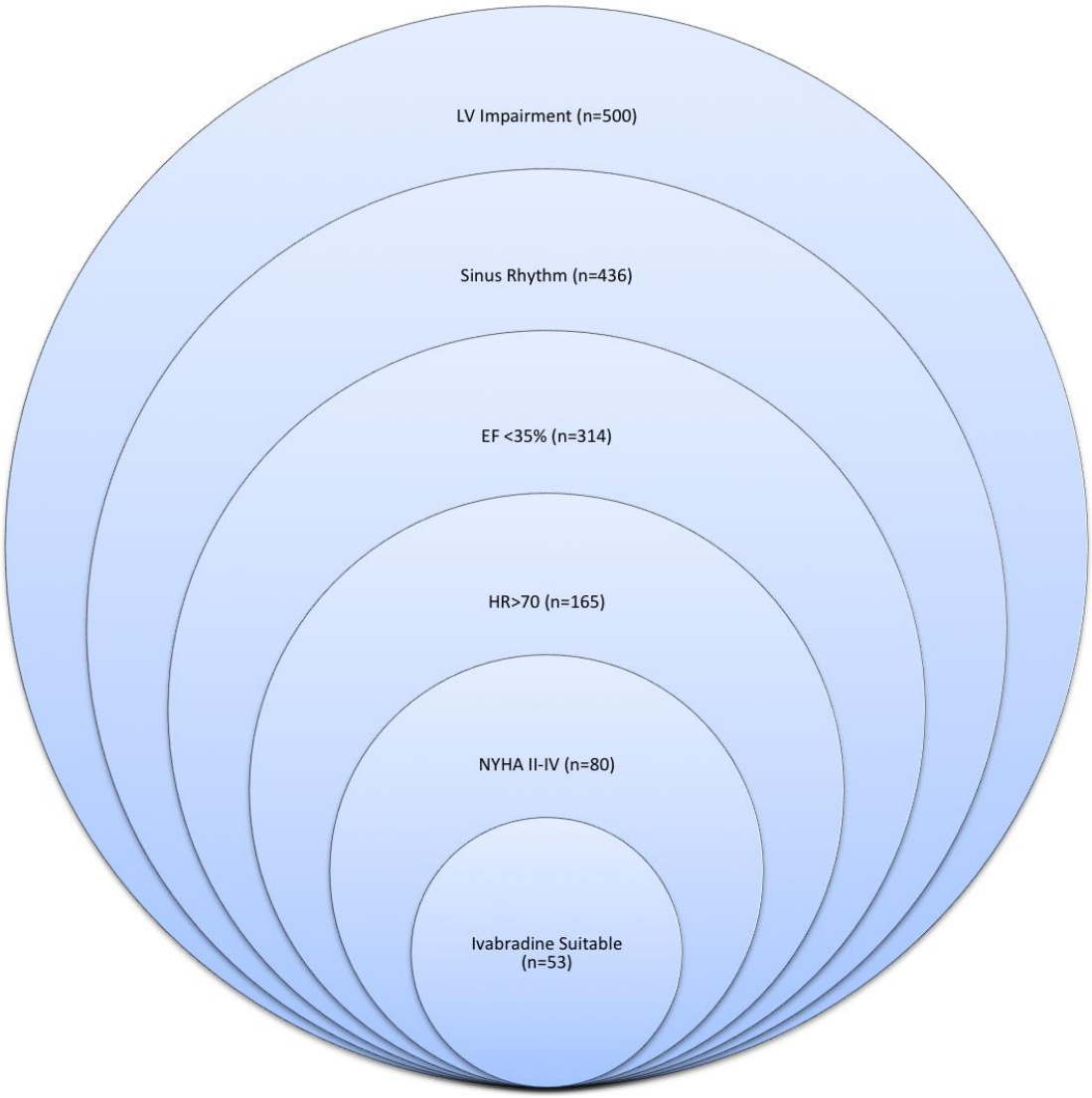


Figure 2 – Relative Proportion of Patients Suitable for Ivabradine

CHAPTER 3: APPENDICES

3.1 Ethics Clearance Certificate

R14/49 Dr Jonathan Bolon et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140611

NAME: (Principal Investigator)	Dr Jonathan Bolon et al
DEPARTMENT:	Cardiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Beta-Blocker Target Dosing and Tolerability in a Dedicated Heart Failure Clinic- Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	27/06/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Pravin Manga
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/02/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.2 Data Collection Sheet(s)

Confidential

MMED Data Input

Beta Blocker Target Dosing and Tolerability _____

Date of Registration _____

First Name _____

Last Name _____

Date of birth _____

Age (years) _____

Gender
- ○ Male
- ○ Female

Race
- ○ Black
- ○ White
- ○ Indian
- ○ Coloured
- ○ Asian
- ○ Not Reported

Date of Diagnosis _____

Follow up Duration(months) _____

Diagnosis 1
- ○ IHD
- ○ Non-IHD

Cause of Heart Failure
- ○ HT
- ○ HIV
- ○ PPCMO
- ○ Chemo
- ○ Alcohol
- ○ Myocarditis
- ○ Other

History of:
- ☐ MI
- ☐ Hypertension
- ☐ Diabetes Mellitus
- ☐ Hyperlipidaemia
- ☐ CVA
- ☐ PAD
- ☐ CAD
- ☐ COPD
- ☐ Asthma
- ☐ Atrial Fibrillation
- ☐ Depression
- ☐ Hyperthyroidism
- ☐ Hypothyroidism
- ☐ Asthma
- ☐ HIV

Beta Blocker
- ○ Carvedilol
- ○ Atenolol
- ○ Bisoprolol
- ○ Metoprolol

HR Base _____

HR Last _____

HR Change _____

HR % Change _____

Reasons(s) for Not at Target
- ☐ Syncope / Pre-syncope
- ☐ Hypotension
- ☐ Cardiac decompensation
- ☐ Raynauds or PAD
- ☐ Bradycardia
- ☐ Bronchospasm
- ☐ Fatigue
- ☐ Logistical
- ☐ Other

eGFR base _____

eGFR last _____

Na++ base _____

Na++ last _____

EF Base _____

EF Last _____

Beta Blocker Dose (Carvedilol) _____

% of Target (Carvedilol) _____

Beta Blocker Dose (other) _____

% of Target (other) _____

Other Treatment
- ☐ ACEi / ARB
- ☐ MRA
- ☐ Cardiac Glycoside
- ☐ Statin
- ☐ Hydrallazine
- ☐ ISMO
- ☐ Thiazide Diuretic
- ☐ CCB
- ☐ Devices (CRT / ICD)

Lasix Daily _____

SBP Base _____

SBP Last _____

6MW Base _____

6MW Last _____

NYHA Base
- ○ I
- ○ II
- ○ III
- ○ IV

NYHA Last
- ○ I
- ○ II
- ○ III
- ○ IV

General Comments

Comments _____

3.3 Turn-it-in Report

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