Does beta-blockade improve cardiopulmonary exercise testing variables and other related static cardiac function measures? Systemic review, meta-analysis and prospective interventional drug trial.

Improving cardiac function in high-risk surgical patients (ICAF-beta): Cardiopulmonary exercise testing, biomarkers and beta-blockade.

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Abstract

**Background:** Beta-blocking agents have demonstrated: an increased survival, improved ventricular contractility and provide symptomatic relief in chronic heart failure (CHF). Cardiopulmonary exercise testing (CPET) has prognostic value for event-free survival in CHF and surgical populations. Therefore, it is reasonable to assume that the improvement seen with beta-blockers would be measurable with CPET. However, debate continues around the effect of beta-blockade on CPET variables, exercise capacity and perioperative outcomes. The objectives were to assess the effect of de novo beta-blockade on CPET variables and related static cardiac function measures in all populations and on a targeted high risk population scheduled to have non-cardiac surgery.

**Method:** Literature searches were conducted using the MeSH terms: adrenergic beta-antagonists, exercise and clinical trials. Studies were eligible if they were interventional trials investigating de novo beta-blockade and included before and after treatment breath-to-breath CPET analysis. Meta-analysis was conducted using a random effects model.

We also designed a prospective proof-of-concept case series study with MHRA and ethical approval. Baseline and post-treatment CPET, echocardiogram and NT-proBNP were conducted on high risk surgical patients treated with a minimum of 10 days bisoprolol 2.5mg

**Results:** 16 of 222 potentially relevant studies met the inclusion criteria with a total of 795 patients. VE/VCO₂ changed by -1.17 (CI -2.33-0.0), anaerobic threshold changed by 0.35ml/kg/min (CI -0.26-0.97), peak oxygen consumption changed by
0.67ml/kg/min (CI -0.14-1.48), and ejection fraction improved by 6.72% (CI 4.93-8.51).

**Conclusions:** Disparity exists between improved cardiac function and symptoms after beta-blockade compared to static objective functional capacity assessment with CPET. These CPET variables may be inadequate to assess the effect of beta-blockade. Perhaps beta-blockade improvements are weighted to disease severity and therefore targeted therapy is desirable. The ongoing case study will conclude whether beta-blocker treatment can effect VE/VCO₂ in high risk patients undergoing non-cardiac surgery.
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Author’s declaration

‘I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised’.
Chapter 1. Introduction

Perioperative beta-blockade

The perioperative management of patients who are taking beta-blockers is complex and has seen many changes in clinical opinion over time. Initial management was to cease beta-blocking agents prior to surgery to potentially avoid intraoperative hypotension, opinion then changed to continuing beta-blockade throughout the perioperative period as this was then thought to reduce the increased myocardial oxygen demand seen with the surgical stress response (Sear et al., 2008). The American College of Cardiology/American Heart Association (ACC/AHA) in 1996 suggested that beta-blockade should continue in patients who are already taking them preoperatively, but they pointed to the lack of high quality evidence to base this decision on (Jørgensen et al., 2018). Over the next decade, interventional trials had mixed outcomes of either significantly reducing cardiac deaths with the use of beta-blockers or conversely showed an increased risk of death.

The PeriOperative ISchemic Evaluation (POISE) trial published in the Lancet (Devereaux et al., 2008) overall demonstrated harm. They reported a reduction in the incidence of myocardial infarction and arrhythmias with the administration of metoprolol 100mg BD PO to all patients deemed at risk of coronary disease. They also reported an increase in excess deaths, 8 per 1000 treated and excess strokes 5 per 100 treated. These adverse outcomes do not support the use of de novo beta-blockers for all preoperative patients at risk of coronary disease. However the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) trials in 1999 and 2009 showed a significant reduction in cardiac
deaths, 97% reduction with beta-blockade (Poldermans et al., 1999, Poldermans et al., 2009). These results were later discredited due to scientific misconduct (Jørgensen et al., 2018).

Devereaux et al., (2005) conducted robust meta-analysis and systematic review of perioperative beta-blocker therapy in non-cardiac surgery. They included 22 randomised control trials. They concluded that perioperative beta-blocking therapy may be associated with a decreased risk of major complications but there is increased risk of bradycardia and hypotension needing treatment. Beta-blocking agents cause both bradycardia and hypotension; this can be easily treated during surgery so this primary end point may be a less meaningful outcome measure in terms of clinical importance than the end point of major perioperative cardiovascular events and death. Devereaux et al., (2005) conducted power analysis calculations to assess whether the sample size was large enough to detect a plausible treatment effect. They report they would require a sample size of 6124 patients- the study only includes 1152 patients and is therefore underpowered to draw meaningful conclusions from. The authors assert that the current body of evidence is insufficient and inconclusive. Interestingly, the majority of studies gave beta-blockers on the morning of surgery or during induction. Subset analysis of studies which titrated treatment in the perioperative period would help to inform whether that practice is preferable- with the caveat that the set of data is too small to make meaningful conclusions from.

Observational trials have demonstrated a survival benefit in patients taking beta-blockers compared to those who are not. These results are based on hundreds of thousands of patients but do have an observational design using regression analysis so
the results need to be interpreted with that in mind (Jørgensen et al., 2018). Interestingly, they show a disease severity response relationship, where the healthier patients have worse outcomes on beta-blocking agents but the more severe a patients cardiovascular disease is the more they benefit from beta-blocking treatment.

There is therefore uncertainty of the benefit of beta-blockade. These results in observational studies coupled with the worsening of outcomes in international trials where low risk patients received beta-blockers adds more weight to the argument that beta-blockade should be targeted to at risk patients of whom the benefit out weights the risk, for example those who have exercise induced cardiac ischemia (Wijeysundera et al., 2010). Assessing which patients are at high risk and management of their medications is part of the preoperative assessment. Assessing which patients are high-risk is complex and will be discussed in chapter 2.2.

The detrimental effects of beta-blockade may be due to the agent given or to the time scale in which they are introduced however this needs to be discussed in the context of practicality. There are clinically important implications for patients who are hypotensive post operatively. The majority of the strokes in the POISE trial were associated with perioperative hypotension. It is interesting to note that patients received the maximum dose of metoprolol on the day of surgery. These patients were blocker naïve and received this dose if their heart rate was above 50bpm and systolic blood pressure was above 100mmHg. This practice therefore is not advocated in current guidelines (Fleisher et al., 2014).
Preoperative risk assessment

Despite an aging population and an increasing co-morbidity burden on patients postoperative mortality and major morbidity is relatively low. The risk of death per surgical admission ranges from less than 1% (NCEPOD, 2011) to 4% in the European Surgical Outcomes study (Pearce et al., 2012). However, amongst some groups of patients the risk of death is dramatically higher. Therefore, preoperative identification of this group of patients who are at greater risk is of upmost clinical importance. There are various ways of assessing fitness which range in complexity and prognostic ability, these will be discussed in detail in chapter 2.2. Cardiopulmonary Exercise testing (CPET) is an objective assessment of cardiopulmonary fitness and therefore a way of assigning postoperative risk (Balady et al., 2010). CPET is an objective measure of whether pharmacological treatments are of benefit in patients with heart failure (Balady et al., 2010).

This leads to the concept of the “high risk patient”. Eighty percent of the postoperative deaths are from a small group (10%) of high risk patients (Pearse et al., 2006). Preoperative risk stratification is therefore important to identify patients who are at high risk to: optimise their condition preoperatively, improve intraoperative care, and improve the use of postoperative resources for patients undergoing surgery (Snowden et al., 2010, Struthers et al., 2008). This thesis will explore the idea of beta-blockade being used as a method of optimising patients medically in the preoperative period. It is recommended that all patients scheduled for major surgery have their functional capacity assessed to identify underlying non diagnosed cardiopulmonary
deficiency or pathology (Mukherjee and Eagle, 2003). How one labels a patient as high risk is difficult and will be discussed in more detail later.

The NCEPOD report shows that the UK is being outperformed by other countries (NCEPOD, 2011, Mcgrath, and Wilkinson 2015). This is echoed in the European Surgical Outcomes Study (EuSOS) which showed a controversially high post-operative mortality and a marked difference between countries (Pearse et al., 2012). The NHS has a significantly higher mortality when compared to hospitals of a similar size and patient population in the USA. There is an eight fold increased mortality in low risk patients (predicted 0-5% group) and a three-fold increased mortality in higher risk group (predicted 11-20% group) when comparing the UK to the USA (Whiteley et al., 1996).

**Chronic heart failure patients as a high risk cohort**

Patients with chronic heart failure (CHF) are one such group where there is an increased risk of major complications and death (Hernandez, et al., 2004). The Rotterdam study was designed to calculate the prevalence, incidence, and lifetime risk of CHF in a cohort of patients followed up for 10 years (Bleumink et al., 2004). The prevalence was higher in men than women, 8.0% and 6.0% respectively. It increased with age from 0.9% in patients aged 55–64 to 17.4% in patients over 85 years old. The combined incidence was 14.4/1000 person-years (95% CI 13.4–15.5). This was again higher in men and women at 17.6/1000 man-years, (95% CI 15.8–19.5) to 12.5/1000 woman-years (95% CI 11.3–13.8). Incidence rate increased with age from 1.4/1000 person-years in those aged 55–59 to 47.4/1000 person-years the over 90s.
Lifetime risk was 33% for men and 29% for women at the age of 55. Survival after incident heart failure was 86% at 30 days, 63% at 1 year, 51% at 2 years and 35% at 5 years of follow-up. By virtue of an aging population and increasing incidence of CHF in the elderly there is an increase in patients with CHF having surgery. Amongst patients undergoing non-cardiac surgery CHF is associated with significantly increased 90 day mortality (Lerman et al., 2019). Interestingly, that is with patients who have and who do not have symptoms.

The EuSOS gave an odds ratio of 2.10 (CI 1.78–2.48) of in hospital death compared to hospital discharge for CHF patients. To put that in perspective, it is the second highest risk factor for death, behind cirrhosis, and higher than metastatic cancer and chronic obstructive pulmonary disease (COPD) (Pearce et al., 2012). The number of patients with CHF who are undergoing surgery is predicted to increase significantly over the next two decades meaning that one role of the perioperative physician is to identify these patients and aim to optimise their treatment (Hernandez, et al., 2004).

Patients who develop major postoperative complications, such as those individuals with heart failure, often demonstrate reduced global or local tissue oxygenation secondary to inadequate cardiorespiratory function (Wilson et al., 2010). In physiological terms, the ability to perform physical activity is determined by the capacity of the cardiorespiratory system to deliver the oxygen to the mitochondria remove waste products such as carbon dioxide (Balady et al., 2010). This is a product of external respiration, transport of blood via the cardiac system and internal respiration. The ability to complete physical activity is complex and involves the
interaction between cardiorespiratory system, vascular system, muscle and cognitive and motional components.

**Preoperative risk assessment tools and CPET**

CPET is an objective way to quantify a patient's cardiorespiratory function, i.e., measure functional capacity. CPET provides breath-to-breath gas analysis alongside ECG and blood pressure measurement at rest and during exercise. The theoretical background to CPET and method of conducting a test is discussed fully in chapter 2.1.

CPET was initially used in sports medicine to measure peak oxygen consumption (Kleber et al., 2004). CPET is now being used for many surgical and medical reasons to provide prognostic and diagnostic data (Balady et al., 2010). It is used preoperatively to guide eligibility for major surgery, to identify high-risk patients, as a predictor of severe cardiovascular events, and to guide resource allocation. It is used medically to investigate unexplained exertional dyspnoea, as a prognostic indicator for patients with cardiac disease, to gauge response to therapy and to optimise therapeutic interventions (Wilson et al., 2010, Malhorta et al., 2016, Guazzi et al., 2016).

**Parallels in the CHF population**

In CHF populations, the ventilatory efficiency for carbon dioxide (VE/\(\dot{V}CO_2\)) is clinically useful as it has a strong prognostic value for mortality and morbidity (Arena
et al., 2004, Arena et al. 2007). The variables of poor prognosis and increase VE/\dot{V}CO_2 are directly proportional. VE/\dot{V}CO_2 is elevated in CHF, COPD (Teopompi et al., 2014) and Ischemic heart disease and is normal in patients who are obese or deconditioned (ATS/ACCP, 2003). This suggests that it is marker of pathology rather than poor cardiovascular conditioning. Peak \dot{V}O_2 is the most widely reported prognostic variable in CPET and it was initially the gold standard prognostic tool in CHF patients. However, many studies have demonstrated that VE/\dot{V}CO_2 has improved prognostic abilities to that of peak \dot{V}O_2. (Arena et al., 2007 [2], Woods et al., 2011). VE/\dot{V}CO_2 has the benefit over peak \dot{V}O_2 of not relying on patient effort or investigator bias as it is a submaximal test (Woods et al., 2011). Cox multivariate analysis has shown VE/\dot{V}CO_2 slope to outperformed peak \dot{V}O_2 in predicting mortality, event free survival and hospitalisation in CHF patients (Arena et al., 2004).

VE and \dot{V}CO_2 are linked as a rise in CO_2 production in anaerobic metabolism causes a rise in minute ventilation. An abnormally raised VE/\dot{V}CO_2 is essentially a measure of ventilation/perfusion mismatching. In heart failure this is demonstrated when there is a disproportionate rise in ventilation to compensate for an inadequate perfusion. An abnormal result significantly correlates with a reduced cardiac output (Balady et al., 2010) and therefore reduced pulmonary perfusion. The VE/\dot{V}CO_2 slope is inversely proportional to the cardiac output (Arena et al., 2007). A VE/\dot{V}CO_2 above 34ml/kg/min is classed as abnormal (ATS/ACCP, 2003).

NICE advocate the use of beta-blockade as first line therapy in CHF as there is overwhelming evidence for its use (NICE, 2018). In large randomised control trials in CHF populations beta-blockade demonstrates: an increased survival, improved rate
control and rhythmic control, improved ventricular contractility and provide symptomatic relief (Chatterjee, et al., 2013, Lechat et al., 1998). Pharmacological management of CHF is targeted to breaking the pathophysiological spiral of decline in the failing heart by blocking one or more of the maladaptive processes (McDonagh et al., 2011). One therapeutic mechanism of action is antagonism of the sympathetic nervous system as this is overly activated in CHF. By antagonising the cardiac beta-receptors the immediate consequence is of reduced heart rate, increasing diastole and therefore increased filling time and end diastolic volume (McDonagh 2011, Ladage et al., 2013).

Malhorta et al., (2016) in their review of CHF and CPET suggest that the future direction of research of CPET is identifying patients who are at risk of cardiovascular disease, including CHF. With the hope of being able to risk strategy, prognosticate and offer treatment. They suggest that CPET is a more complete tool than relying on risk factors or other static single organ tests. ICAF- beta study meets this remit aiming to identify those with a raised VE/ VCO₂ who otherwise may not have any formal diagnosis of cardiorespiratory disease.

**Thesis hypothesis**

CPET predicts risk in CHF, CHF is the major risk for surgery and hence CPET predicts risk from surgery. Raised VE/VCO₂ predicts risk in CHF and presurgical patients. Therefore if we can identify a high-risk group (those with a raised VE/VCO₂) is this a marker of CHF and therefore amenable to treatment with beta-blockade.
This trial will test the hypothesis that pre-surgical patients with a raised have a ventilation/perfusion mismatch, due to an exaggerated ventilatory response and poor pulmonary perfusion i.e. the same pathophysiology as CHF, and would therefore benefit from beta-blockade. This would be evident in a reduction in VE/V̇CO₂ on retesting post beta-blocker treatment.

Patients with a lower VE/V̇CO₂ have an improved prognosis in the CHF population and postoperative population (Wilson et al., 2010, Sarullo et al., 2010). What is unknown is whether reducing a patients VE/V̇CO₂ with beta-blockade will improve morbidity and mortality associated with major abdominal surgery.

**Research questions**

Does de-novo beta-blockade improve CPET variables in all patient populations? Investigated using a systematic review and meta-analysis.

Does a course of de-novo bisoprolol 2.5mg (minimum of 10 days) reduce the VE/V̇CO₂ of high risk surgical patients? Investigated using the ICAF-beta interventional drug trial.

Does a course of de-novo Bisoprolol 2.5mg improve the oxygen pulse relationship and anaerobic threshold of high risk surgical patients and as such reduce the surgical risk score? Investigated using the ICAF-beta interventional drug trial.
**Null hypothesis:** There will be no change in VE/\(\dot{V}CO_2\) or risk profile on retesting in any patient cohort.

**IACF Beta Study aim**

In this study, we aim to investigate whether administering Bisoprolol (2.5mg OM) to patients with objective evidence of impaired VE/\(\dot{V}CO_2\) (value 34 or greater) on CPET improves cardiac function, and hence has the potential to reduce surgical risk for patients.

**Hypothesis:** Beta-blockade with Bisoprolol can improve the exercise testing results (AT and VE/ \(\dot{V}CO_2\)) and therefore lower the postoperative risk profile of high risk surgical patients.
Chapter 2. Literature Review

Introduction

This review has two different areas of interest. Firstly, a broader topic will be investigated using a systematic review and meta-analysis to explore the effects of beta-blockade on CPET variables in all adult populations. The meta-analysis will then focus on the effect of de novo beta-blockade on CPET variables before and after treatment. This will lead to a more specific review of topic of beta-blockade and perioperative risk stratification in preoperative surgical patients.

This second more specific question will be explored by critically appraising the background evidence which has informed the ICAF-beta study. There are three main topics. Firstly, the topic of preoperative beta-blockade in patients undergoing non-cardiac surgery. Secondly, the topic of preoperative risk assessment. Thirdly, the topic of CHF and how the pathophysiology underpins the rationale for the ICAF-beta study.

The ICAF-beta literature search was conducted with MEDLINE searched using the OvidSP interface on 18/08/17 for the period 1946 to Present. The full search 23 step strategy is shown in appendix 1. This search yielded 15 papers were found dating between 1980 and 2015. The search was not limited to the modern era of breath-to-breath CPET analysis (1990) as older studies have used more invasive measures of cardiac function, such as the right and left sided heart catheterisation which is can measure some of the physiological effects of beta-blockade and may not now gain ethical approval due to the risks associated with such invasive monitoring. Backward
chaining was used to yield a larger number of related articles. Grey literature was searched. The Prospero database was searched for any registered unpublished systematic reviews.

There were no studies found with the same study aim and primary outcome measure of change VE/\(\dot{V}CO_2\) with beta-blockade in pre-operative non-cardiac surgical patients. However, VE/\(\dot{V}CO_2\) was reported in one study using de novo Bisoprolol in preoperative non-cardiac surgical patients (West, et al., 2015). This study involved patients with abdominal aortic aneurysms (AAA) which may be amenable to surgery, so by definition are pre-surgical patients. However, these patients have a much longer observational period and in fact may not even have surgery. The ICAF-beta study investigates AAA patients but also includes preoperative patient who may have malignancy and as such surgery is expedited. No other study has investigated this population. There are many other studies which have detailed the effect of beta-blockade on fitness either measured by CPET or other means.

The systematic review literature search was conducted on 28/08/18 and repeated on 08/07/19 with MEDLINE searched using the OvidSP interface for the period of 1990 to Present. This was to investigate the wider topic of beta-blockade and fitness. This was not limited to the perioperative period as most of the work thus far has focused on patients with CHF and included non-CPET measures of fitness. This is documented fully in chapter 2.1. Appendix 2 and 3 show the full search strategy and consort diagram for studies screened and selected for review. There are no other published systematic review or meta-analysis with the same specific focus of VE/\(\dot{V}CO_2\) and beta-blockade.
Ismali et al., (2013) published a systematic review and meta-analysis comparing the effects of exercise training in CHF patients who are and who are not taking beta-blockers. They reported that VE/\( \dot{VCO}_2 \) in the exercising group taking beta-blockers is significantly improved. This study is different to this systematic review as they investigate fitness regimes as the treatment intervention and the populations were beta-blocked patients compared to those without beta-blockade. This is interesting for clinicians who are considering pre optimisation with exercise for patients who are beta-blocked but does not investigate whether de novo beta-blockade will improve fitness.

Abdulla et al (2006) conducted a systematic review and meta-analysis of studies comparing beta-blockade to placebo with the primary outcome of NYHA classification and exercise tolerance in CHF patients. They showed beta-blockade significantly improved NYHA classification and improved exercise tolerance measured by improved exercise time. They also concluded that there was no statistically significant improvement in peak oxygen uptake and no statistically significant reduction in 6 minute walk test. This mixed picture shows a pattern of some objective tests such as 6 minute walk and peak oxygen consumption worsening while symptoms in the patient improving and their ability of carry out prolonged exercise improving.

Montero and Flammer (2017) conducted a meta-analysis on NYHA and peak \( \dot{VO}_2 \) measured by CPET in CHF populations. This meta-analysis was found on the second literature search, it has a focus on peak \( \dot{VO}_2 \) and does not investigate other CPET
variables or measures of ejection fraction. They conclude that peak \( \dot{V}O_2 \) does not improve but NYHA does. There is a consistent message from retrospective work and systematic reviews that CPET or measures of exercise tolerance does not improve on beta-blockers but symptoms and quality of life do. Therefore this thesis is well placed to examine other CPET variables (\( VE/\dot{V}CO_2 \), and AT) along with static cardiac function measurements.

The systematic review and meta-analysis in chapter 2 is well placed to investigate the effect of de novo beta-blockade on all subjects with the objective testing of breath-to-breath analysis of CPET.
Chapter 2.1. Systematic Review and Meta-analysis

Introduction:

Randomised controlled trials in subjects with CHF have shown that beta-blockers increase event free survival, improve heart rate and rhythmic control, increase ventricular contractility and provide symptomatic relief (Chatterjee, et al., 2013, Lechat et al., 1998). Due to these effects The National Institute for Heath and Care Excellence advocate the use of beta-blockade as first line therapy in CHF (NICE, 2018). However, there is no consensus on the effect of beta-blockers have on exercise capacity (Ladge et al., 2013).

Although there are various methods of assessing exercise capacity which range in complexity, prognostic ability and practicality cardiopulmonary exercise testing (CPET) is the gold standard of assessing cardiopulmonary fitness (Moran et al., 2016), and provides an integrated quantitative evaluation of the cardiorespiratory system between rest and maximal exercise (West et al., 2015). CPET measured variables such as anaerobic threshold (AT), peak oxygen consumption (peak VO$_2$) and ventilatory equivalent for CO$_2$ (VE/VO$_2$) have clinical utility in predicting event free survival in CHF population (Arena et al., 2004, Arena et al. 2007).

CPET is also used in other patients groups such as those with COPD, obesity, ischaemic heart disease, cystic fibrosis, and also healthy subjects such as elite athletes (Guazzi et al., 2016 and Perim et al., 2011). CPET can be also used for preoperative assessment in a range of surgical specialties, in which it demonstrates predictive utility for mortality and mortality. As CPET is used to evaluate a patient’s cardiorespiratory response to the stress of exercise, it therefore also evaluates a
patient’s physiological reserve to deal with the physiological stresses of major surgery and postoperative complications (Wilson et al. 2010 and Wilson et al., 2019).

Gläser et al., studied 1203 volunteers, who were without structural heart disease or pulmonary disease, who underwent an incremental CPET. They used retrospective regression analysis and they suggest the chronic use of beta-blockers has minimal effect, if any, on CPET variables (Gläser et al., 2010), with no change to oxygen utilisation variables such as peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT (Gläser et al., 2010 and West et al., 2015). The implication is that CPET can be conducted on or off beta-blockade, and hence current guidelines are for patients to continue beta-blockers prior to CPET. It has been reported that beta-blockers improve cardiac function but do not change CPET variables (Gläser et al., 2010). This statement appears contradictory for two reasons; firstly CPET is a measure of cardiopulmonary function and hence improving ventricular functions should translate into an improvement in CPET variables. Secondly, CPET variables are validated for CHF prognostication and beta-blocker therapy improves prognosis in this CHF population. Therefore if a patient gains an improved prognosis by beta-blockade then it is plausible to assume that it would be demonstrated as an improved CPET result.

This study aimed to examine, using meta-analysis of clinical trials rather than a retrospective analysis, the association between CPET variables and cardiac function and the administration of de novo beta-blockade.
Population and intervention:

The population of interest in this review is all adult patients who underwent CPET as part of an interventional trial. The intervention is de novo beta-blockade with any beta-blocking agent. The scope of this review is to examine the class effect of beta-blockade rather than to investigate the superiority of one drug.

Comparator and outcomes:

The comparator for this review is cardiopulmonary fitness before and after beta-blockade assessed by CPET variables and cardiac imaging. The CPET outcome measures of interest are:

1. VE/\dot{V}CO_2, which is a submaximal variable quantifying ventilatory efficiency and defined by the slope of CO_2 production to the minute ventilation.
2. AT, which is a submaximal measure of cardiorespiratory reserve defined as the rate of oxygen consumption at the point at which aerobic metabolism begins to be supplemented by anaerobic metabolism.
3. Peak VO_2 defined by the maximal oxygen utilisation in a given CPET suggesting the true limit of exercise tolerance. (Balady et al., 2010).

The cardiac function measure of interest was EF measured by echocardiography, cardiac MRI or radionuclide ventriculography.
CPET background and variables of interest

CPET involves a patient performing exercise whilst their cardiorespiratory function is being measured. The patient has baseline oxygen saturation measurements, blood pressure alongside continual electrocardiographic (ECG) analysis. The patients inspired and expired gases are measured in terms of volume, flow and gas constituents to measure breath-to-breath oxygen consumption (V̇O₂), carbon dioxide output (V̇CO₂), and ventilation (VE) (Balady et al 2010). The patient then undergoes graded exercise, usually increasing in intensity until exhaustion. Exercise is conducted using either a treadmill which can increase in speed and gradient or a cycle ergometer which is electrically braked to provide the desired watt resistance.

During the exercise test there is real time analysis of cardiac function via ECG waveform analysis. Pulse oximetry is applied and measures oxygen saturations either before the test or during the test. There is breath-to-breath gas analysis from which the following measurements can be calculated: Maximum aerobic capacity (maximal oxygen uptake or peak oxygen uptake- peak V̇O₂), Ventilatory or anaerobic threshold (AT), respiratory exchange ratio, minute ventilation-carbon dioxide output relationship (VE/V̇CO₂). By using a pneumotacograph respiratory flow is also calculated breath-to-breath for respiratory function.

The optimal exercise time is 8 to 12 minutes and a protocol should be chosen to allow a patient to reach maximum effort in this time (Balady et al., 2010). Treadmill testing gains a higher peak V̇O₂ test than bicycle ergometry as it does not rely so heavily on quadriceps strength. The cycle test can terminate early due to muscle power fatigue.
rather than the true limit of cardiovascular endurance. Bicycle ergometry is a preferred modality in patients with poor mobility as it is seated (Kleber et al., 2014). The protocol can be a ramped test or an incremental test. Ramping is a set continual increased in watt per minute. An incremental test has flat stages of effort which then step up to the next level of higher intensity. The Naughton protocol uses a treadmill which incrementally increases in speed and gradient every two minutes which is the equivalent of 1 MET (metabolic equivalent for task) (Kleber et al., 2014). Protocols with large stage to stage increments have a weaker relationship to \( \dot{V}O_2 \) and work rate (Balady et al., 2010). For patients with mild disease a Bruce protocol may be used as it will provide an opportunity to gain peak \( \dot{V}O_2 \) in 8-12 minutes (Kleber et al., 2014). The Bruce protocol uses a 3 minute staged progression of exercise (Bruce et al., 1973). The most widely used protocol is the used protocols are the individualised ramping, Naughton, and the Balke and Ware protocols. The York Teaching Hospitals NHS Foundation Trust uses an individualised ramping protocol. The rationale for the selected protocol in the ICAF-beta trial is explained in detail in chapter 3.

CPET has been described as the gold standard of cardiopulmonary fitness assessment and its role in CHF and surgical risk prediction are discussed further in chapter 2.2 (Moran et al., 2016).

*M Maximum \( \dot{V}O_2 \) and peak \( \dot{V}O_2 \)*

Maximum \( \dot{V}O_2 \) is the measure that defines the maximum limits of the cardiopulmonary system, i.e. the point at which the patient’s physiological limit has been reached. Historically this was regarded as the best measure of cardiorespiratory
fitness. Maximum $\dot{V}O_2$ is defined as a plateau in $\dot{V}O_2$ between the final two exercise work rates and requires maximal sustained effort for a set time period (Balady et al., 2010). As this is a subjective measure and is rarely observed in patients with cardiopulmonary pathology a submaximal term, peak $\dot{V}O_2$, is often reported to define exercise capacity (Balady et al., 2010). Maximum $\dot{V}O_2$ is rarely observed in non-athletes and therefore may be unachievable in the elderly or patient with cardiovascular disease or may even be unsafe. Maximum $\dot{V}O_2$ and peak $\dot{V}O_2$ are used interchangeably in the literature. However, Maximum $\dot{V}O_2$, by definition has to be a maximal test. When the test is not maximal the term peak $\dot{V}O_2$ should be used as the maximum oxygen consumption in that given test. The criteria used to define a maximal test are described in chapter 3 “CPET Procedure and Rationale”. For the purposes of this review, meta-analysis and thesis the term peak $\dot{V}O_2$ was used.

Peak $\dot{V}O_2$ is measured in ml/min but can also be expressed as ml/kg/min to allow for subject to subject comparison. Patients with a larger mass with have a larger $\dot{V}O_2$ just by virtue of having more mass (Balady et al., 2010). Without CPET peak $\dot{V}O_2$ can be estimated at peak exercise using the following formula: Peak $\dot{V}O_2$ = (Heart rate x Stroke volume) x [C(arterial-venous)O$_2$].

$\dot{V}O_2$ may be estimated and expressed in METs (metabolic equivalents) which is the $\dot{V}O_2$ divided by 3.5 (Jette et al., 1990). Alternatively, other forms of exercise which are the limit of a patients status, ie walking up stairs, may be estimated using the METs system which predicts the $\dot{V}O_2$ for that intensity. The American Thoracic Society/American College of Chest Physicians (ATS/ACCP, 2003) report the usual response patterns of CPET variables for specific diseases. In terms of peak $\dot{V}O_2$, It is
decreased in CHF, COPD, interstitial lung disease, pulmonary vascular disease, and deconditioning. Peak $\dot{V}O_2$ is also decreased in obesity expressed in ml/kg due to excess weight but may be normal when for ideal body weight is used as the denominator. In CHF populations peak $\dot{V}O_2$ is prognostic of event free survival and mortality. Keteyian et al. (2016) studied 2100 CHF patients enrolled on the HF-ACTION trial. All CPET variables (AT, peak $\dot{V}O_2$, VE/\dot{V}CO$_2$ slope) and were predictive of mortality. The authors demonstrated an inverse relationship between mortality and peak $\dot{V}O_2$ and concluded that in men peak $\dot{V}O_2$ was the strongest single predictor for mortality. Interestingly, they found a significant sex differentiation in terms of risk and peak $\dot{V}O_2$. Men who had a peak $\dot{V}O_2$ below 10.9ml/kg/min had a 1 year mortality of 10% but women had to have a peak $\dot{V}O_2$ 5.3ml/kg/min for the same 1 year mortality. It is known that women have a lower peak $\dot{V}O_2$ but this sex difference is not adjusted for in the risk calculation (Keteyian et al., 2016).

Balady et al., (2010) quote a peak $\dot{V}O_2$ figure of $<14$ml/kg/min as criterion for consideration of cardiac transplant in patients with systolic heart failure. Patients who have a peak $\dot{V}O_2 >14$ml/kg/min pre-operatively had a 94% one year survival. Of the patients who had cardiac transplantation, there was a marked difference in one year survival between the cohorts who had a peak $\dot{V}O_2$ below 14ml/kg/min and those with a peak $\dot{V}O_2$ above 14/ml/kg/min. The one year survival rates were 47% respectively 70%.

Beta-blockade has had a significant improvement on mortality and symptomology of patients with CHF but this is not reflected in an increase in peak $\dot{V}O_2$. However, in populations taking beta-blockers the cut off value of peak $\dot{V}O_2 >14$ml/kg/min is still
predictive for mortality (Koelling et al., 2004, Guimaraes et al., 2010). Guimaraes conducted a similar study in Brazil, finding that CPET measured peak $\dot{V}O_2$ was still predictive of 1 year mortality in CHF patients taking beta-blockers (tracking follow up period of the study was 36.9 months +/- 28.1 months, range 1–111). They identified a cut off value of 12.5ml/kg/min to have optimal sensitivity and specificity on ROC curve analysis, with a diagnostic accuracy of 0.8 and a sensitivity of 82% and specificity of 26% (Guimaraes et al., 2010).

The European Association of Preventive Cardiology and American Heart Association (EACPR/AHA) pre-surgical risk assessment tool has 4 categories for peak $\dot{V}O_2$- Class A to D (Guazzi et al., 2016). There is an inverse relationship between with worsening prognosis and increasing surgical risk to reduced peak $\dot{V}O_2$. They are as follows:

Class A >20ml/kg/min, Class B 16-20ml/kg/min, Class C 10-15.9ml/kg/min and Class D <10ml/kg/min (Guazzi et al., 2016).

AT is a submaximal test. Submaximal tests are suggested to be more useful owing to their submaximal nature and that proposed superior prognostic abilities. VE/\(\dot{V}CO_2\) and AT have been shown to be more predictive of outcomes than peak $\dot{V}O_2$ as they do not require maximum effort. AT is therefore independent of patient motivation and thus effort independent (Balady et al., 2010, Gitt et al. 2002). Gitt et al., (2002) studies 223 patients with CHF who were at risk of early death and used cox regression analysis to construct Kaplan-Meier survival curves for peak $\dot{V}O_2$ and submaximal tests and a combination thereof. They found that a combination of AT below 11mg/kg/min and VE/\(\dot{V}CO_2\) above 34 better identified patients at higher risk of death that peak $\dot{V}O_2$ alone (Gitt et al. 2002). It is not surprising that looking at a
combination of the CPET variables gives a more accurate picture of a patient’s cardiorespiratory function that looking at a single measure, this will be discussed in more detail later.

**Anaerobic threshold**

AT is a submaximal measure of cardiorespiratory reserve defined as the rate of oxygen consumption at the point at which aerobic metabolism begins to be supplemented by anaerobic metabolism. Anaerobic metabolism increases due to deficit in oxygen delivery and is a gauge of cardiovascular fitness (Beaver et al., 1986). At this physiological point, lactate production is buffered by bicarbonate and there is an exponential rise in CO₂. AT is independent of patient effort. The method used to detect AT is not universally accepted and even though the terms ventilatory, anaerobic and lactate are used interchangeably they are actually different but related events (Balady et al., 2010). AT will be the term used in this thesis. AT is measured in ml of oxygen/kg/min.

Wasserman, in 1963 first described this point of the onset of anaerobic metabolism being invasively measured in three ways.

1- The point at which there was increased blood lactate production.

2- The point at which there is reduced blood bicarbonate concentration and pH.

3- The point there is an increasing respiratory exchange ratio (Older, 2013, Beaver et al., 1986).
However current practice is not to use an arterial cannula so it can be measured noninvasively in three ways:

1- The point at which there is departure of $\dot{V}CO_2$ from line of $\dot{V}CO_2$ plotted against $\dot{V}O_2$- the V slope method (Beaver et al., 1986).

2- The point at which VE/$\dot{V}O_2$ increases without a significant rise in VE/$\dot{V}CO_2$.

3- The point at which there is a rise in end tidal $O_2$ with an absent decrease in end tidal $CO_2$ (Balady et al., 2010). AT normally occurs at 50-60% of peak $\dot{V}O_2$

Initial work in the CHF suggested 11ml/kg/min as the optimal cut off value for mortality prognostication. Older (1999) applied the same cut off variables found in the CHF population to a surgical population in a seminal paper which is the basis of most protocols and further work published in this population (Wilson et al., 2018). Older described a cut off value for the anaerobic threshold of 11ml/kg/min as within his elderly surgical population there was an 18% mortality compared to 0.8% mortality in the cohorts either side of this boundary. Wilson et al., (2010) also found a 6 fold increase risk of mortality in a cohort of 847 patients undergoing major abdominal surgery.

EACPR /AHA (2016) quotes a cut off of 11ml/kg/min as the division between low and high risk for preoperative non-cardiac surgical patients (Guazzi et al., 2016). York Teaching Hospitals NHS Foundation Trust uses the same cut off for the assessment of surgical patients and has used its CPET dataset to give a predictive mortality for patients undergoing surgery at that hospital. An AT below 11 ml/kg/min
has been consistently found to be prognostic of increased mortality postoperatively (Guazzi et al., 2016, Gitt et al., 2002).

AT is used in preoperative risk assessment tools to assign risk but it can also be used to tailor training. By knowing a patients peak \( \dot{V}O_2 \) and AT one can use the heart rate and workload at AT to design a training program which is personalised to an exercise intensity for that patient (Guazzi et al., 2016). This use of heart rate and or work load also means exercise programmes can be completed without specialised equipment or personnel.

**Ventilatory efficiency for carbon dioxide**

Ventilatory efficiency for carbon dioxide is assessed by analysis of the minute ventilation relative to the \( \dot{V}CO_2 \) excreted. The VE/\( \dot{V}CO_2 \) slope is the mostly widely reported index this is calculated by linear regression \( y=mx+b, \) \( b=\)slope (Balady et al., 2010). The AHA (2010) defines a normal VE/\( \dot{V}CO_2 \) as below 34. VE and \( \dot{V}CO_2 \) are tightly linked as a rise in CO\(_2\) production in anaerobic metabolism during exercise causes a rise in minute ventilation. VE/\( \dot{V}CO_2 \) is essentially a measure of ventilation: perfusion mismatching. It is elevated in cases of either ventilatory dysfunction, cardiac dysfunction or both. Patients with a raised VE/\( \dot{V}CO_2 \) which is primarily due to a VE problem have either increased alveolar dead space ventilation secondary to either reduced lung perfusion or a reduced diffusion area or an exaggerated exercise induced hyperventilation. This increased ventilation, for any given metabolic rate, leads to the symptoms of breathless on exertion classically seen in CHF and is characterised by reduced ventilatory efficiency (Agostoni et al., 2010). A raised
VE/\dot{V}CO_2 is also from the \dot{V}CO_2 side of the ratio when there is an abnormally low \dot{V}CO_2 for a given VE due to lung hypo-perfusion. An abnormal result therefore significantly correlates with a reduced cardiac output as this reduces the lung perfusion (Balady et al., 2010).

A normal response to early exercise is a drop in VE/\dot{V}CO_2 to its nadir shortly after AT. It reduces in a hyperbolic nature at low work rates and then rises at the end of exercise as the patient reaches the respiratory compensation point (ATS/ACCP, 2003). The nadir in healthy individuals is approximately 25 but may be 30 in older adults. In health a VE/\dot{V}CO_2 would be expected to be below 32 at AT and below 36 at peak exercise.

A VE/\dot{V}CO_2 greater than 34 is classed as abnormal (ATS/ACCP, 2003) this is based on the CHF population (Arena et al., 2007). The EACPR/AHA diagnostic stratification of pre-surgical patients gives 4 ventilatory classes: I- <30, II- 30-35.9, III- 36-44.9, IV- >45. An increasing score gives an increasingly poor prognosis (Guazzi et al., 2016).

Arena et al., (2007) argued that the VE/\dot{V}CO_2 slope has a superior prognostic validity when compared to peak \dot{V}O_2. They cite 11 studies including 2633 patients comparing the prognostic abilities of the VE/\dot{V}CO_2 slope compared to peak \dot{V}O_2. In 10 of the 11 studies the VE/\dot{V}CO_2 slope was superior and in the 11th study it was superior in diastolic HF and similar in systolic HF. The majority of studies used a cut off of 34.
The previous chapter explained the major CPET variables and quoted the widely accepted normative values produced by the AHA/ACCP, ATS/ACCP, and EACPR/AHA guidance along with primary research which has examined the optimal cut off values. However, whilst drawing a line between high risk and low risk patients, based on their CPET score, is practical but it may be an oversimplification of a more complex issue (Wilson, 2018). Making the scoring binary is perhaps more useful for patients who fall well beyond the threshold but may be less useful in those who are close to the threshold as variation from within the subject or within the interpretation may change their risk scoring between the binary functions. Rose et al. (2018) have proposed a revised model for risk stratification adding in an intermediate fitness grading. They analysed 213 patients scheduled for colorectal surgery and they have suggest that for AT the intermediate group is 9.2 to 13.6ml/kg/min and above and below those figures are high and low risk respectively. For peak \( V\dot{O}_2 \) they suggest the intermediate group are between 14.2 and 18.3 ml/kg/min whilst above and below those figures are high and low risk respectively. They also suggest for \( VE/V\dot{CO}_2 \) that the intermediate risk group lie between 32.7 and 40.1 and above and below those figures are high and low risk respectively. This appears to be a sensible suggestion as the all or nothing of high and low risk scores runs the risk of misclassifying patients who are close either side to the boundaries of risk. Rose et al., (2018) report that a large number of patients moved between the boundaries between high and low risk when they applied a model of critical difference (biological variation) to the results. Arena et al., (2007) add to this as they tested the premise that a dichotomous threshold between fit and unfit for \( VE/V\dot{CO}_2 \) is less clinically useful than a multilevel
classification system. Their Kaplan- Meier analysis demonstrates a “dose response” curve where the higher the VE/VCO₂ measured the worse the prognosis with a reducing event free survival curve over 2 years in patients with CHF (Arena et al., 2007).

The intervention in this systematic review and meta-analysis is beta-blockade. The history and pharmacology of beta-blockade will now be discussed.

**Beta-blocker pharmacology**

Sir James Black invented Propanolol in 1962 based on the idea that attenuating the harmful effects of catecholamines in patients with ischaemic heart disease would lead to a reduced oxygen demand and therefore reducing angina pain (Black and Stephenson, 1962 in Ladage et al 2013). He later went on to be awarded the Nobel Prize in 1988 as beta-blockade has been shown to reduce all measures of adverse cardiac events in CHF patients (Beattie et al., 2014).

Beta-blockers have numerous clinical uses: CHF, post myocardial infarction, in prevention and treatment of arrhythmias, and second line therapy for hypertension. They are also used in pheochromocytoma, prevention of migraines, glaucoma and in anxiety disorders.

The ICAF-beta study uses Bisoprolol Fumerate which is a cardioselective beta 1 adrenoceptor antagonist. Chemical formula of (C₁₈H₃₁NO₄)₂.C₄H₄O₄. The full
rationale for the selection of this drug is explained in Chapter 3, subsection “study drug”

Beta-blocking agents can be categorised into cardioselective and non-cardioselective agents (i.e. receptor affinity) and by the degree of vasodilatory effects or by generation (Ladage et al., 2013). Another categorisation is agents with or without sympathomimetic activity. Beta-blockers are not a homogeneous drug classification as they differ in receptor selectivity, degree of lipophilicity, degree of inverse agonism, sympathomimetic properties and the presence of ancillary properties (Marazzi et al., 2011).

Beta-blocking agent’s pharmacodynamics properties are of competitive beta-receptor antagonism. There are 3 types of beta-adrenoceptor: beta-1 which are prominently found in the heart, beta-2 which are predominately found in the lung and vascular smooth muscle, and beta-3 which are predominately found in adipocytes (McCorry, 2007). Beta-adrenoceptors are G-Protein coupled receptors therefore extra-cellular agonism leads to a cascade of intracellular reactions which ultimately lead to increased intracellular calcium and increased chronotropy and inotropy (McCorry, 2007).

There is significant evidence that beta-blockade should be used in CHF. There is controversy on which beta-blocker to select in CHF (Chatterjee et al 2013). Beta-blockade was thought to be harmful in CHF as it would block what was thought to be a vital adaption and as such it was contraindicated (McDonagh et al., 2011).
In CHF beta-blockade has been shown in some large randomised control trials to increase survival, improve rate control and rhythmic control, improve ventricular contractility and provide symptomatic relief (Chatterjee et al 2013, Lechat et al., 1998). Meta-analysis of 3023 patients in 18 trials compared outcomes for patients with CHF taking beta-blockers or placebo. They provide compelling robust evidence that beta-blockade provided a significant improvement in mortality and morbidity. They quote a 32% risk reduction of mortality, a 41% reduction in hospitalisation and a 37% combined risk reduction for mortality and morbidity. This data is robust and statistically significant as it could only be negated by removing 90% of the data. They provide evidence that ejection fraction increased by 29% which was statistically significant. They showed a statistically significant (p=0.04) improvement in NYHC functional class but this result was not robust as it relied heavily on a single study (Lechat et al., 1998).

Pharmacological management for CHF is aimed at breaking the pathophysiological spiral of decline in the failing heart by blocking one or more of the maladaptive processes (McDonagh et al., 2011). Activation of the sympathetic nervous system is a maladaptive feature of CHF. An increased level of noradrenaline has been demonstrated to be predictive of worse survival in patients with CHF (Rector, 1987). From this concept, the counter intuitive idea of prescribing beta-blockade in CHF gained theoretical credence (McDonagh et al., 2011). Current practice is that beta-blockade and angiotensin converting enzyme inhibitors are the first line of pharmacological management for patients with CHF (NICE, 2016). Beta-blocking agents do not have an effect solely via beta-receptors, their vasodilatory effects are either via alpha-adrenoceptor blockade or via nitric oxide (Ladage et al., 2013). The
haemodynamic effects of beta-blockade have previously been discussed in “Chapter 2.1 Discussion” where it is suggested that beta-blockade does not only increase diastole time but also improves myocardial stroke work, ventricular performance and contractility (Gilbert et al., 1990, Olsen et al., 1995, Woodley et al., 1991, Andersson et al., 1994, Eichhorn et al., 1994, and Metre et al., 1994).

Beta-blocking agents are also thought to have the ability to block gene expression, have anti-inflammatory, antioxidant, and anti-proliferative properties which reduce myocardial cell damage (Ladage et al., 2013). Beta-blockers may also improve gas exchange via beta-2 receptors in the lung by regulating fluid reabsorption and therefore improving the diffusing capacity. There is an association between beta-blockade and insulin sensitivity, glucose uptake and dyslipidaemia. However, these effects are not seen in highly selective agents and current guidelines advocate the use of beta-blockers in diabetic patients (Ladage et al., 2013).

In Lechat et al., (1998) meta-analysis cardio selective and nonselective beta-blockers both demonstrated similar improvement in ejection fraction and rates of hospitalisation in CHF patients. However, nonselective beta-blockade showed a larger improved reduction in all-cause mortality when compared to selective beta one receptor antagonists. This is may be due to the down regulation of beta one receptors and thus higher proportion of beta two receptors in CHF. (Lechat et al., 1998, McDonagh et al., 2011) However, 90% of the included studies using nonselective beta-blockers used Carvedilol which has an alpha blocking property which may be the molecular reason for differences in results. Chatterjee et al., (2013) conducted head to head comparison of different beta-blockers compared to placebo or standard
treatment. They studied 23122 patients in 21 studies and reported that beta-blockade as a drug class provided reduced mortality irrespective of treatment duration. However they found no different in risk of all-cause mortality, pump failure mortality, or discontinuation of therapy between different beta-blockers. (Chatterjee et al., 2013).
**Methods:**

**Search Strategy:**

The protocol for this systematic review was registered on PROSPERO (CRD42019116137). Comprehensive MEDLINE, EMBASE and Google Scholar searches were conducted on 29/08/18 and then repeated on 08/07/19 using the following MeSH terms: adrenergic beta-antagonists, exercise and clinical trials. The AND function was used to combine MeSH terms and the OR function was used to increase searching terms to include: specific beta-blocking drug names, cardiopulmonary exercise testing and fitness testing, exercise stress testing and CPET variables used as primary end points. This review followed the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) when designing and preparing this review. The searching was conducted by MW and a qualified clinical librarian. Full search strategy supplied as Appendix 2.

Grey literature was searched; no other systematic reviews are currently registered or ongoing for this research question. Hand searching using backward chaining was employed to increase relevant studies. Authors of identified studies were contacted across multiple platforms requesting missing data to increase study inclusion.

Two authors blindly reviewed title and abstract (MW, JM). Full texts were reviewed and any disagreement at any stage was resolved by consensus.
Eligibility and Inclusion:

Studies were deemed eligible if they were interventional trials investigating the effect of de novo beta-blockade on CPET variables. The studies must include before and after treatment comparison of breath-to-breath CPET analysis. Studies which were either randomised control trials, comparison studies or before and after studies were considered. Retrospective and observational studies were excluded. Studies involving animals were excluded. Studies were also excluded if they assessed fitness via another modality which was not breath-to-breath CPET analysis such as 6 minute walk test or treadmill exercise testing using non breath-to-breath gas analysis. Only papers with English language translations were considered.

Endpoints:

Four main end points were considered, change in: VE/VCO₂ (unitless variable reported as the gradient of the slope or the value at AT), AT (ml/kg/min), peak VO₂ (ml/kg/min) and EF (%).

Assessment risk of bias:

For randomised control trials a risk assessment of bias and quality review was conducted using the Revised Cochrane Risk of Bias tool for randomised trials (RoB 2.0). Before and after comparison trials were reviewed using The Risk of Bias in non-randomised studies of interventions (ROBINS-1) assessment tool.
Data extraction:

Data for study design, sample size, beta-blocking agent, and treatment duration were extracted along with the methods of assessing fitness and specific CPET variables. Data for the primary end points and study design was extracted from all included studies.

VE/\dot{V}CO_2 was extracted when reported as VE/\dot{V}CO_2. When mean values of VE (ml) and \dot{V}CO_2 (mls) were presented separately, mean VE/\dot{V}CO_2 could not be calculated and the corresponding authors were contacted to provide raw data. Peak \dot{V}O_2 and \dot{V}O2 at AT were extracted in ml/kg/min and authors were contacted to request the correct units when not presented as such. Only \dot{V}O_2 data in ml/kg/min was used for meta-analysis. Ejection fraction was extracted as a percentage and the method of measurement was noted. Data extraction was checked for accuracy by a second reviewer (JM AM).

Statistical Analysis:

The estimate of the non-standardised mean difference was calculated and its corresponding 95% confidence interval for each outcome via a random effects meta-analysis. Randomised controlled trials that compared two beta-blockers were incorporated into the meta-analysis. Firstly data was extracted for each treatment group (mean and standard deviation) of the outcome before and after de novo beta-blockade. The data was then extracted from each group as though it had come from a before and after study, which allowed for pooling of the results with the studies that
had a true before and after design. A similar method was used for randomised controlled trials that compared beta-blockers with placebo, however in this case the placebo group was not used. Forest plots and funnel plots (see Appendix 6) were produced using Review Manager 5.3. (RevMan, 2014)
Results:

A total of 229 studies were identified for title and abstract screening; 207 were found using the search strategy and 22 studies were identified from hand searching. 177 were removed as they did not meet the inclusion criteria. 46 full texts were reviewed and 29 of these did not meet the inclusion criteria. Out of those excluded; 6 did not assess beta-blocking agents or exercise testing, 16 used another measure of fitness assessment other than CPET and 6 were either review articles or retrospective studies. A Total of 18 studies were therefore included. 10 studies reported VE/\(\dot{V}CO_2\), 6 reported AT, 18 reported peak VO\(_2\) and 11 reported EF. The PRISMA flow diagram is presented in Fig. 2.1.1. VE/\(\dot{V}CO_2\) was expressed as the VE/\(\dot{V}CO_2\) slope in all studies which reported VE/\(\dot{V}CO_2\) bar West et al., (2015) who reported VE/\(\dot{V}CO_2\) at AT. EF was primarily assessed using echocardiography (n=6). However, cardiac MRI (n=3) and radionuclide ventriculography (n=2) were also used.
Figure 2.1.1

Consort diagram for systematic review.

2008) and 1 studied patients with AAA prior to surgery (West et al., 2015). The study characteristics are shown in Appendix 6.

The beta-blocking agents used were: metoprolol in 1 study (Metra et al., 2000), bisoprolol in 7 studies (Dubach et al. 2002, Issa et al., 2006, West et al., 2015, Norozi et al., 2008, Witte et al., 2005 and Beloka et al., 2008) carvedilol in 5 studies (Witte et al., 2005, Nessler et al., 2007, Volterrani et al. 2011, Metra et al., 2000, Krum, 1995) atenolol in 3 studies (Nodari et al., 2003, Vanhees et al., 2000 and Van Bortel and Van Baak, 1992), and nebivolol in 2 studies (Nodari et al., 2003, Conraads et al., 2012, Van Bortel and Van Baak, 1992). The treatment course ranged from one week (West et al., 2015) to 1 year of medication (Witte et al., 2005, Nessler et al., 2007, Metra et al., 2000, Dubach et al. 2002)

**Primary End points:**

VE/\(\dot{V}\)CO\(_2\) was analysed in 6 studies for 197 patients in 8 drug treatment groups. The pooled result shows an improvement of -1.17 (CI -2.33-0.00) (figure 2.1.2A). AT was analysed in 8 studies for 357 patients in 11 drug treatment groups. The pooled result shows an increase of 0.35ml/kg/min (CI -0.26-0.97) (figure 2.1.2B). Peak \(\dot{V}\)O\(_2\) was analysed in 15 studies for 443 patients in 18 drug treatment groups. The pooled result shows an increase of 0.67 ml/kg/min (CI -0.14-1.48) (figure 2.1.2C). Ejection fraction was analysed in 11 studies for 414 patients in 12 drug treatment groups. The pooled result shows an increase of 6.72% (CI 4.93-8.51) (figure 2.1.2D).
**Figure 2.1.2**

Forest plots and raw data for (A) VE/VCO₂, (B) AT, (C) Peak VO₂, and (D) Ejection fraction.
**Heterogeneity and Funnel Plots**

The Cochrane handbook states heterogeneity is inevitable in meta-analysis as clinical and methodological diversity always occurs (Higgins and Green, 2011). The potential limitations heterogeneity may have caused on this meta-analysis is discussed in the limitation section. It must be noted interpretation of I², which is the percentage of the variability in effect estimate which is due to heterogeneity rather than chance (sampling error), may be misleading as it depends on the effect size and strength of evidence of heterogeneity I² can be broadly classified into 4 categories: might not be important (0% to 40%) may represent moderate heterogeneity (30% to 60%), may represent substantial heterogeneity (50% to 90%) and considerable heterogeneity (75% to 100%) (Higgins and Green, 2011).

VE/\dot{V}CO₂ meta-analysis demonstrated heterogeneity from the category of “might not be important” with a \( \text{Tau}^2 = 0.63 \), df (degrees of freedom) = 7 and \( I^2 = 24\% \) giving an overall effect of \( Z=1.96 \) (\( p=0.05 \)). AT meta-analysis also demonstrated heterogeneity from the category of “might not be important” with a \( \text{Tau}^2 = 0.39 \), \( \chi^2 = 16.62 \), df = 10 (\( p=0.08 \)) and \( I^2 = 40\% \) giving an overall effect of \( Z=1.14 \) (\( p=0.25 \)). The observed value of a small effect size and a Chi (\( p=0.08 \)) which is significant using the conventional level of significance of 0.1) (Higgins and Green, 2011). Peak \dot{V}O₂ meta-analysis data may represent substantial heterogeneity with a \( \text{Tau}^2 = 1.12 \), df = 17 and \( I^2 = 63\% \) giving an overall effect of \( Z=1.58 \) (\( p=0.11 \)). However the is a small effect size and a statistically significant chi² p value (0.0002). EF meta-analysis data also may represent substantial heterogeneity with a \( \text{Tau}^2 = 0.63 \), df = 12 and \( I^2 = 69\% \) giving an overall effect of \( Z=6.96 \) (\( p=0.00001 \)).
Funnel plots are presented in Appendix 6 as a graphical estimation of publication bias. The plots for peak $\dot{V}O_2$ and AT, do not show any asymmetry suggesting non-publication. EF shows some asymmetry in the bottom left suggesting smaller negative tests may not have been reported. VE/ $\dot{V}CO_2$ has been reported however there are fewer than 10 included studies so this should be viewed cautiously (Higgins and Green, 2011). It shows there is asymmetry in positive results being published with a reduced density on the bottom left hand side.
Table 2.1.3

Table showing the baseline (test 1) and post treatment (test 2) blood pressure and heart rate measured in each study.

<table>
<thead>
<tr>
<th>Study</th>
<th>BP mm/Hg or MAP</th>
<th>HR resting bpm</th>
<th>HR peak bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test 1</td>
<td>Test 2</td>
<td>Significance</td>
</tr>
<tr>
<td>Witte et al., 2005</td>
<td>132.1/82.4</td>
<td>125.9/78.4</td>
<td>(p=0.24)</td>
</tr>
<tr>
<td>Nodari et al., 2003</td>
<td>151/91</td>
<td>139/83</td>
<td>(p=&lt;0.001)</td>
</tr>
<tr>
<td>Vanhees et al., 2000</td>
<td>Placebo MAP 106</td>
<td>MAP 97</td>
<td>(p=&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>Placebo MAP 106</td>
<td>MAP 99</td>
<td>(p=&lt;0.05)</td>
</tr>
<tr>
<td>Volterrani et al., 2011</td>
<td>125.3/74.4</td>
<td>115.6/68.5</td>
<td>(ns)</td>
</tr>
<tr>
<td></td>
<td>123.6/71.1</td>
<td>118.3/69.4</td>
<td>(ns)</td>
</tr>
<tr>
<td>West et al., 2015</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Issa et al., 2006</td>
<td>119.1/75.6</td>
<td>110/70.4</td>
<td>(ns)</td>
</tr>
<tr>
<td>Dubach et al. 2002</td>
<td>125/82</td>
<td>138/85</td>
<td>(ns)</td>
</tr>
<tr>
<td>Nessler et al., 2007</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metra et al., 2000</td>
<td>MAP 91</td>
<td>Map 91</td>
<td>(ns)</td>
</tr>
<tr>
<td></td>
<td>Map 92</td>
<td>Map 91</td>
<td>(ns)</td>
</tr>
<tr>
<td>Krum, 1995</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Bortel and Van Baak, 1992</td>
<td>Placebo MAP 91</td>
<td>MAP 84</td>
<td>(p=&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>Placebo MAP 91</td>
<td>MAP 83</td>
<td>(p=&lt;0.05)</td>
</tr>
<tr>
<td>Hulsmann et al., 2001</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genth-Zotz et al., 2000</td>
<td>115/76</td>
<td>122/79</td>
<td>(p=0.001)</td>
</tr>
<tr>
<td>Broch et al., 2016</td>
<td>133/66</td>
<td>124/58</td>
<td>(p=0.001)</td>
</tr>
<tr>
<td>Terzi et al., 2003</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beloka et al., 2008</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conraads et al. 2010</td>
<td>128/80</td>
<td>122/76</td>
<td>(p=0.001)</td>
</tr>
<tr>
<td>Norozzi et al. 2008</td>
<td>115</td>
<td>108</td>
<td>(ns)</td>
</tr>
</tbody>
</table>
Secondary end points

Table 2.1.3 shows the baseline and post treatment recordings for blood pressure and heart rate at rest and at peak exercise. Thirteen studies demonstrated that with beta-blocking therapy heart rate reduced at rest and during exercise to a statistically significant amount. Three studies showed an impressive reducing in heart rate but reported them as not significant (Bortel and Van Baak, 1992, Volterrani et al. 2011, and Terzi et al., 2003). Conrads et asl. (2010) reported a significant reduction in maximal heart rate but a presumed mistake in their table suggests the maximal heart rate was 17 bpm. Seven studies showed a statistically significant reduction in blood pressure. Whereas 3 studies reported a non-significant reduction in blood pressure on treatment and 1 study reported a non-significant increase in blood pressure (Dubach et al. 2002).

Studies excluded from meta-analysis:

If one variable from a study was excluded the other variables would be included if eligible. Peak $\dot{V}O_2$ was reported in ml/kg for 2 studies (Van Bortel et al., 1992 and Vanhees et al., 2000) and as such they were excluded from the peak $\dot{V}O_2$ analysis. VE/$\dot{V}CO_2$ was presented as mean VE and mean $\dot{V}CO_2$ in 3 studies (Terzi et al., 2003, Genth-Zotz et al., 2000, and Dubach et al., 2002). These authors were contacted and full raw data was requested. However, no further data was collected and therefore, the VE/$\dot{V}CO_2$ data was excluded from meta-analysis. This data is presented in Appendix 8.
West et al. (2015) had 2 arms in their study, a de novo beta-blockade group which was included in meta-analysis and a cohort which were tested before and after a period of beta-blockade cessation. This second cohort, along with combined cohort results, was excluded from meta-analysis.
Discussion:

Primary findings

This robust analysis of prospective clinical trials confirms earlier assumptions based on retrospective data (Gläser et al., 2010) and previous meta-analysis (Montero and Flammer 2017). These findings do not deny the potential clinical benefits patients derive from beta-blockers but they do question the general consensus that de novo Beta-blocker use favourably alters cardiorespiratory fitness in all patients.

There is a consistent message from previous meta-analyses of the paradoxical finding that fitness capacity does not improve, as measured by CPET and 6 minute walk test, however NYHA functional class does improve (Montero and Flammer, 2017). This meta-analysis adds to this by highlighting the disparity between improved ejection fraction when on beta-blocking therapy with CPET variables showing statistically non-significant changes in peak VO2, VE/VCO2 and AT.

There are a number of explanations for this paradoxical finding. Firstly, there is a type II error ie a false negative for the CPET variables as these CPET variables are inadequate to assess the effect of beta-blocking agents or but this review is unable to detect this change due to the heterogeneity and small sample sizes of the studies. Secondly, the CPET variables are a true negative and NYHA functional class and static measures of cardiac function are not associated with change in exercise capacity. The latter is less plausible as the theoretical physiological basis for improving CPET variables, particularly VE/VCO2, on beta-blockade is secondary to improved ventilation/perfusion matching.
This meta-analysis demonstrates a non-significant change in peak \( \dot{V}O_2 \) and AT. These results are statistically non-significant however; this may confer some clinical significance. In a coronary artery disease (CAD) population a 10% reduction in cardiac mortality was observed with every 1ml/kg/min increase in measured peak \( \dot{V}O_2 \) when taken as a continuous variable (Kavanagh et al., 2003). However, this is a statistically non-significant finding of a change which may be within the limits of test accuracy.

This meta-analysis also demonstrates statistically non-significant change in VE/\( \dot{V}CO_2 \), this result is the closest to being significant of all the CPET variables (CI - 2.33-0.00). This result is not significant as it includes 0, however if more dismal places were taken it would be significant. The effect on VE/\( \dot{V}CO_2 \) may be underestimated in this meta-analysis as the 4 studies excluded from analysis, as they did not report mean VE/\( \dot{V}CO_2 \), all demonstrated a modest improvement in either mean VE and or mean \( \dot{V}CO_2 \) (Vanhees et al., 2000 Terzi et al., 2003, Genth-Zotz et al., 2000, and Dubach et al., 2002). However, these results were statistically non-significant.

Based on this meta-analysis, the use of beta-blockers is associated with improvement in static cardiac function as measured by EF. This finding is in keeping with cardiac catheterisation studies demonstrating both improved systolic and diastolic function after beta-blocker therapy, both at rest and during exercise. The main findings in these studies are of: improved EF, cardiac index, stroke work, pulmonary artery wedge pressure, and LV filling (Gilbert et al., 1990, Olsen et al., 1995, Woodley et al., 1991, Andersson et al., 1994, Eichhorn et al., 1994, and Metre et al.,1994).
This meta-analysis and systematic review has highlighted the disparity between improved static cardiac function when on beta-blocking therapy with CPET variables showing statistically non-significant changes in peak $\dot{V}O_2$, $VE/\dot{V}CO_2$ and AT. Perhaps these CPET variables are inadequate to assess the effect of beta-blocking agents. The theoretical physiological basis for improving CPET variables, particularly $VE/\dot{V}CO_2$, on beta-blockade is secondary to improved ventilation/perfusion matching. All beta-blockers competitively inhibit beta-receptors to antagonise the effects of catecholamines (Ladage at al., 2013). Beta-blockers improve cardiac output which improves lung perfusion and reducing alveolar dead space. Improved cardiac output also improves muscle blood flow reducing the metaboreflex seen in exercise which would otherwise increase chemosenstivity and activate the sympathetic nervous system further (Beloka et al., 2008). Furthermore, beta-blockers reduce sympathetic tone and thus reduce the hyperventilation seen in CHF (Agostoni et al., 2010). These combined factors lead to improved ventilation/perfusion matching (Beloka et al., 2008).

In summary, this meta-analysis has results which are consistent with previous meta-analysis and has theoretical plausibility. Improving cardiac function has been seen also in cardiac catheterisation studies adding more weight to this meta-analysis observed improvement in EF.
Beta-blockers and $\text{VE/\dot{V}CO}_2$

Patients with a raised $\text{VE/\dot{V}CO}_2$ have either increased alveolar dead space ventilation secondary to either reduced perfusion or reduced diffusion area or an exaggerated exercise induced hyperventilation. This increased ventilation, for any given metabolic rate, leads to the symptoms of breathless on exertion and is characterised by reduced ventilatory efficiency (Agostoni et al., 2010). As beta-blocking agents can improve cardiac output in patients with CHF it is theoretically plausible that beta-blocking agents should reduce $\text{VE/\dot{V}CO}_2$.

In the CHF population mortality progressively increases as $\text{VE/\dot{V}CO}_2$ increases from normal to above 40 (Balady et al., 2010). A reduction in $\text{VE/\dot{V}CO}_2$ should theoretically also confer a mortality benefit as Kaplan-Meier analysis for $\text{VE/\dot{V}CO}_2$ to cardiac event free survival demonstrate a worsening prognosis with an increased $\text{VE/\dot{V}CO}_2$ in CHF patients (Arena et al., 2007). This is mirrored in the pre-surgical population where increasing $\text{VE/\dot{V}CO}_2$ gives an increasingly poor prognosis postoperatively (Guazzi et al., 2016, Wilson et al., 2010).

Beta-blockers are the most effective CHF treatment in terms of prognosis and quality of like but the effect on exercise capacity is less well defined (Ladage et al., 2013). Nodari et al., (2003) showed both a significant improvement in $\text{VE/\dot{V}CO}_2$ with nebivolol and an increase in $\text{VE/\dot{V}CO}_2$ with atenolol. They conducted this interventional study over 6 months in a cohort of patients with hypertension and CHF. They compared 23 patients who underwent CPET (20W ramped cycle ergometer), echocardiography and pulmonary artery catheterisation pre and post beta-blockade.
They conclude that both atenolol and nebivolol improve LV function at rest and during exercise, however nebivolol has a superior improvement likely due to its ancillary properties. They reported an improved a/e on echocardiography in both groups post beta-blockade from 0.84 (+/- 0.12) to 0.89 (+/- 0.15) p<0.05 and 0.79 (+/- 0.13) to 0.91(+/- 0.11) p<0.001 in the atenolol and nebeviolol groups respectively. Pulmonary artery wedge pressure at peak exercise was improved in both groups with a more marked reduction in the nebivolol group. The authors classified these patients as having diastolic CHF, however, their baseline characteristics are of an ejection fraction of 56%.

Volterrani et al. (2011) conducted a 12 week study in patients with CHF where patients received carvedilol as either monotherapy (n=38) or dual therapy with ivabradine (n=42) or ivabradine alone (n=41). They tested CPET, echocardiography, muscle power and 6 minute walk test. The dual therapy group showed an improvement in VE/V̇CO₂ from 32.4 (+/-4.9) to 28.8 (+/-5.1) (statistically non-significant). The carvedilol monotherapy group were the same at 29.36 to 29.57 (statistically non-significant) post treatment. 6 minute walk test results improved in both groups but only the dual therapy group was statistically significant. They concluded that exercise capacity was improved in the ivabradine and dual therapy groups but was not improved in the carvedilol monotherapy group. The paper reports an improvement in AT, however the tables demonstrate a worsening of the AT from 7.9 to 7.3 and 8.3 to 7.8ml/kg/min in the dual therapy compared to carvedilol monotherapy (Williams, 2018). This study also has the added treatment of cardiac rehabilitation during the study period, both groups had cardiac rehabilitation so this should not be an added confounder but it does mean the differences seen could be due
to the lifestyle change and not the medication. Furthermore, 66% of patients were on beta-blockers at the start of the study who were then stopped and re-titrated. These patients would have benefitted from the cardiac remodelling before the study started as they were not receiving true de novo beta-blockade in the study. The conclusions of this study are further questioned by inaccuracies in the tables and figures. The graphs demonstrate a large (40%) improvement in 6 minute walk testing but the table only shows a 26% improvement (Williams, 2018).

West et al., (2015) also demonstrated a statistically significant improvement in VE/\dot{V}CO_2. They conducted a study where patients who had AAA were given 1 week of bisoprolol (n=28) and had CPET pre and post treatment. They also studied a group of patients who were on bisoprolol and they stopped this medication for a week and retested the patients. They concluded that on beta-blockers the patients had an overall improved VE/\dot{V}CO_2, workload achieved in testing and an improved oxygen pulse. Oxygen pulse increased by 1.21ml/beat. However, the peak oxygen consumption was not improved and as such the oxygen pulse improvement was improved by virtue of the decreased heart rate. VE/\dot{V}CO_2 stayed static in the de novo beta-blocker group at 37.93 to 39.18 and worsened in patients taken off beta-blockade. When VE/\dot{V}CO_2 was analysed with all patients on beta-blockers vs all patients off beta-blockade it showed VE/\dot{V}CO_2 reduced by 0.68 (p=0.011). AT improved in the de novo beta-blockade group from 12.71 to 13.15ml/kg/min (not statistically significant) and stayed the same in the group where beta-blockade was stopped. These results are based on a single week of treatment, or without treatment, suggesting that beta-blockade may improve cardiac function by other mechanisms other than chronic remodelling. The reduction in VE/\dot{V}CO_2 is statistically significant however its clinical benefit may not
be, however, on balance this study does show that with a brief period of treatment fitness, measured by CPET, improves. This is of clinical benefit as it shows promise that with a short (1 week) treatment there may be a conferred benefit which useful for pre-operative patients who are scheduled for surgery and have limited time for medical pre-optimisation.

The further four studies which reported VE/VCO₂ will now be discussed. Witte et al., (2005) Studied 35 CHF patients over one year who were either given carvediolol or bisoprolol. They had an echocardiography and a CPET using the Bruce protocol on a treadmill. VE/VCO₂ rose from 36.7 to 37.3 (p=0.7). This study excluded patients with an FEV1 below 80% which is a merit of the study as the cohort of CHF should have a VE/VCO₂ abnormality caused by a cardiac pathology which in theory should be more amenable to treatment with beta-blockade.

Nessler et al. (2007) reported no significant change in VE/VCO₂ in 87 CHF patients given carvedilol over 1 year. They used a CPET, echocardiography and blood work (BNP, ET-1 and IL-6) as pre and post comparators. This study has the merits that it is large and it demonstrated a relationship between fitness capacity and BNP and inflammatory markers. I.e.as fitness assessment (peak VO₂) was higher BNP was lower. This is further theoretical grounding for the ICAF-beta study secondary outcome measure of pro-NT-BNP and will be discussed in Chapter 3. This study had some limitations, namely there were inaccuracies in the tables and not all parameters measures were reported.
Vanhees et al. (2000) gave healthy patients either placebo or bisoprolol or atenolol. When compared to placebo bisoprolol improved $\frac{VE}{\dot{V}CO_2}$ from 30.5 to 28.5 and atenolol improved it from 30.5 to 29.9. Both results were statistically non-significant. This was a very small study with a crossover design so the results need to be viewed within this context.

Another small study with results with large confidence intervals was Issa et al. (2006) who reported a change in $\frac{VE}{\dot{V}CO_2}$ from 35.3 to 40.7 which was also statistically not significant.

Dubach et al., (2002) reported MV and $\dot{V}CO_2$ mean values. It can therefore not be calculated what the mean $\frac{VE}{\dot{V}CO_2}$ was and as such this study was excluded from meta-analysis. However, the mean MV was lower and mean $\dot{V}CO_2$ was higher after treatment. If this study had included the calculations and had been included in meta-analysis $\frac{VE}{\dot{V}CO_2}$ may have shown an improvement post treatment.

In summary, $\frac{VE}{\dot{V}CO_2}$ has been investigated in a number of studies listed above. Using meta-analysis has shown there to be no statistically significant improvement in this variable post beta-blockade. The studies included were heterogeneous in terms of study drug, patient selection and treatment duration. The included studies were small and had large confidence intervals. The studies had weaknesses which are described above. The larger studies showed an improvement in $\frac{VE}{\dot{V}CO_2}$ which shows promise that this variable could be used to target beta-blocker therapy to those who may have the most benefit. This concept is discussed further in the chapter titled “Perioperative beta-blockade and surgical outcomes”. However, the study that excluded patients with
lung pathology showed a worsening of VE/\dot{V}CO_2 which is contrary to the assumption that there should be an improvement in a targeted patient cohort. However, this was statistically not significant and the VE/\dot{V}CO_2 baseline was lower than one would expect in a heart failure cohort

**Peak VO_2 and other cardiac measures with beta-blockade**

Peak VO_2 in healthy and CHF populations have reported to be reduced by beta-blockers. This is explained by the negative chronotropic and inotropic effects of beta-blockade which reduces the oxygen transport to the muscle during exercise (Beloka et al., 2008). However, this meta-analysis shows a non-significant increase in peak VO_2. Peak VO_2 demonstrated mixed results in cardiac catheterisation studies. Olsen et al., (1995) treated CHF patients with carvedilol and after four months patients repeated exercise testing, echocardiography and arterial blood sampling. They demonstrated no increase in peak VO_2, however demonstrated a significantly increased exercise duration and lower rate-pressure product. This is explained by the reduction of peak heart rate and is suggestive that the patients can have a greater efficiency with a greater power output for an equal oxygen consumption. Increasing efficiency has been reported in other studies (West et al., 2015, Witte et al., 2005). Eichhorn et al., (1994) conducted a double blind placebo control trial on patients with dilated cardiomyopathy using metoprolol. They reported improved EF, ventricular performance measured via stroke work and minute work without an increase in myocardial oxygen consumption which is suggestive of increasing myocardial efficiency. Carvedilol (Olsen et al., 1995) in the CHF population also showed an increase in stroke work index. Similar work in patients with dilated cardiomyopathy
demonstrates an association of significant improvement in stroke work index after beta-blockade with metoprolol (Andersson et al., 1994), buindolol (Gilbert et al., 1990), and nebivolol (Wisenbaugh et al., 1993). Therefore, assessment of maximal exercise capacity based on peak VO2 alone may be inadequate (Olsen et al., 1995).

Olsen et al., (1995) reported an increased left ventricular EF with a reduction in pulmonary artery pressure suggesting an improvement in intrinsic ventricular function rather than merely improved loading conditions. Wisenburg et al (1993) also report an improved EF and reduced pulmonary artery pressure suggesting an improved contractile performance in patients with dilated cardiomyopathy on beta-blockade. Andersson et al., (1994) also demonstrated an increased EF and cardiac index along with a reduction in pulmonary artery pressure and severity of symptoms during exercise. This is clinically important as it infers that the mechanism of beta-blockade is more complex that merely slowing ventricular rate and thus allowing for more filling. Improving a patients cardiac efficiency is more important as the aim is to improve cardiac performance during exercise, or times of physiological stress, rather than simply blunting tachycardia.

**Fitness capacity assessment**

The overall quality of the studies included in this systematic review and meta-analysis was good (Appendix 4 and 5). However, most studies had a small sample size and a large number of outcomes of fitness capacity. As fitness capacity assessment is complex it is difficult to make meaningful conclusions when some variables have worsened on treatment and some variables have improved in the same cohort.
Selective reporting of the variables which demonstrate most change leads to binary conclusions of improved or worsening exercise capacity when the issue is more complex.

Ladage and colleagues (2013) have compiled 15 studies investigating beta-blockade and exercise capacity. They report 2 studies showed a reduction in exercise capacity, 5 studies showing no change and 8 studies showing an increase in exercise capacity. These studies were heterogeneous in terms of study drug (namely bisoprolol, cavedilol, nebivolol, and atenolol), study population (namely HF, dilated cardiomyopathy and healthy subjects) and one study was based on animal models (Dalla Libera et al. 2009). They were heterogeneous for study duration and all used different parameters to assess exercise capacity (Ladge et al., 2013).

When critically appraising these studies it is apparent that the conclusion of increasing, decreasing or not changing exercise capacity is a difficult to objectively quantify. All of the studies had multiple end points using different modalities. Most studies demonstrated an improvement in some and no change or a worsening in other parameters. For example, Issa et al., (2006) studied 14 patients with CHF before and after 3 months beta-blockade using bisporolol titrated from 2.5mg to 10mg. They found that VE/VCO₂ increased in a non-statistically significant manner from 35.5 to 40.7, Peak VO₂ reduced from 20.9 (+/- 6.8) to 15.1 (+/- 3.5) (p<0.001), heart rate and LVEF improved, BNP reduced from 368 to 211 (not statistically significant) and quality of life and NYHA classification also improved. They conclude that bisporolol improves the symptoms and haemodynamic status of patients but reduces their exercise capacity. This study has a small sample size and very wide confidence
intervals which suggest that it is not sufficiently powered to make any firm conclusions.

This meta-analysis was in a heterogeneous cohort of patients. Beta-blockade may produce differing quantitative responses in different patient cohorts (Woodley et al., 1991). Four studies concluded that beta-blockade reduced fitness capacity (Van Bortel and Van Baak, 1992, Vanhees et al., 2000, Beloka et al., 2008 and Issa et al., 2006). Of note, these include the only 3 studies using healthy young participants (Van Bortel and Van Baak, 1992, Vanhees et al., 2000, Beloka et al., 2008). Issa et al., 2006 studied 14 CHF patients and reported mixed results of an improved clinical and haemodynamic status on bisoprolol but a worsened fitness capacity as measured by a reduction in peak VO2 and a raised in VE/VCO2. This study had a small sample size and therefore underpowered to show a difference in the chosen variables.

This leads to the idea of clinical response being weighted to severity of disease. This idea has biological plausibility as beta-blockers have both a negative chronotropic and inotropic effect thus reducing maximal cardiac output and therefore reduced oxygen delivery during exercise (Beloka et al., 2008). This has a detrimental effect on healthy subjects who have a baseline of ventilatory efficiency. However, CHF patients have ventilatory inefficiency and may therefore benefit from the increased diastolic filling, improved stroke work, and reduced sympathetic tone seen with beta-blockade.

Two studies concluded there was an overall reduction in fitness capacity when taking beta-blockade (Van Bortel and Van Baak, 1992, Vanhees et al., 2000) Of note, these are the only two studies using healthy young participants. Van Bortel and Van Baak,
(1992) conducted a cross over design study looking at 21 healthy volunteers. They were treated with nebivolol, atenolol or placebo for 2 weeks each in a cross over fashion with washout periods, drug levels were taken in the treatment and washout periods. They underwent maximal testing using a 3 minute stepped CPET protocol starting at 100W as well as a stepped endurance protocol to 90 minutes or to exhaustion. The authors concluded that atenolol reduced exercise duration and increased perceived exertion. When compared to placebo atenolol showed a reduction in exercise time from 65 to 50 minutes and an increased exertion score. Nebivolol did not show a change in peak VO₂, perceived breathlessness or exercise time. They did however show an improve stroke volume from 121ml in the placebo group to 152 and 156 in the nebivolol and atenolol groups respectively. This adds weight to the idea that beta-blockers decrease functional capacity in healthy populations.

Vanhees et al. (2000) studied 12 healthy men using a crossover design study of placebo, bisoprolol and atenolol. They used CPET cycle ergometry on a 20 watt ramped protocol along with cardiac output calculations using venous blood samples and the modified Fick principle. They concluded exercise capacity was reduced on both cardio selective and non-cardio selective agents. This conclusion is based on the reduction of exercise time by 19.4 seconds and 29.8 seconds in the bisoprolol and atenolol groups respectively and the time at 70% max exercise (endurance exercise) was significantly reduced.

Gullestad et al., (1996) studied propranolol administration to healthy men and women either acutely before a CPET intravenously or as a 2 week oral course. They conducted maximal muscle strength testing, hand grip measurements and wet
spirometry. Peak VO$_2$ was reduced by 4.7% and 7.5% in the acute and 2 week course groups, exercise time was also reduced in both groups by 5.3%. There was no change in hand grip or muscle strength with either treatments. This study reported a reduction in exercise capacity but was excluded from meta-analysis as they used a Douglas bag and wet spirometry rather than breath-to-breath CPET analysis.

Ejection fraction was measured in the majority of studies (n=10). This was either by echocardiography (Witte et al., 2005, Issa et al., 2006, Nodari et al., 2003, Nessler et al., 2007, Volterrani et al. 2011), Radionuclide Ventriculography (Metra et al., 2000, Krum, 1995) or MRI (Dubach et al. 2002 and Norozi et al., 2008). Six results demonstrated a statistically significant improvement in stroke volume ranging from a percentage change of 6.4% to 11.2% increase. One study showed an improvement in stroke volume but reported it as not statistically significant (Volterrani et al. 2011).

These results are mirrored in other literature using echocardiography pre and post beta-blockade using nebivolol and carvedilol in dilated cardiomyopathy patients and CHF patients (Patrianakos et al., 2005, Marazzi et al., 2011). These studies too showed an improvement in EF of 4.7% over 3 months of treatment (Patrianakos et al., 2005) and 4.4%- 4.9% improvement over a 24 month treatment period (Marazzi et al., 2011). Wisenbaugh et al., (1993) studied 24 patients with dilated cardiomyopathy. They treated with nebivolol for 3 months then complete before and after treatment assessments of heart function using invasive haemodynamic with right and left side heart catheterisation during exercise. They demonstrated that ejection fraction improved from 23% to 33%. They concluded that long term use of beta-blockers had a negative chronotropic effect, increased inotropic effect, and reduced left ventricle
filling pressures leading to increased cardiac output. Eichhorn et al., (1994) add to this with another invasive study of 24 patients with non-ischemic cardiomyopathy. Over 3 months they gave metoprolol and studied the patients before and after treatment using invasive cardiac catheterisation, thermodilution and angiography. They too showed and increased ejection fraction of 11%, from 22% to 33%. They reported increased cardiac efficiency as there was an increased stroke work without an increase in myocardial oxygen consumption.


Abdulla et al. (2006) conducted meta-analysis of functional status of patients before and after beta-blocker therapy. They concluded that long term beta-blockade improves breathlessness, improves NYHA classification and improves exercise time. However, it does not significantly change 6 minute walk test or peak oxygen uptake. Ismail et al (2013) conducted meta-analysis on exercise training in patients on and off beta-blockade in a CHF population. This meta-analysis aims to answer the question of beta-blockade potentially hampering exercise capacity as it will reduce heart rate during exercise. They found that there was a greater improvement in patients taking beta-blocking therapy and exercising compared to those who were not, furthermore they suggest that there was no difference in change of peak VO₂ between cardio and non cardioselective beta-blockers. They also concluded that VE/VO₂ is improved in the groups who are exercising by a mean difference of 3.14. However this is based on
only 2 studies and 24 patients between them. Lechat et al., (1998) conducted meta-analysis of randomised control trials for beta-blockers vs placebo in CHF population with the end points of mortality, hospitalisation and clinical end point of ejection fraction. They concluded that beta-blocking agents had a significant reduction in morbidity and mortality as there was a 32% reduction in mortality, a 41% reduction in heart failure related hospitalisation and a combined risk reduction of 37% for mortality and morbidity (Lechat et al., 1998).

To summarise, meta-analysis in the heart failure population appears to have benefit on exercise capacity, mortality and morbidity. Further work on other end points of objective measures of fitness is required (Lechat et al., 1998).

**CPET variability**

The results presented in this meta-analysis must be viewed in the context of CPET test retest reliability, inter-observer reliability and intra-observer reliability. The HF ACTION (2009) study recommended there was no need in multicentre trials for more than one baseline CPET as the test retest data showed equal mean observations for VE/\(\dot{V}CO_2\) and peak \(\dot{V}O_2\), however, they do show significantly different within subject variability.

There are various sources of measurement error that can occur when considering data obtained from a CPET. These can be classified in 4 ways. 1- Repeatability error or test–retest, seen in variations in repeated measurements for the same subject. 2- Inter-observer error- variations in the same measurement of the same subject but by
different observers. 3- Intra-observer error seen as variations in the same measurement of the same subject by the same observer over time. 4- Specific to the measurement of the AT there are also variations in the methodology in how this is obtained, which may be via the V-slope method, or by changes in the ventilatory equivalents of oxygen and carbon dioxide.

CPET has been reported to have an excellent inter-observer reliability (Barron et al., 2014) and a within subject variability of between 0.12- 1.3 ml/kg/min for AT (Barron et al., 2014 and Bensimhon et al., 2008). Bensimhon et al., (2008) reported a significant coefficient of variation (CVAR) (defined as the within-person standard deviation/within-person mean × 100%) for CHF patients who underwent two CPET 14 days apart. They report a CVAR of 5%, 6.6%, and 7.8% for VE/VCO₂, peak VO₂ and AT respectively. Lower CVAR have been reported of <2.2% for VE/VCO₂ and peak VO₂ (Hansen et al., 2004). However, Janicki et al. (1990) reported significantly higher CVAR in stable CHF of 10.5% and 12.5% for peak VO₂ and AT respectively. This meta-analysis results observed increase in AT of 0.39ml/kg/min is within this wider tolerance.

A number of studies have investigated the reproducibility of the CPET using a test retest methodology (ATS/ACCP, 2003). The results are conflicting to whether there is a learning effect between tests. These results are based on small sample sizes, between 6 and 30 patients in each study, and were conducted in normal individuals, COPD, CHF and interstitial lung disease patients. The majority of studies showed there was no a significant difference in retest and there was no learning effect. (ATS/ACCP, 2003). VO₂ coefficient of variation spanned from 3- 9%. However, AT and VE/VCO₂
are submaximal measures so not influenced by patient effort and therefore should be independent of learning.

**Context of previous meta-analysis**

This is the first meta-analysis to investigate fitness capacity using breath-to-breath CPET variables to assess the effect of de novo beta-blockade. Two other meta-analyses have investigated fitness capacity and beta-blockers, however they had different aims to this study. Ismali et al., (2013) published a systematic review and meta-analysis comparing the effects of exercise training in CHF patients who are and who are not taking beta-blockers. They report that VE/VCO₂ in the exercising group taking beta-blockers is significantly improved. That meta-analysis and systematic review has two major differences: firstly, they investigated the intervention of fitness regimes, and secondly the patients were on beta-blocking agents rather than de novo administration. Their findings are interesting for clinicians who are considering pre-optimisation with exercise for patients who are beta-blocked. This is useful in the chronic disease population but less relevant in the preoperative population when the time between diagnosis, pre-assessment and surgery restricts a structured exercise program.

Another systematic review and meta-analysis (Abdulla et al 2006) studied beta-blockade vs placebo with the primary outcome of NYHA classification and exercise tolerance in CHF patients. They too reported the paradoxical finding of significantly improved NYHA classification and improved exercise tolerance with a non-
significant improvement in peak VO\(_2\) and a non-significant reduction in 6 minute walk test. This paradox is consistent and repeated in the literature.
Limitations:

This study has some noteworthy limitations. Although the majority of the included studies are in the CHF population, there is heterogeneity within that population spanning from mild CHF with HT to severe advanced LVSF. Further heterogeneity is introduced by the inclusion of healthy volunteers and preoperative surgical patients. This heterogeneity makes it difficult to make firm conclusions for specific patient cohorts.

The search term “clinical trials” was used which may reduce the amount of non-randomised control trial found in the search. This risk was minimised by the use of hand searching, backward chaining and searching grey literature. Five of the studies included were no randomised control trials.

There were 5 study drugs included which are all beta-blocking agents but have differing pharmacodynamics properties and the treatment duration spanned from one week to two years. Therefore the beta-blocking regimen is another source of heterogeneity. The method and CPET protocol also varied in each study.

Cardiac function was only analysed using EF. This is likely to under-estimate the benefit of beta-blockade as numerous studies have shown improvement cardiac function measures using cardiac catheterization techniques. Echocardiography was the predominate assessment tool used to evaluate EF. Studies have reported a considerable inter and intra-observer variability in reporting echocardiography for EF. Furthermore assessment of test-retest reliability have shown a potentially clinically
significant difference in EF (≥10%) in 2-26% of tests (van Royen et al., 1996). More modern approaches to reliability assessment are needed in EF and CPET.

Another potential limitation is that two cohorts of patients were included from the same study. The data was then analysed with a random effects model. This may have added a unit-of-analysis error. The Cochrane handbook states that it is reasonable to include independent comparisons into meta-analysis as if they were from 2 studies however it may introduce subtle errors. One way to correct for this is to conduct a fixed-effect meta-analysis across comparisons within a study, and a then the random-effects meta-analysis across studies (Higgins and Green, 2011). This study did not do this analysis.

Conclusions:

This systematic review and meta-analysis confirms that de novo beta-blockade has no statistically significant effect on CPET measured variables. An association between an increase in ejection fraction and administration of de novo beta-blocking agents was statistically significant.
Chapter 2.2. Literature Review- ICAF-beta

This chapter aims to answer a more specific question in a pre-operative population. The evidence which has informed the ICAF-beta study will be critically appraised. Context will be given to the topic by exploring the history of the use of beta-blockers in the surgical population and the effect of beta-blockers on functional capacity and fitness. Then the tools currently used to assess surgical risk will be explored. CPET variables used in the ICAF-beta study will then be explored.

As most of the published work on beta-blockers have focused on patients with CHF, and CHF leads to ventilation/perfusion mismatching and as such causes raised VE/VCO₂ (Balady et al., 2010), the topic of CHF will be explored. CHF pathology will be summarised to highlight relevant points and theoretic principles which underpin the rationale for the ICAF-beta study.

Perioperative beta-blockade and surgical outcomes

Preoperatively the use of beta-blockers has seen many changes of opinion over time. Historically, the initial opinion was to stop beta-blockade thus avoiding cardiovascular collapse due to the inability to mount a tachycardia in the presence of surgical stress (Sear et al., 2008). This idea was counterintuitive when surgery is a time where the heart may need to be protected from the surge of catecholamines, increased heart rate, increased myocardial oxygen demand and reduced diastole time for coronary artery filling. The consensus opinion changed as mounting evidence that
beta-blockers reduce the hypertension caused by direct laryngoscopy, and decreased the incidence of ventricular arrhythmias and myocardial ischemia (Sear et al., 2008).

The ACC/AHA (1996) reported the lack of quality evidence on the use of beta-blockers in the perioperative period and gave guidance that the continued use of beta-blockers in patients who were already taking them to avoid beta-blocker withdrawal and a rebound tachycardia (Jørgensen et al., 2018). In 1999, the DECREASE I trial was published which showed that administration of bisoprolol could reduce the cardiovascular risk of death by 91%. This was added to by the DECREASE IV trial which showed a decrease in cardiac deaths by 66% in intermediate risk patients. However, both papers results have been discredited due to claims of fraudulent data. The Erasmus Medical centre found that there was scientific misconduct and as such these results positive cannot be trusted (Jørgensen et al., 2018).

In 2008, the POISE trial was published. The authors conducted a prospective trial where patients were treated with a de novo prescription of beta-blocker on the day of surgery to all patients with cardiovascular risk factors. This study showed the converse that there was an increase in mortality and stroke (Sear et al., 2008). These results need to be interpreted with caution as the patients were given a large de novo dose on the morning of surgery thus leading to intraoperative bradycardia and hypotension. The result of an increased mortality with the administration of metoprolol can be interpreted as causal. However, the treatment group experienced a larger proportion of intra-operative hypotension which is thought to be associated with increased rates of stroke, myocardial damage and renal injury in an elective surgical population (Sessler et al., 2019). The timing of administration therefore
allows for the negative effects of beta-blockade and does not allow time for the improved cardiac remodelling and anti-inflammatory effect to occur (Sear et al., 2008). Furthermore the cohort of patients was rather broad in terms of surgery type and patient selection. They included all patients with presumed cardiac risk factors and for a wide variety of surgeries.

Adding more evidence to the case that beta-blockade causes harm Bouri et al. (2014) conducted a meta-analysis which suggested there was a 27% increase in mortality with beta-blockade due to presumed intraoperative hypotension. They excluded the DECREASE study data as the authors have been evaluated to be negligent and scientifically incorrect (Jørgensen et al., 2018).

In 2014 ACC/AHA revised guidelines suggested the following recommendations:1- patient who are currently taking beta-blockers should continue, 2- patients who are high or intermediate risk it may be reasonable to start beta-blockers, 3- beta-blockers to reduce risk should be started early enough that one can assess the effect prior to surgery, and 4- that beta-blockers should not be started on the day of surgery (Jørgensen et al., 2018). This guidance is based on level B evidence (weak evidence) systematic review level of evidence (Fleisher et al., 2014, Jørgensen et al., 2018).

Observational studies have added to this evidence base. London et al. (2013) studied over 75000 patients who were either taking or not taking beta-blockers. They used propensity score matching in a cohort of US veterans. They showed a decrease in mortality in patients on beta-blockade. Furthermore they showed an increase reduction in risk when the patients had a progressively higher revised cardiac index
score (RCIS). This is added to by similar conclusion from Andersson et al. (2014) who used Cox regression modelling in a cohort of ischemia heart disease patients. Lindenaue et al. (2005) conducted a logistic regression modelling study on a cohort of over 785,000 patients. They demonstrate an interesting relationship between RCIS and risk of mortality with low risk patients showing and increased risk when taking beta-blockers. However there is an increased risk reduction benefit as risk score increases. Jørgensen et al. (2015) show an increased risk of perioperative mortality in a cohort of over 56,000 patients with uncomplicated hypertension. These observational studies add to the interventional trials and suggest that beta-blockade should be targeted to those patients who are at high perioperative risk (Jørgensen et al., 2018).

More recently the “Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Non-cardiac Surgery” (2017) advise not to start beta-blockers 24 hours prior to surgery (Duceppe et al. 2017). The European Society of Cardiologists (ESC), but not the ACC/AHA, perioperative guidelines recommend the use of atenolol or bisoprolol if a beta-blocker is started before surgery. This is based on level of evidence B and recommended as “may be considered” (Jørgensen et al., 2018).

To summarise, the role to perioperative beta-blockade is uncertain. How a clinician targets treatment, when to start treatment and which regime to use is currently based on low level evidence in national guidance.
Preoperative fitness capacity assessment

International guidelines stress the importance of preoperative risk assessment using measures of cardiopulmonary fitness or functional capacity for patients undergoing non-cardiac surgery (Wijeysundera et al., 2018). There are numerous ways of assessing fitness which range in complexity and prognostic ability. The American College of Cardiology and American Heart Association (ACC/AHA) suggest that patients who are capable of more than four METS of activity without symptoms should proceed directly to elective and major non-cardiac surgery (Wijeysundera et al., 2018).

Risk is an important consideration for the patient who has to decide whether to undergo surgery and for the medical team who are planning perioperative care (Prause, et al., 1997). Surgical intervention has connotations for patients as conferring an inherent risk. As doctors this is re-enforced when using the word “conservative” to mean non-surgical management (Chand et al., 2007) suggesting that surgery is a therefore a riskier approach or a “non-conservative” one. The risk of surgery can be classified as the surgical and patient risk factors. The preoperative risk stratification tools and fitness assessment tools will now be appraised.

Functional capacity is measured either subjectively or objectively with varying levels of validity. These include subjective fitness questionnaires such as the Duke Activity Status Index (DASI) questionnaire and Veterans activity questionnaire index (VASI). Objective exercise or strength tests include such measures as hand grip strength test, 6 minute walk test (6MWT), or CPET. These tests give a result which is either an
estimation of fitness or an objective measure, which is either a direct or indirect measure of cardiopulmonary reserve. In the case of CPET it is an assessment of breath-to-breath of cardiopulmonary fitness. CPET is the gold standard of assessment of cardiorespiratory reserve (Moran et al., 2016).

The clinical application of these assessment tools is based on the premise that all-cause mortality increases with a decreasing fitness level (Celis-Morales, 2018). The UK biobank analysed 502,293 patients aged between 40 and 69 and used grip strength as a measure of fitness. They demonstrated that all cause, cardiac and respiratory mortality were all associate with decreasing grip strength (Celis-Morales, 2018). All cause mortality had an increased hazard ratio of 1.2 and 1.16 for men and women respectively with lower grip strength.

Wijeysundera et al., (2010) conducted a large population based (n=271,082) retrospective study looking at outcomes following moderate to major elective non-cardiac surgery. They compared two cohorts of patients those who had preoperative stress testing and those who did not. They concluded that non-invasive cardiac stress testing was associated with an improved one year survival and a reduced length of stay.

In apparently healthy subjects aerobic capacity is the strongest predictor for future adverse events (Guazzi et al., 2016). Interestingly, the term apparently healthy denotes a state where there is no formal diagnosis of disease not the presence of high cardiovascular reserve. In the USA the majority apparently healthy patients present with reduced cardiovascular fitness, increased body mass index and poor health
variables such as high blood pressure, high cholesterol and hyper glycaemia (Guazzi et al., 2016). Thus demonstrating the importance of CPET in the preoperative assessment as underlying abnormalities can be addressed before the patient suffers the initial adverse event (Guazzi et al., 2016).

The earliest, easiest to use and perhaps crudest measure of patient fitness status is the American Society of Anaesthesiologists (ASA) grading system (Older, 1999). This is a 5 incremental assessment of a patients physical status (Prause, et al., 1997). The ASA grade by definition is not a measure of risk, however, Prause et al. (1997) conducted a study of 16000 patients undergoing surgery to assess the correlation between ASA grade and cardiac risk index (CRI) with postoperative mortality. Unsurprisingly, patients who had a higher ASA grade had a higher CRI and those with a higher score in either had a higher mortality, however, those with both a high ASA and CRI had the worse postoperative outcomes suggesting these scoring systems are predictive for risk.

The 2007 ACC/AHA guidance recognises the importance of preoperative assessment of functional capacity. However, it does not prescribe CPET as routine. CPET may be a more reliable way of assessing function capacity than other preoperative measures (Struthers et al., 2008). CPET has been described as the gold standard of fitness capacity assessment (Moran et al., 2016) however it is not available in all centres and requires specialised equipment and trained staff. Therefore simple subjective assessments or questionnaire based evaluation of functional capacity are an attractive alternative to CPET. However, subjective assessment has limitations. The primary limitation is that there is poor accuracy when used to predict postoperative death or
complications and poor correlation with validated measures of functional capacity (Wijeysundera et al., 2018).

The revised cardiac index (RCRI) (Lee et al., 1999) has 6 independent risk factors which have been validated to predict cardiac complications postoperatively. These are: high risk surgery, history of CHF, history of ischemic heart disease, history of cerebrovascular disease, insulin therapy, and serum creatinine above 2.0mg/dL. Lee et al., (1999) studied 4315 patients undergoing non-cardiac surgery and measured rates of cardiac complications. The rate of major cardiac complications in patients with 0, 1, 2 or 3 and above risk factors was 0.5%, 1.3%, 4% and 9% respectively. They suggested the RCRI is a sensitive and specific tool to identify those who are low and risk thus can proceed straight to surgery and those who are at higher risk and require further risk stratification.

The association between RCRI and postoperative non-cardiac morbidity and prolonged hospital stay after elective orthopaedic procedures was investigated by Ackland et al., (2010). The authors studied 560 elective orthopaedic patients in a two centred observational study and concluded that RCRI was associated with increased risk of non-cardiac morbidity and increased length of stay. They reported that non-cardiac complications were more common than cardiac complications yet were associated with a higher RCRI score. They also concluded that RCRI is inadequate for prediction of post-operative morbidity. They suggest CPET may be an improved way of assessing risk. However, in the orthopaedic cohort this may be impractical due to lower limb joint pain.
Struthers et al. (2008) conducted a comparison study of the DASI questionnaire and incremental shuttle walk test (ISWT) compared to CPET results of cardiorespiratory reserve. They found that a patient with high scores on DASI (above 37.45) and ISWT (able to walk more than 320m) had a statistically significant correlation with good CPET results (AT above 11ml O₂/kg/min and peak V̇O₂ above 15ml O₂/kg/min). However, a significant proportion of their patients with poor DASI and ISWT had good CPET results therefore identifying patients as high risk when they are not. More worryingly, the low NPV of the DASI and ISWT did not reliably identify patients with poor functional status thus marking patients as having low risk when in fact they would be high risk based on their CPET result.

Snowden et al. (2010) add to this by using multivariate regression modelling to compare AT with preoperative risk indexes, namely the POSSUM, risk factors derived from cardiac risk scoring index, and validated activity questionnaire. They concluded that AT was lower in the patients who developed complications and that AT significantly adds to the preoperative prediction of surgical risk when compared to questionnaires alone.

Wijeysundera et al., (2018) conducted a multicentre international prospective cohort study (the METS study) which compared the prognostic accuracy of subjective assessments compared to the DASI and CPET. They studied 1378 patients who were scheduled for major elective non-cardiac surgery. They concluded that preoperative subjective assessment should not be used in clinical practice as it lacks accuracy to identify patients with a low functional capacity or those at risk of postoperative morbidity and mortality. They base this assertion on result that subjective assessment
of functional capacity had no significant association with death or myocardial infarction within 30 days after surgery or death within 1 year after surgery. Peak $\dot{V}O_2$ was predictive of postoperative complications. However, contrary to other large meta-analysis (Moran et al., 2016) which concluded AT and peak $\dot{V}O_2$ to be predictive of postoperative mortality in major abdominal surgery Wijeysundera et al., (2018) reported no association with myocardial infarction or myocardial injury. This is contradictory to the emphasis of practice guidelines on functional capacity which suggest AT and peak $\dot{V}O_2$ should be used in preoperative risk stratification.

Wijeysundera et al., (2018) conducted a large study in many centres or many types of procedure this makes the results very generalizable to patients in the developed world but is less applicable to specific cohorts in specific centres. They also had a rather low recruitment rate of 27% of eligible patients, the authors suggest this is as the idea of “unnecessary” strenuous exercise put patients off enrolment. One may assume this introduces a selection bias of younger, fitter patients who are willing to participate in exercise enrolling and thus improving the fitness of the enrolled patients and reducing the complication rate. They did find a lower than expected complication rate. Their baseline demographics did reflect this with 34% of patients being ASA 3 or about and 55% of patients were RCRI class 2 or above. The baseline age was 65 and 1% having CHF, 15% being current smoker and 19% having diabetes.

Older et al., (1999) published a method of detecting patients at lower risk of surgery to help guide management postoperatively. They used CPET with the cut off of AT to split the patients into 3 groups. 1- those with >11ml/kg/min deemed low risk and to have ward based care (51%). 2- patients with >11ml/kg/min but ventilatory
inefficiency (VE/\dot{V}CO_2 >35) or myocardial ischemia to be intermediate risk and have high dependency care. 3-high risk patients who have a <11ml/kg/min for intensive care admission. The overall cardiovascular mortality was 0%, 1.7% and 4.6% for low, intermediate and high risk respectively. This elegant solution to perioperative management allowed a more reasoned approach to admission to intensive care and reduced the number of patients attending due to age alone or due to having surgery specific risk. The reported cardiac risk is likely to be under-estimated in this cohort as the higher risk patients receive higher levels of care and therefore one would expect improved management to avoid cardiac death. The intensive management in these patients is rather outdated now as all received a pulmonary artery catheter but the triage system employed did limit the cardiac deaths to only the intermediate and high risk groups. However, not reported here and potentially more useful is cardiac and all cause morbidity.

Older et al., (1999) triage tool is used only AT and VE/\dot{V}CO_2 to manage patients. Perhaps this is an oversimplification of the complex tool of CPET. Wijeysundera et al., (2018) suggest that other CPET metrics, ie not peak VO_2 and AT, might be more useful for the prediction of cardiac complications postoperatively. They suggest variables such as exercise and heart rate relationships may be more specific. This assertion adds to previously stated theory stated in Chapter 2.1 meta-analysis results that perhaps conventional CPET variables are insensitive to cardiac risk and therefore insensitive measures of cardiac improve with drug treatment (namely beta-blockade). These alternative CPET variables will be discussion in the following chapter to give the theoretic background to their inclusion in the ICAF-beta study.
CPET variables important to surgical risk and ICAF-beta

CPET variables have previously been described in chapter 2.1. This section will focus on describing CPET variables which are important to the ICAF-beta trial as they make up part of the inclusion criteria. These are: oxygen pulse relationship and oxygen work rate (WR) relationship and their theoretical basis will be discussed below.

Oxygen pulse

The oxygen pulse is common term for the volume of oxygen extracted per heart beat and is the ratio of $\dot{V}O_2$ to heart rate (ATS/ACCP, 2003) sometimes reported as $\dot{V}O_2$/Heart Rate (HR) or $\dot{V}O_2$:HR. This is displayed on Wasserman Panel 2 plotted against HR, WR and time.

Oxygen pulse is a surrogate for stroke volume (SV), (ATS/ACCP, 2003). The modified Fick equation states: $\dot{V}O_2$/HR=SV x [C(arterial-venous)O$_2$] (where C=content). As the C(arterial-venous)O$_2$ is assumed to constant oxygen pulse therefore is equal to SV. However this is controversial and may be unreliable in patients who desaturate.

Wasserman panel 2 plots oxygen pulse and heart rate against time and is used to assess a patients stroke volume response with increasing exercise intensity compared to the heart rate response. A normal response is to observe a linear coupled increase of SV and HR over the exercise intensity. When there is mechanical dysfunction in the
myocardium there is a compensatory response which lead to an increase in HR to increase cardiac output when SV is unable to increase (Chaudhry et al., 2018). Chaudhry et al., (2018), in their work in obstructive and non-obstructive CAD patients and CPET, report a cascade of outcomes secondary to mechanical dysfunction with increasing work rate. This starts with hypo perfusion leading to metabolic derangement leading to diastolic then systolic dysfunction and ending with ECG changes and finally angina pain. They report that at the stage of diastolic and systolic dysfunction there is an increased HR due to an inappropriate SV response.

The formal measurement of HR change over time has been suggested as measuring the change in HR to work rate mid-exercise compared to change in HR to work rate in the final 2 minutes of exercise. A normal response is one of both HR and SV to increase to the predicted level in a linear fashion without inflection (Chaudhry et al., 2018). The ICAF-beta trial uses Wasserman panel 2, HR to SV as evidence of demonstrable myocardial dysfunction during exercise and thus is an inclusion criteria. An abnormal response is defined as a flat or inflected SV response. Oxygen pulse is also recorded at rests, AT and peak $\dot{V}O_2$.

**$\dot{V}O_2$ and $\dot{V}CO_2$ work rate relationship**

The ICAF-beta trial uses Wasserman panel 3, the $\dot{V}O_2$ and $\dot{V}CO_2$ work rate (WR) relationship. Work rate is plotted against L/min of $\dot{V}O_2$ and $\dot{V}CO_2$. The slope is represented by $\Delta \dot{V}O_2 / \Delta WR$ (Wasserman et al., 2004). On this panel there is also a plotted normal predicted line of slope of, for example several reports of normal subjects demonstrated a slope of 10ml/min/watt (Balady et al., 2010). For the cell to increase cellular respiration and use ATP for muscular contraction over increasing
workloads the transport of O₂ and CO₂ must increase in parallel. A normal response has the gas L/min increasing in parallel to the increasing workload- 1 watt to 10ml/min increase.

This relationship is representing a complex transport system and relies on the function of respiratory muscles, lungs, pulmonary circulation, blood, heart and the peripheral circulation (Wasserman et al., 2004). Defects in any part of this system can lead to an abnormal response of a flattened, inflected or downward appearance of the plot. Wasserman et al., (2004) describes the pathological appearance of CAD, dilated cardiomyopathy, peripheral vascular disease, lung disease and obesity. The failure to increase oxygen consumption, particularly in the later stages of exercise, is multifactorial but in the CAD can identify myocardial ischemia (Chaudhry et al., 2018).

**Heart failure**

As CHF is a condition with a raised VE/VO₂ (Balady et al., 2010) and is an independent risk factor for surgery (Lee et al., 1999) it is an important pathology for discussion in relation to the ICAF-beta study. The ICAF-beta study is hypothesising that patients with an increased VE/VO₂ potentially have an element of undiagnosed CHF which is evident from the ventilation/perfusion mismatching and signs of reduced SV response to exercise and is therefore amenable to drug treatment with beta-blocking agents. The following chapter will discuss the pathophysiology, diagnosis, clinical biomarkers of CHF.
Heart failure background and pathophysiology

CHF is a common condition. The British Heart Foundation (BHF) estimated that in 2012-13 there were over 151,000 hospital admissions due to heart failure and based on current prevalence data there are over half a million people with heart failure (HF) in the UK (Huntley et al. 2016, BHF 2014). CHF has a male preponderance. HF incidence is not rising, however the prevalence is (Hammill et al., 2008). The rising prevalence is due to the combined effect of: improved survival following myocardial infarctions so more patients subsequently develop CHF, the treatment of CHF has improved leading to increased survival, and CHF is a disease of the elderly- and the elderly population is growing (Jacobs et al., 2017). In the national cardiac audit programme (NCAPR) 2018 the mortality for patients with CHF was 8.4% and 12.9% for those seen by a HF specialist and those who were not (NICOR, 2018).

Classically HF was defined as the inability for the heart to meet the metabolic demands of the body through a reduced cardiac output despite adequate filling pressures. I.e. upstream congestion leading to a state of downstream hypoperfusion (Arrigo et al., 2016). This definition is less useful in CHF as most patients who are adequately treated have a normal cardiac output and filling pressure and are able to meet the metabolic demands at rest. During exercise or times of increase metabolic stress they are unable to meet this demand and thus leading to the cardinal sign of CHF of exercise intolerance and limitation (Arrigo et al., 2016).
CHF can be categorised into HF with reduced ejection fraction and HF with preserved ejection fraction (HFrEF and HFpEF). HFrEF will be discussed first then HFpEF will be discussed.

The pathophysiology of CHF is complex, it involves: haemodynamic responses, adverse ventricular remodelling, neurohormonal activation, and inflammatory responses (McDonagh et al., 2011). In response to reduced myocardial contractility there are a number of adaptive mechanisms to maintain cardiac output. These mechanisms improve cardiac output but chronically become maladaptive and start a spiral of decline in the failing heart.

The haemodynamic responses are modulated primarily by three mechanisms. Firstly, by hypertrophy of the cardiac myocytes which increases contractility. Secondly, by activation of the rennin-angiotensin-aldosterone system (RAAS) which increases contractility and preload. Lastly, and most importantly, modulated by the Frank-Starling response to increase cardiac output with an increased preload (Arrigo et al., 2016).

These mechanisms will now be discussed. Ventricular remodelling has two phases. Initial remodelling is concentric where there is an increase in left ventricular wall thickness and mass. This is followed by eccentric remodelling where there is dilation of the ventricle. This is causes reduced systolic function and leads to valvular regurgitation. (Johnson, 2014).
Evolutionary mechanisms are adapted to protect against sudden death by exsanguination, which increase blood pressure and critical organ perfusion. These mechanisms are activated in CHF low cardiac output state. Activation of the sympathetic nervous system leads to increased catecholamine release causing increased vasoconstriction, chronotropy, inotropy and lusitropy (Woodley, et al. 1991). Myocardial oxygen uptake therefore increases. Increased circulating catecholamines are cardiotoxic leading to cellular death and remodelling. In the CHF patient the generalised increase in adrenergic activation as the disease severity increases (Woodley, et al. 1991). This is accompanied by is a reduced ability to respond to the catecholamine surge of stress or exercise due to the down regulation of beta one adrenoceptors. Studies have demonstrated that in CHF patients and those with dilated cardiomyopathy that there are increased levels of circulating catecholamines and by treating these patients with beta-blocking agents these levels can be significantly reduced (Woodley, et al. 1991, Gilbert et al.,1990 and Andersson et al., 1994). This is accompanied by a reduction in symptoms and improved physiological markers ie ejection fraction and stroke work.

RAAS activation leads to increased level of angiotensin II which is a powerful vasoconstrictor. It also causes vascular and myocyte hypertrophy and the release of: aldosterone, vasopressin, endothelin and catecholamines. Two landmark trials in 1991 and 1992 demonstrated that ACE inhibitors were the first pharmacological treatment to decrease mortality in CHF. (Pearse et al., 2014). ACE inhibitors, along with beta-blockers are now first line management for patients with CHF. Aldosterone causes sodium and water retention increasing preload. There is an increased potassium loss which is arrhythmogenic. Aldosterone also causes myocardial fibrosis.
Non-specific chronic inflammatory changes may play a role in the pathophysiology of CHF. TNF alpha and IL-6 have been shown to be independent prognostic indicators (McDonagh et al., 2011).

**Heart failure diagnosis and biomarkers**

To diagnose CHF signs and symptoms are useful to raise clinical suspicion but are neither sensitive nor specific enough for its diagnosis. Therefore, objective evidence of cardiac dysfunction is required. Serum B-type natuieritic peptide (BNP) is released due to stretch of the cardiac myocytes. BNP and NT-proBNP (the inactive polypeptide fragment of proBNP) are well known to be elevated in patients with left ventricular systolic dysfunction. A level above 400 pg/ml or 2000 pg/ml for BNP and NT-proBNP respectively is likely to be diagnostic of CHF. A normal level, below 100 pg/ml or 400pg/ml for BNP and NT-proBNP respectively has a 99% negative predictive value, as such it is used as a rule out test for patients with unknown dyspnoea in the emergency department and signs of acute HF (Arrigo et al., 2016).

An ECG is part of the diagnostic workup. A normal ECG has a negative predictive value of over 90%. NICE guidelines (2018) suggest NT-proBNP <400 ng/l is not suggestive of CHF, NT-proBNP 400-2,000 ng/l requires urgent referral to cardiology within 6 weeks and NT-proBNP> 2,000 ng/l requires referral within 2 weeks. Patients should receive an echocardiogram as part of this work up.

Transthoracic echocardiography (TTE) was endorsed as the single most useful diagnostic test in CHF patients by The ACC/AHA. TTE is used to assess left
ventricular function in terms of size and shape, global and regional systolic function, diastolic function, intracardiac haemodynamics and left ventricular synchrony (Duncan, 2011).

An ejection fraction less than 55% is classified as abnormal. Mild, moderate and severe CHF cut offs are defined as 55-45%, 44- 36%, and below 35% respectively. On TTE a normal wall thickness is 0.6-1.2 cm, Normal LV volume at end diastolic and end systolic is 67-155ml and 19-49mls respectively for men (Duncan, 2011).

It is recognised that approximately 50% of patients with the clinical presentation of HF have normal systolic function (Udelson 2011). This is commonly called HF with preserved ejection fraction (HFpEF). There is not agreement on HFpEF pathophysiology and treatment. Abnormal diastolic filling and ventricular stiffness is proposed to be the main mechanism however this was not a universal finding in HFpEF patients. Tissue Doppler measurement of LV relaxation does appear to be consistently abnormal in HFpEF patients (Udelson 2011).

The following chapter will detail how CHF is demonstrated on CPET testing then the topic of CHF and surgical outcomes will be addressed.

Heart failure and CPET

Reduced exercise capacity is a cardinal symptom of CHF this can be objectively measured using CPET. Patients with CHF have a characteristics collection of results on CPET of reduced: peak $\dot{V}O_2$ and AT, and often reduced: $\Delta \dot{V}O_2 /\Delta WR$, peak HR,
peak $\dot{VO}_2$/HR. Post exercise FEV$_1$ is unchanged compared to rest FEV$_1$ and SaO$_2$ is normal. VE/\dot{VCO}_2 is often raised in CHF (Balady et al., 2010). CHF can be defined by an impaired ability to increase cardiac output in response to the demand of exercise. This leads to a ventilation/perfusion mismatch. In CHF there must be a disproportionate rise in ventilation to meet the metabolic demands to compensate for the reduced perfusion (Balady et al., 2010) thus leading to breathless and exercise intolerance.

In CHF the cardiovascular system is unable to meet demands due to an abnormal cardiac output caused by reduced ventricular contractility, chronotropic incompetence and functional mitral regurgitation (Malhotra et al., 2016). Filling pressures during exercise can dramatically rise due to a decreased diastole time, increased venous return, and reduced vasoreactivity. Furthermore, in CHF there is often reduced oxygen carrying capacity secondary to anaemia and oxygen utilisation is reduced by a diminished capillary density, reduced sympatholysis, decreased mitochondrial volume and selective loss of type 1 muscle fibres (Malhorta et al., 2016). Additionally, there is an increased ergoreflex signalling via intramuscular afferents leading to an exaggerated ventilator response to exercise (Malhorta et al., 2016).

Peak $\dot{VO}_2$ is the most widely used parameter to predict survival and hospitalisation in CHF. It is also used to assess select patients for heart transplantation where patients with a peak $\dot{VO}_2$ below 14ml/kg/min have a worse prognosis (Sarullo et al., 2010). There are a number of problems with measuring peak $\dot{VO}_2$ in CHF patients. Firstly, it requires maximal effort which may not be possible or safe in CHF patients. Secondly, it may be underestimated due to premature termination of the test due to low patient
motivation or termination by the physician (Gitt et al., 2002). Thirdly, patients with heart failure have different body compositions having a higher percentage body fat and tissue oedema. This increases weight but has minimal oxygen consumption so it is argued that lean body weight is more accurate denominator rather than actual body weight min/kg/min (Balady et al., 2010). Finally, patients with CHF may have their test terminated early due to patient or physician factors.

Sarullo et al. (2010) demonstrated that a peak $\dot{V}O_2$ below 12.2 ml/kg/min was good prognostic indicator for mortality and morbidity. They showed CHF patients with a peak $\dot{V}O_2$ below this threshold to have a 1 year cardiac mortality of 66% and cardiac hospitalisation of 63% compared to those above the threshold having 34% and 37% respectively ($p < 0.0001$) (Sarullo et al., 2010). Mancini et al. (1991) had similar results with a large difference in mortality when patients were divided into cohorts of those with a peak $\dot{V}O_2$ of over 14ml/kg/min and those who had peak $\dot{V}O_2$ below this value. They reported a 1 year survival of 94% and 70% in the groups respectively. They argued that this allows for surgical planning and safe deferring of surgery for those with a peak $\dot{V}O_2$ above 14ml/kg/min. The problem with dichotomous data is that it is useful as a population basis but at an individual level it is less useful as a single marker when the patient is very close to the threshold value. This is illustrated when peak $\dot{V}O_2$ is added to a significant co-morbidity then the 1 year survival for such a cohort was 47% (Mancini et al., 1991). This illustrates the point that peak $\dot{V}O_2$ should not be viewed in isolation when risk assessing patients. The other problem with this binary view of a continuous variable is that patients close to the threshold may be misclassified and the errors which make be seen in peak $\dot{V}O_2$ have been previously discussed.
Guimaraes et al., (2010) examined CHF patients who were on beta-blocking agents for at least 3 months to investigate whether the idea that peak $\dot{V}O_2$ was predictive of mortality and if so at what threshold. They argued that beta-blockade has little to no effect on peak $\dot{V}O_2$ therefore aimed to investigate whether CPET was predictive of event free survival in the “beta-blocker era”. They concluded that CPET retained its predictive value in CHF patients on beta-blocking therapy. The threshold value of peak $\dot{V}O_2$ of 12.5/ml/kg/min had an area under the curve of 0.8 ($p<0.001$) on ROC curve analysis which showed impressive differences in Kaplan-Meier survival curves in cohorts above and below the threshold. Event free survival was 28% and 2.8% respectively for cohorts below and above 12.5ml/kg/min. One must be mindful that this is published as a letter to the editor and as such is not peer reviewed. Furthermore the cohorts had a significant difference in terms of baseline characteristics. The cohort with a reduced peak $\dot{V}O_2$ were older, had a higher proportion of other medications, and a reduced exercise tolerance. However, the mix of male to female was 41% female in the lower $\dot{V}O_2$ group compared to 24% and women are known to have lower peak $\dot{V}O_2$.

$VE/\dot{V}CO_2>40$ is a strong indicator of poor prognosis and mortality progressively increases as $VE/\dot{V}CO_2$ increases from normal to above 40 (Balady et al., 2010). Sarullo et al. (2010) reported $VE/\dot{V}CO_2$ above as a good prognostic indicator of mortality with a sensitivity of 89% and specificity of 84.7% on ROC curve analysis. Their data shows that CHF patients above this threshold had a 1 year cardiac mortality of 75% and a cardiac hospitalisation rate of 77% compared to those below the threshold having 25% and 23% respectively ($p<0.0001$).
Poggio et al. (2010) conducted a 12 study meta-analysis and concluded that VE/$\dot{V}CO_2$ slope was able to predict risk of death in patients with CHF. Interestingly, Wilson et al. demonstrated that elderly patients with abnormal CPET (reduced AT below 11 ml/kg/min and VE/$\dot{V}CO_2$ above 34) were more likely to die, whether or not they had clinical cardiac risk factors. This suggests that CPET is a more useful tool than preoperative using risk factors alone. Furthermore, it suggests that functional capacity assessment in those without formal risk factors is useful as those without risk factors and a measurable low functional capacity have a higher mortality so would benefit from functional capacity assessment to identify them as high risk and subsequently optimise their care.

Patients with HFpEF and HFrEF appear to have the same degree of impaired aerobic capacity with an equally diminished oxygen uptake slope when compared to healthy individuals. However, VE is lower in those with diastolic compared to systolic dysfunction (Balady et al., 2010).

The ability to detect AT in patients with CHF is reduced for two reasons. Firstly due to patients terminating the test before the AT is reached and secondly an abnormal ventilator response makes the interpretation more difficult secondary to an oscillatory breathing pattern (Balady et al., 2010).
Heart failure and surgical outcomes

The number of patients with CHF who are undergoing surgery is predicted to increase significantly over the next two decades (Hammill et al., 2008). This is due the combined effect of an increasing prevalence of CHF in the general population, an increasing elderly population (50% predicted increase) and an increase in surgical procedures (25% predicted increase) (Hammill et al., 2008). The RCRI cites CHF as an independent risk predictor for major postoperative cardiac complications (Lee et al., 1999). The relative risk for major cardiac complications is quoted as 3.4% in CHF patients. CHF has been identified as a risk factor for post-operative death both nationally and internationally (Pearse et al., 2012).

Patients with CHF may not be able to mount an appropriate physiological response to exercise hence they are also unable to compensate for the systemic inflammatory response and subsequent increased oxygen consumption that major surgery generates. Global oxygen uptake can increase by 50% following major surgery (Older, 2013). Thus, patients who cannot increase their oxygen supply (by increasing cardiac output and tissue perfusion) are more likely to develop postoperative organ dysfunction, morbidity and mortality (Wilson et al., 2010 and Struthers et al., 2008).

Much work has been done with the CAD population preoperatively to attempt to reduce the risk of non-cardiac major surgery. The same improvements have not been seen in the CHF cohort and yet they carry a higher risk of mortality (Hammill et al., 2008 and Hernandez et al., 2004). Hammill et al. (2008) and Hernandez et al., (2004) both call for improvements to be made in the perioperative management of CHF.
Hernandez et al. (2004) conducted a retrospective study using multivariable logistic regression modelling to examine the adjusted mortality and readmission rates of CHF patients undergoing non-cardiac surgery compared with patients without CHF. They also studied a cohort of patients with CAD for comparison. They included 1532 CHF patients, 1757 CAD patients and 44512 controls. They reported a mortality rate for CHF, CAD and controls as 11.7%, 6.6% and 6.2% respectively. Furthermore, they reported a 30 day readmission rate for CHF, CAD and controls as 20%, 14.2% and 11% respectively. The increased mortality in the CHF cohort was across all surgeries and represented an odds ratio of 2.187 (CI 1.88-2.545) (Hernandez et al., 2004). Interestingly the control vs CAD cohorts have very similar risk profiles with a 30 day mortality odds ratio of 1.078 (CI 0.884-1.315). Illustrating the point that the CAD population have benefited from a much improved perioperative management strategy compared to the CHF populations. As previously mentioned having CHF, with or without symptoms, is associated with a significantly raised 90-day post-operative mortality in non-cardiac surgery (Lerman et al., 2019). Those patients undergoing non-cardiac surgery with symptomatic CHF have the single highest risk for post-operative mortality.

CHF patients have a background higher risk of hospitalisation however this is quoted at 5.4%, thus the post-operative differences in the groups cannot be explained merely by an increased background risk alone. It is not reported in Hernandez et al., work whether the readmissions were due to a surgical cause, HF or other cause therefore it is difficult to assess whether the causes for readmission were cardiac in nature. Also 30 day time periods for mortality and readmission have the benefit of being close to surgery and therefore the assumption is that it is a surgical cause but more modern
post-operative research favours 90 day mortality as it identifies a larger number of mortality outliers (Byrne et al., 2013).

Hernandez et al., (2004) suggest that future studies should look at pre-optimisation of CHF medically with beta-blockade and angiotensin-aldosterone antagonism. Beta-blockade titration is normally done over several weeks rather than the shorter period between pre-assessment for surgery and the procedure. This time frame is even shorter in the emergency setting where patients level of decompensation need to be assessed and rapidly optimised pre-surgery. Current guidelines only suggest not starting beta-blockade 24 hours prior to surgery and that the effect of treatment should be monitored but what time frame this should be done over is not clear. Hernandez et al., (2004) show the survival function between controls and CHF in Kaplan-Meier curves for elective, urgent and emergency and as the urgency of surgery increases the disparity in survival increases between control and CHF.

Hammill et al., (2008) investigated the CHF population undergoing non-cardiac surgery and compared the 30 day mortality and 30 day readmission rates to a CAD population and control group. They found a mortality of 8%, 3.1% and 2.4% in the CHF, CAD and control groups respectively. Regression analysis demonstrated an adjusted risk of 1.63 (CI 1.52-1.74) and a 1.51 (CI 1.45-1.58) for 30 readmission in the CHF compared to the control group. The authors controlled for confounding and for surgery type. Both the Hammill et al., (2008) and Hernandez et al., (2004) were conducted in the USA in fee paying hospitals so the generalisability to the NHS is uncertain.
Maile et al., (2014) conducted a multi-centred retrospective cohort study with the aim of characterising the types of complications patients suffered in those with new or worsening HF and those without. The previous work described has focused on cardiac complications; this study took a broader perspective to better understand the relationship between HF and other organ system complications. Maile et al., (2014) used cohort matching for age, sex, comorbidities and surgical factors to reduce confounding variables. As expected the unmatched cohorts contained a higher proportion of elderly patients and complex surgery was more prevalent. When cohorts were matched the results show an in the hazard ratio for all complications. Nine of the complications were statistically significant and 10 were not. Hazard ratio for composite all cause morbidity was 1.54 (CI 1.4-1.69) and mortality was 2.08 (CI 1.75-2.46). Interestingly, HF patients had a significantly higher risk of respiratory, renal and infectious complications. These patients did not have a statistically significantly higher incidence of stroke or myocardial infarction contrary to the previously studies described above. This has biological plausibility as the pathophysiology of heart failure is not of restricted flow to the coronary arteries but is of poor flow globally which would lead to pulmonary complications of increased days ventilated and renal complications such as acute renal failure.

The NICOR audit project (2018) reported that there is a significant difference in inpatient mortality between CHF patients admitted to a general medical ward vs those admitted to a cardiology ward, 10.4% and 7% respectively. Suggesting that patients with CHF receive better care and thus better outcomes on a cardiology ward. Post-operative patients with CHF will be admitted to a surgical ward. This data is not presented but is an interesting point to reflect on. It is standard practice for post-
operative orthopaedic patients to be seen by a geriatrician. Perhaps an intervention to reduce post-operative morbidity and mortality may be a specialist medical review in patients assessed as high risk of complications would improve patient outcomes.

To summarise, large retrospective analysis has demonstrated a significant increase in post-surgical risk in terms of mortality and morbidity for CHF patients undergoing non-cardiac surgery meaning perioperative services have to be able to identify these patients, optimise them and plan their care to aim to reduce mortality.
Chapter 3. ICAF-beta Methodology

Study Design

We designed a prospective proof-of-concept, case series study, with patients acting as their own controls in terms of before and after comparisons of cardiac function. CPET derived measures of impaired myocardial response (primarily $\text{VE/}\text{VCO}_2$), NT-pro BNP levels and echocardiographic measured parameters of systolic and diastolic function were compared before and after administration of beta-blockade.

Study Setting

This is an MRHA approved single centre study conducted at York Teaching Hospital NHS Foundation Trust. The study sponsor is York Teaching Hospital NHS Foundation Trust and gained ethical approval (REC 17/YH/0222. IRAS number 2264 32YNP. Eudract: 2017-002443-15).

Eligibility criteria

Patients aged 55 years or over, scheduled for major intra-abdominal surgery and presenting for routine CPET as part of pre-assessment were considered for the study. They were scheduled for either: colorectal, major urology, or aortic surgery, which was not taking place within fourteen days of pre-assessment.
Inclusion Criteria

• Aged 55 years or over
• Scheduled for major intra-abdominal surgery
• Presenting for routine CPET as part of pre-assessment
• Not currently taking any Beta-blocker medication and not taken Beta-Blocker medication within 1 month prior
• Consent to GP being informed
• VE/\(\dot{V}CO_2\) 34 or greater on CPET, as either the value measured at \(\dot{VO}_2\) at AT, or the lowest measured value, plus at least one of the following:

1. Presence of a known history of a clinical risk factor for major adverse cardiac events (MACE) after surgery:
   - Ischaemic heart disease
   - Cerebrovascular disease
   - Renal insufficiency (creatinine > 170 mmol.L\(^{-1}\))
   - Chronic heart failure

2. Evidence of abnormal myocardial response on exercise testing
   - Flattened or inflecting oxygen uptake to heart rate response (oxygen pulse response, \(\dot{VO}_2/HR\), panel 2)
   - Flattened or inflecting oxygen uptake to work rate response (\(\dot{VO}_2/Watt\), panel 3)

3. Anaerobic threshold <11mls/kg/min
**Exclusion Criteria**

- Refusal or unable to give informed consent
- Fewer than 10 days before scheduled surgery at pre-assessment appointment surgery
- Current beta-blocker medication or having taken any beta-blocker within 1 month prior
- Contra-indications to beta-blocker medication including:
  - bronchial asthma
  - reversible airways disease
  - decompensated heart failure (NYHA class IV)
  - fluid overloaded
  - hypotensive
  - severe liver impairment
  - second or third degree A-V block (unless pacemaker fitted)
  - SA block
  - sick sinus syndrome (unless pacemaker inserted)
  - cardiogenic shock
  - bradycardia (heart rate less than 60 bpm)
  - Prinzmetal's angina
  - Untreated Phaeochromocytoma
  - metabolic acidosis
  - poor blood circulation in the hands and feet
  - severe peripheral arterial insufficiency
- known hypersensitivity to bisoprolol or its ingredients (lactose monohydrate, silica colloidal anhydrous, crospovidone (Type A), crospovidone (Type B), povidone 30, sucrose, magnesium stearate)
- co-prescription with negative chronotropic agents such as digoxin, diltiazem, verapamil, amiodarone
- co-prescription with medications that affect the plasma concentrations of bisoprolol such as rifampin, cimetidine, quinidine, fluoxetine, paroxetine, propafenone, digoxin, reserpine, monoamine oxidase inhibitors, clonidine

**Study intervention**

Patients were recruited from the routine CPET clinic; they were invited by letter with a patient information sheet for the study included. As part of the perioperative service at York Teaching Hospitals NHS Foundation Trust patients who are over 55 and scheduled for major abdominal surgery will be routinely reviewed preoperatively by a pre-assessment nurse, anaesthetist in CPET clinic, have routine phlebotomy and have dedicated time to see a research nurse or doctor. The aim of the clinic is to take a full preoperative assessment on which to base a preoperative optimisation plan, intraoperative monitoring and anaesthetic plan, and postoperative destination for care. It also allows open dialogue with the patient and MDT about an individualised risk of surgery.
Appendix 9 shows the study flow diagram for the study. When the patient met the inclusion criteria at CPET testing they were invited to meet with a member of the study delegation to be formally screened and consented to be part of the study. If at any stage they declined or were considered to meet the ineligibility criteria they were excluded from the study.

The inclusion criteria of VE/VCO2 above 34 and AT below 11 ml/kg/min is based on ATS/ACCP (2003) guidelines for normative values. Historically, an AT of 11 ml/kg/min was chosen as it was the cut off value shown for moderate to severe heart failure. Older et al. originally used this cut off to demonstrate the increased risk in surgical patients of 0.8-18% mortality in the fit vs unfit cohorts (Wilson et al., 2018). More recently, Rose and colleagues (2018) have suggested that a zoned approach of low, medium and high risk groups in relation to patients fitness is more useful that the binary distinction of 11 ml/kg/min being the gateway between fit and unfit. For this study the ATS/ACCP (2003) guideline parameters were used as these parameters were used in the Wilson et al. (2010) study for a cohort of patients in York Teaching Hospital. As such, the risk assessment tools used in York Teaching Hospital and the mortality rates quoted to patients are based on this study.

At the first visit the patients had a baseline echocardiogram and NT pro-BNP added to their baseline blood tests which were taken before exercise. NT pro-BNP has been demonstrated to add to preoperative assessment prediction of 30 day myocardial injury or death, and 1 year death post major non-cardiac surgery (Wijeysundera et al., 2018). Baseline NT pro-BNP was taken prior to CPET as exercise is known to cause a statistically significant transient rise in NT pro-BNP in healthy and CHF populations.
The peptide is stimulated and released in response to increasing wall stress caused by raised intra-cardiac pressure or volume (Krupicka, 2010). Studies of marathon runners BNP level demonstrated a transient rise in level which did not return to a normal value until 3 hours post exercise and Krupicka and colleagues demonstrated that levels did not return to normal until 4 hours post CPET in healthy individuals (Krupicka, 2009). For this reason, blood samples after CPET were not used for the study.

Baseline echocardiography was completed to investigate heart function and markers of heart failure using the BHF echocardiography: guidelines for Chamber Qualification which is adapted from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography (Lang 2005).

When analysing serial scans on the same patient the preferred method of measurement is to have the same images side-by-side and be measured at the same time, by the same person. The imaging technique requires skill and expertise (Lang 2005). In this study echocardiography was conducted by the Senior Chief Cardiac Physiologist (JA), as there was not dedicated clinic time for echocardiography a pragmatic approach was taken that another senior cardiac physiologist (LD) would conduct the scan in JAs absence. All reports were analysed by the Senior Chief Cardiac Physiologist. The echocardiogram variables of interest are: ECG rate (BPM), ECG rhythm (Sinus rhythm, Atrial fibrillation, LBBB, RBBB, or other ECG abnormality abnormal), LV dimensions (ml), LV volumes (ml), LA volume (ml), Ejection fraction
The patient was then prescribed the study drug of Bisoprolol 2.5mg once daily for a minimum of 10 days.

After a minimum of 10 days the patients were invited back for a repeat echocardiogram, CPET, and NT pro-BNP studies. In a large meta-analysis of CHF patients the mortality benefit was irrespective of treatment duration with beta-blocking agents (Chatterjee et al., 2013). As reported in Chapter 2.1 studies investigating beta-blockade using CPET had a treatment during of 1 week to 1 year. West et al., (2015) used a minimum of 1 week treatment duration in a pre-surgical population. The decision for 10 days of therapy was pragmatic as CPET clinics run weekly on Mondays and Thursdays thus a practical time frame is 7, 10 or 14 days. As there is a time pressure between CPET clinic and surgery 10 days was chosen. This was later shortened to 7 days to increase recruitment.

The study terminated when second set of tests was completed. The patient then proceeded to the planned surgery. The study drug was continued, as agreed by cardiology, and the patient was then be reviewed by a cardiologist for their future management. Outcome data for length of stay and mortality was collect. This study is not powered to detect short term of long term mortality or morbidity outcome data.
Equipment

Medgraphics Cardiorespiratory Diagnostics-The Ultima Series™ CPX all in one metabolic stress system. BreezeSuite™ cardiorespiratory diagnostic software. SunTech™ Tango+ stress BP and wireless ECG. Lode Carival cycle ergometer were used.

Protocol: 3 minutes of unloaded work followed by 10 Watt/Minute ramping protocol. The system has regular maintained and tests by the manufacturer. The system is two point calibrated manually before each clinic and calibrated between each patient. This will reduce calibration errors between retests and improve quality control (ATS/ACCP, 2003).

CPET Procedure and Rationale

Patients are screen by an anaesthetist prior to CPET to assess whether the patient is safe or appropriate to conduct the test. This involves taking a medical history and assessing baseline physical observations, namely: heart rate, blood pressure, oxygen saturation and respiratory rate. If the patient cannot follow or understand commands then they are not able to complete CPET. The American College of Sports Medicine suggest all patients are screen prior to CPET to assess risk of cardiac events during exercise (Ferguson, 2014). Patients who are at low risk do not require a medical examination or supervision from a doctor for submaximal or maximal testing, patients at moderate risk require a medical examination before a maximal test but do not require a doctor present for the test, and patients who are high risk require a medical
examination and a doctor present for maximal and submaximal testing (Ferguson, 2014). All CPET at York Teaching Hospitals NHS Foundation Trust is conducted with a consultant anaesthetist present. Adverse events during CPET are very rare. Serious complications are reported in large case series with patients with and without disease in less than 1 per 10000 tests and the risk of death as approximately 0.5 per 10000 tests (Balady et al, 2010). In the HF–ACTION study, 2037 patients with heart failure were investigated with CPET and there were no reported deaths and less than 0.5 per 10000 major nonfatal cardiac events (Balady et al, 2010).

Based on the literature a treadmill is the preferred modality as patients can gain a 10-20% increase in recorded peak VO$_2$ compared to other modalities. The other benefit of the treadmill is it does not rely on patient cooperation to keep a steady pedal speed (Balady et al, 2010). The treadmill uses more muscle groups than cycle ergometry and thus is not prone to quadriceps fatigue and termination of testing due to over use of one muscle group (Balady et al., 2010, Levitt et al., 2018). At York Teaching Hospitals NHS Foundation Trust the standard CPET is conducted on a cycle ergometer on a ramped 10watt/min protocol. For patients who have lower limb pathology there is access to a hand cycle ergometer and for bariatric patients there is a reclined cycle ergometer. Only patients who used the cycle ergometer were considered for the study to create a homogeneous sample. The cycle ergometer is preferred in York Teaching Hospitals NHS Foundation Trust as the patient group is elderly with co-morbidities so often have balance and orthopaedic problems. The cycle ergometer also allows for improved electrocardiogram visualisation as there is reduced trunk movement and this is important for high risk patients. Cycle ergometer also confers the benefit that the patient cannot change upper limb position to gain
support from hand rails during the test which is the case in many treadmill protocols. If a patient were to hold the hand rails during a treadmill test it would reduce the work done and changes the relationship between work rate and $\dot{V}O_2$ (Balady et al., 2010).

Several studies have demonstrated a reliable relationship between the two modalities of static cycle and treadmill at submaximal and maximal testing, however Peak $\dot{V}O_2$ is constitutently lower on the cycle ergometer (Balady et al., 2010, Buchfuhrer et al. 1983, Myers et al. 1991). Submaximal such as VE/$\dot{V}CO_2$, AT and heart rate are more consistent between the modalities and the differing protocols (Myers et al, 1991, Buchfuhrer et al. 1983). A ramping protocol is preferred as this provides a more linear relationship between work rate and $\dot{V}O_2$ over the staged protocol where there are large incremental changes in work between each stage (Balady et al. 2010). The linear relationship on the graph is easier to interpret the AT infection point.

The aim of the protocol is to produce cardiopulmonary fatigue limited end points between 8 and 12 minutes duration (Balady et al. 2018, Buchfuhrer et al, 1983). Therefore patients who are fitter would require a steeper ramping protocol to reach the end point before 12 minutes. Tests under 6 minutes are a test of power and over 12 are a test of muscle endurance rather than cardiopulmonary limitation (Balady et al, 2010).

AT was estimated by the V slope method (Wasserman et al., 2012, ATS/ACCP, 2003). BreezeSuite™ cardiorespiratory diagnostic software estimates the AT using an algorithm, in this study this was then validated visually by an experienced reviewer who adjusted the AT to the correct position.
The patients were risk classified based on their pre-intervention CPET results, the patient then underwent the post-intervention CPET where the second anaesthetist had preferably not seen the first result. This was designed to reduce reporter bias. Arena et al. (2007) give suggestions how to conduct serial tests. The repeat test was conducted on the same equipment in the same well ventilated room. Background medications were taken at the patients normal regime.

The CPET results were then reported blindly by a second reviewer. The reviewer was blinded to the patient’s name, date of test and whether it was a pre or post-intervention test. This was to minimise any bias and mitigate for tests were the second test was carried out by an anaesthetist who knew the first test result or knew that it was a retest. When there was agreement between the reviewers (margin of less than 10% difference) the original test result was used for analysis. When there was disagreement a third senior reviewer analysed the test blindly and their assessment was used.

The reviewer analysed 10 randomised tests per sitting to reduce fatigue. The test was blinded and the AT line was moved to the start of the test. The reviewer then reviewed the test using the BreezeSuite™ software. The AT was then selected and VE/\dot{V}CO_2 at AT was used. Abbott et al. (2018) analysed 2414 tests to assess intra-rater reliability. These tests were analysed by 28 participants ranging from junior doctors, consultants and clinical physiologists. They report an intra-class correlation coefficient (ICC) for the numerical value AT, peak \dot{V}O_2 and presence of AT. The presence of AT had an excellent ICC of 0.93 and AT and peak \dot{V}O_2 had a respective ICC of 0.83 and 0.88. Barron et al. (2014) investigated test retest reliability of CPET
parameters, namely peak \( \dot{V}O_2 \), Oxygen uptake efficiency slope, \( O_2 \) pulse and \( VE/\dot{V}CO_2 \). Peak \( \dot{V}O_2 \) showed an intra-class correlation of 0.95 and \( VE/\dot{V}CO_2 \) of 0.92. All parameters showed an excellent within subject variation of less than 0.12ml/kg/min for \( \dot{V}O_2 \) at anaerobic threshold (Barron et al., 2014). Therefore, CPET demonstrates excellent intra and inter test reliability and as such any change in primary outcome will be due to the intervention rather than the reproducibility of the test in the patient or the interpretation of the test by the examiner. Older (2013) suggests that it is impossible to state the inter-rate reliability with any certainly as it relies on the particular clinicians who are reporting the tests. As it is not customary to re-report blindly the routine tests the level of agreement at York Teaching Hospitals NHS Foundation Trust perioperative service is unknown. However, Older goes on to conclude that within his laboratory there is rarely significant disagreement (Older, 2013). Rose et al. (2018) have conducted a study to investigate the differences in clinically measured CPET variables due to natural variation in the same patient. They state as CPET is a dynamic variable it is prone to natural variation and thus the results should be viewed with caution. They used a healthy population of volunteers who completed multiple CPET tests to calculate the “critical difference” for \( VE/\dot{V}CO_2 \), AT and peak \( \dot{V}O_2 \). They then applied this variation to a set of colorectal patients to assess whether this would cause a reclassification of risk. They found a difference of 13%, 19% and 10% for \( VE/\dot{V}CO_2 \), AT and peak \( \dot{V}O_2 \) respectively in the healthy population (Rose et al. 2018). This work adds more weight to the need for blind reassessment and a 10% margin of error for differences seen due to imprecision of measurement and biological variation.

CPET can either be maximal or submaximal. Historically peak \( \dot{V}O_2 \) was the gold standard for assessing fitness. However, more weight is now attributed to AT and
more recently VE/\(\dot{V}CO_2\), especially in the clinical populations as VE/\(\dot{V}CO_2\) is a marker of pathologically low pulmonary perfusion or ventilator dead space (Arena, 2017). At York Teaching Hospitals NHS Foundation Trust the routine CPET uses submaximal variables as the risk stratification is based on AT and VE/\(\dot{V}CO_2\) at AT. As such these submaximal measures are the primary outcome measures of the study.

Maximal tests are designed to take the patient to the physiological limit (Beltz et al. 2016). The definition of maximal oxygen uptake is:

‘Maximal oxygen uptake is the greatest amount of oxygen a person can take in during physical work and is a measure of the maximal capacity to transport oxygen to the tissues of the body. It is an index of maximal cardiovascular function’

Mitchell and Blomqvist (1971)

The protocol for defining a maximal test can use:

1- A plateau in oxygen consumption-exercise intensity relationship. Typically defined as an increase in \(\dot{VO_2}\) <2 ml.kg.min\(^{-1}\) using 30-60 second data.

2- A final RER raised, typically of > 1.15.

3- A final heart rate of within 10 bpm of predicted age-related maximum,

4- A post-exercise (4-5 min) blood lactate concentration of >8mmol/l.

Authors have defined maximal testing based on one or a combination of these parameters (Beltz et al. 2016, ATS/ACCP, 2003). AT is typically at around 50% of peak \(\dot{VO_2}\) in healthy patients (Buchfuhrer et al., 1983) and can be significantly higher
in endurance trained athletes (Balady et al. 2010). Therefore, peak VO₂ can be estimated from the AT.

Submaximal tests, such as AT or VE/VO₂, have the advantage of improved reproducibility, reduced learning effect and does not rely on maximum patient effort or the observer terminating the test. (ATS/ACCP, 2003). Although the risks from maximal testing are low, submaximal testing also has the added advantage that it is safer in a clinical cohort (ATS/ACCP, 2003).

**Study Drug**

This study used bisoprolol 2.5mg once morning per orally as the study agent. When choosing a beta-blocking drug, it has to have favourable effects on cardiovascular system, namely blood pressure and heart rate, and minimal detrimental effects on the haemodynamic system and skeletal muscle at times of exercise or surgical stress (Ladge et al., 2013).

There is no clear president set for which agent to use from other studies starting beta-blocker therapy on preoperative patients. West et al., (2015) used bisoprolol whereas the POISE used metoprolol. The discredited DECREASE 1 and IV used bisoprolol (Jørgensen et al., 2018). The ESC perioperative guidelines recommend the use of atenolol or bisoprolol if a beta-blocker is started before surgery but this is only a recommendation to be considered and based on level B evidence (Jørgensen et al., 2018). Jørgensen et al., (2017) conducted a cohort study for patients taking different
subtypes of beta-blocking agents. They used logistic regression modelling to investigate whether there was a difference in perioperative risk (measured by MACE and all-cause mortality) between the cohorts of patients on different beta-blocking agents. They concluded that there was no difference in perioperative outcome with different beta-blocking agents (Jørgensen et al., 2017).

Beta-blockers are categorised on their receptor affinity, i.e. cardio-selectivity and on their vasodilatory effects. The Beta-1 selective antagonists such as bisoprolol, atenolol and metoprolol are suggested to have an increased antihypertensive effect over the Beta-2 receptor antagonist effect caused by non-selective agents such as carvedilol, propranolol or labetalol. This is due to the blockade of beta-2 receptors reducing peripheral vasodilation in the presence of circulating adrenaline (Ladge et al., 2013). Agents which cause vasodilation are either mediated by nitric oxide (carvedilol) or via Alpha-receptor antagonism (carvedilol and labetalol). The improved antihypertensive effect is around 2-3mm/Mg this is statistically significant but such a small improvement in blood pressure is not clinically significant.

There is strong (1A level) evidence that beta-blockade prolongs survival in CHF patients (Ladge et al., 2013). However, only bisoprolol, metoprolol and carvedilol have demonstrated this effect in large randomised trials.

The effect of beta-blockade is unlikely to be due to receptor affinity alone. The differing mechanisms have previously been discussed in Chapter 2.2 “Beta-blocker pharmacology” section.
Carvedilol has the advantage of having ancillary properties such as: being an antioxidant, anti-proliferative and reduces gene expression for myocardial damage (Ladge et al., 2013). There is evidence that beta-blockade with carvedilol can stop muscle wastage associated with CHF. Carvedilol also reduces the hyperventilation seen with an aggregated ergoreflex caused by reducing the peripheral chemosensitivity seen in CHF (Malhorta et al., 2016 et al., Ladge et al., 2013). Carvedilol also had the largest numerical advantage of mortality benefit and the largest drug tolerability rates when analysed in meta-analysis. However, these results were not statistically significant (Chatterjee et al., 2013)

Carvedilol is nonselective and it therefore has a larger effect on beta-2 receptors. These receptors are upregulated in CHF and in animal models blockade to beta-2 has shown an impaired adaption to endurance exercise to a great extent than beta-1 selective agents (Ladge et al., 2013). Therefore, in a study aimed at increasing exercise tolerance another agent may be preferable.

Bisoprolol causes a reduction in alveolar wall diffusing distance by increasing fluid re-absorption from alveolar surfaces (Ladge et al., 2013). This is mediated by Beta-2 receptors. This improves gas exchange as governed by Ficks Law of diffusion.

Overall, beta-1 selective agents are suggested in patients engaging in exercise training (Ladge et al., 2013). The increase in metabolic demand in exercise is analogous to surgical stress. Bisoprolol, carvediolol and metoprolol have been shown to improve exercise capacity. Dabach et al., (2002) showed an increase in ejection fracture and exercise duration in patients treated with bisoprolol over placebo. They also report an
improved, but not statistically significant reduction in VE/\dot{V}CO_2, this was not the primary measure of this study. They also showed no improvement on peak VO_2. Agostoni et al. (2010) concluded that a reduction in VE/\dot{V}CO_2 is unique to carvedilol and is not seen with bisoprolol. However, this is based on observational retrospective data.

In summary, the most favourable agents appear to be bisoprolol, carvedilol and metoprolol due to the proven history in increasing survival in CHF. Metoprolol has a short half life and requires 2-3 daily dosing and is not first line therapy in CHF. Therefore, the question is whether a cardioselective agent is better than an agent with added benefits. I.e. is bisoprolol a better choice than carvedilolol.

To complicate the issue further, in vitro studies have demonstrated that clinically used cardio selective agents have little selectivity for either beta-1 or 2 although they do have differing potencies (Ladge et al., 2013). In a large meta-analysis of head to head comparison of beta-blocking agents there were no differences in the risk of death, sudden cardiac death, death due to HF, or drug discontinuation rates (Chatterjee et al., 2013)

On balance, as there is no clear superior agent, a pragmatic approach was taken to prescribe an agent which is familiar to GP, is funded by the Clinical Commissioning group and is in regular supply in the York Teaching Hospital Pharmacy.
Follow up

Patients received cardiology follow up when the study drug was continued. This referral was expedited when patients had raised NT pro-BNP in line with NICE guidance (2018). Patients who have a significantly raised NT pro-BNP (over 2000 ng/l) have a poor prognosis and as such should be rapidly referred. Those patients with a NT pro-BNP between 400 and 2000 ng/l require referral within 6 weeks (NICE, 2018).

This study is not powered to look for outcomes postoperatively. However, the notes were reviewed for length of stay and postoperative mortality.

Statistical Analysis

This thesis is unable to carry out interim analysis as to do so in the recruitment phase will increase the chance of a type one error. However, please see statistical analysis plan in appendix 10 for full description of the analysis for IACF-beta. This thesis will report the baseline characteristics of the patients enrolled and will report median and standard deviations. Microsoft excel was used to calculate these functions.
Chapter 4. ICAF-beta baseline results

ICAF-beta started recruitment on 22/2/18. After one year of recruitment (21/2/19) 235 patients had been screened of which 18 patients were recruited. 12 further patients met the inclusion criteria but either declined (n=5), were missed (n=2) or had their surgery date within the 10 days required treatment duration (n=5). Table 4.1 details all the patients screened and the reasons for non-enrolment.

Table 4.1
Table of patients screen and reason for non-enrolment.

<table>
<thead>
<tr>
<th>Reason</th>
<th>n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Beta blocker</td>
<td>28</td>
</tr>
<tr>
<td>VE/VCO2&lt; 34</td>
<td>67</td>
</tr>
<tr>
<td>Unable to cycle</td>
<td>23</td>
</tr>
<tr>
<td>Surgery elsewhere</td>
<td>31</td>
</tr>
<tr>
<td>VE/VCO2 &gt;34 but no other inclusion criteria</td>
<td>13</td>
</tr>
<tr>
<td>Contraindication (asthma/ dementia)</td>
<td>15</td>
</tr>
<tr>
<td>Not for surgery</td>
<td>8</td>
</tr>
<tr>
<td>Declined</td>
<td>5</td>
</tr>
<tr>
<td>Medical patients not for surgery</td>
<td>20</td>
</tr>
<tr>
<td>Surgery too soon</td>
<td>5</td>
</tr>
<tr>
<td>Missed</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>217</td>
</tr>
</tbody>
</table>

There are two preoperative CPET clinics per week. Monday clinics have 5 patient slots per session and Thursday clinics have 8 patient slots per session. The rate of enrolment was 1.5 patients per month. The study goal for recruitment is 40 patients allowing for a 10% drop out rate therefore aiming for 44 patients recruited. For complete recruitment, 26 further patients will need to be enrolled. At a rate of 1.5 per month this will take an estimated 17 month. At the current recruitment rate the predicted completion date will be 23/7/20.
Sixteen patients completed the study as 2 withdrew before the second follow-up round of retesting. One patient had symptomatic hypotension and therefore was withdrawn from the study. The second patient reported having increased hypoglycaemia and the inability to detect these symptoms so was withdrawn from the study. Therefore 18 patients completed the first stage of testing and this chapter will report the baseline results for these 18 patients.

Table 4.2 outlines the baseline demographic, surgical and risk scoring details of the 18 patients along with the mean results and standard deviations. The mean age of the patients was 72.4 years (SD 6.2) with a female preponderance 10:8 (f:m). The patients had a mean BMI of 27.5kg/m2, which is in the normal range. 1 patient was underweight, 6 were normal, 6 were overweight and 5 were obese. 11 patients were scheduled for colorectal surgery, 4 for vascular procedures and 3 for large urological procedures.

Five of the patients had a single MACE risk factor the remaining 13 patients had no MACE risk factors. When applying the colorectal risk scoring system to the whole cohort the mean score was 2.5 (SD 0.6) and mode score was 3, i.e. high risk.
Table 4.2

Table of baseline demographic, surgical and risk scoring data. Risk scoring is based on colorectal risk scoring for all patients. Key: CR= colorectal, UR= urology, VS= vascular surgery.

<table>
<thead>
<tr>
<th>BIS</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>BMI (kg/m²)</th>
<th>Surgery type</th>
<th>MACE risk factors (n=)</th>
<th>Risk score CR (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>f</td>
<td>55.6</td>
<td>1.64</td>
<td>20.7</td>
<td>CR</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>m</td>
<td>66.2</td>
<td>1.63</td>
<td>24.9</td>
<td>CR</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>f</td>
<td>93</td>
<td>1.54</td>
<td>39.2</td>
<td>CR</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>m</td>
<td>75.3</td>
<td>1.71</td>
<td>25.8</td>
<td>VS</td>
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<td>3</td>
</tr>
<tr>
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<td>69</td>
<td>f</td>
<td>54.3</td>
<td>1.77</td>
<td>17.3</td>
<td>CR</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>m</td>
<td>82</td>
<td>1.84</td>
<td>24.2</td>
<td>VS</td>
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<td>3</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>f</td>
<td>77.8</td>
<td>1.56</td>
<td>32.0</td>
<td>CR</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
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<td>f</td>
<td>65.2</td>
<td>1.79</td>
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</tr>
<tr>
<td>9</td>
<td>75</td>
<td>f</td>
<td>61</td>
<td>1.64</td>
<td>22.7</td>
<td>CR</td>
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<td>3</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>m</td>
<td>64.2</td>
<td>1.71</td>
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<td>CR</td>
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<td>2</td>
</tr>
<tr>
<td>11</td>
<td>84</td>
<td>f</td>
<td>66.9</td>
<td>1.55</td>
<td>27.8</td>
<td>CR</td>
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<tr>
<td>12</td>
<td>69</td>
<td>f</td>
<td>76</td>
<td>1.61</td>
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<tr>
<td>13</td>
<td>76</td>
<td>f</td>
<td>75.6</td>
<td>1.54</td>
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<td>14</td>
<td>81</td>
<td>m</td>
<td>97.1</td>
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<td>31.0</td>
<td>VS</td>
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<td>1</td>
</tr>
<tr>
<td>15</td>
<td>80</td>
<td>m</td>
<td>81.9</td>
<td>1.7</td>
<td>28.3</td>
<td>UR</td>
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<tr>
<td>16</td>
<td>69</td>
<td>m</td>
<td>87</td>
<td>1.73</td>
<td>29.1</td>
<td>CR</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>74</td>
<td>f</td>
<td>113.5</td>
<td>1.63</td>
<td>42.7</td>
<td>CR</td>
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<tr>
<td>18</td>
<td>67</td>
<td>m</td>
<td>77.6</td>
<td>1.76</td>
<td>25.1</td>
<td>VS</td>
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<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>72.4</td>
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<td>76.1</td>
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</tbody>
</table>

The baseline CPET variables are presented in table 4.3. The mean VE/\(\dot{V}CO_2\) at AT was 39.8 (SD 5.7). AT was achieved in 17 of the 18 patients. The mean AT was 10.3 ml/kg/min (SD 1.8) lowest AT 7.4 ml/kg/min and highest of 14.6ml/kg/min. The patients reached a mean peak oxygen consumption of 15ml/kg/min. The maximum workload was a mean of 70.6 watts. 2 of the 18 patients had ischemia during the CPET. The resting heart rate was a mean of 83.2 bpm which rose to a mean 127.6 bpm. Wasserman panel 2 oxygen pulse relationship was normal in 4 of the 18 patients and was normal in 13 of the 18 patients Wasserman panel 3 \(\\dot{V}O_2\) workrate plots.
Table 4.3

Table of baseline CPET variable data

<table>
<thead>
<tr>
<th>BIS</th>
<th>Anaerobic threshold (mL/kg/min)</th>
<th>Peak oxygen consumption (mL/kg/min)</th>
<th>VE/VCO2 at rest</th>
<th>VE/VCO2 at AT</th>
<th>VE/VCO2 peak VO2</th>
<th>Maximum workload (watts)</th>
<th>Oxygen pulse at rest (mL/beat)</th>
<th>Oxygen pulse at AT (mL/beat)</th>
<th>Oxygen pulse at peak VO2 (mL/beat)</th>
<th>Heart rate rest (bpm)</th>
<th>Heart rate AT (bpm)</th>
<th>Heart rate peak (bpm)</th>
<th>Panel 2 (oxygen pulse)</th>
<th>Panel 3 (VO2 workrate)</th>
<th>Maximum RER</th>
<th>Resting RER</th>
<th>ECG ischaemia</th>
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<td>0.9</td>
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BIS: Baseline Insulin Sensitivity
Table 4.4 demonstrates the baseline characteristics of cardiac function measured by NT-Pro BNP and echocardiography. 15 of the 18 patients had baseline NT-Pro BNP taken. When the recorded value was less than 50ng/l, 50ng/l was used in the analysis. A normal value is 0-399ng/l. The mean was 346.3 ng/l with a large SD of 490.7 ng/l. 3 patients had an elevated NT-Pro BNP which warranted referral to cardiology as per NICE guidelines.

All 18 patients completed a baseline echocardiography however only 9 patients had complete data for left and right heart function with reported ejection fraction, LV function, left atrial volume and TAPSE. The mean EF was normal at 60%. The TAPSE, Ejection fraction and LAV were normal at a mean of 24.1mm, 60% and 51ml respectively. One patient had mildly abnormal left ventricular systolic function the other 17 had normal left ventricular systolic function. A normal TAPSE is a result above 16mm. A normal LAV is between 18-58ml.
Table 4.4

Table of baseline cardiac function measured by NT-Pro BNP and echocardiography. Key LV-Left ventricle, LAV- left atrial volume, TAPSE- tricuspid annular plane systolic excursion.

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Chapter 5. Discussion

The aim of this study was to answer the question of whether a short (minimum of 10 days) course of bisoprolol could improve the CPET variables in high risk surgical patients. Although the ICAF-beta study continues to recruit the review, rationale, method and baseline analysis is directly informed by my work and thus forms part of this thesis. This chapter will therefore discuss the baseline characteristic of this study cohort with the baseline characteristics of the current evidence base. It will then go on to discuss the limitations of the study.

West at al., (2015) are the only investigators to study a pre-surgical population with CPET and the administration, and cessation, of beta-blockers. They have similar baseline characteristics to the ICAF-beta study in terms of mean age and BMI (70 vs 72.4 years and 28.7 vs 27.5kg/m²). Of note, ICAF-beta has a female preponderance however, West at al., have a strong male preponderance (90%). This is unsurprising as the incidence of AAA is higher in males. The notable difference is that a large proportion of the West at al. cohort have MACE risk factors, 40% have IHD and 29% have had an MI. Furthermore, 81% were current or previous smoker and 15% had COPD. This makes the West at al., a higher risk cohort. ICAF-beta has a higher proportion of apparently healthy patients. The term apparently healthy is used as they do not have any formal diagnosis of pathology but their CPET risk score reports them as being high risk.

West at al., (2015), recorded lung function testing and COPD status and the ICAF-beta study does not record lung function tests. ICAF-beta has the exclusion criteria of
reversible airway disease as this is a relative contraindication due to risk of bronchospasm with beta-receptor antagonism. Ventilatory inefficiency is the main trial outcome measure, it is affected by both ventilation and perfusion, the trial drug primarily effects perfusion and therefore can be argued that by inclusion patients with ventilatory dysfunction they may not benefit from the treatment. During exercise the dead space (V_d) to tidal volume (VT) ratio reduces as there is reduced V_d and improved alveolar capillary recruitment, i.e. improved perfusion (Balady et al., 2010). In both respiratory disease and cardiac pathology the V_d/VT does not reduce as it would in health and thus add to ventilatory inefficiency seen in both cohorts.

However, chronic heart failure and airway obstruction produce overlapping syndromes (Lizak et al., 2009) so by grouping those into cohorts of patients who have ventilator inefficiency due to cardiac or respiratory causes may be an over simplified view of a more complex interaction. Lizak et al., (2009) report that existing criteria for grading airway obstruction may be inadequate in CHF patients. They conducted pulmonary function tests in 29 patients pre and post cardiac transplantation. After one year, forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) significantly improved post-operatively. FEV_1: FVC remained the same. This suggests there is a significant cardiac contribution to pulmonary function testing. This is added to by Faggiano et al. (1993), who demonstrated a significant improvement in FVC and FEV_1 in patients with severe CHF after intensive medical management. The patients did not have a demonstrable improve in systolic function on echocardiography but did have evidence of a reduced pulmonary capillary pressure. The authors postulate that this will reduce pulmonary interstitial oedema and bronchial wall congestion and therefore improving gas exchange via improved gas
permeability. However, both these studies are conducted in patients with severe CHF and therefore will have lung involvement. The patients in the ICAF-beta study are apparently healthy so if they had airway obstruction it is very unlikely to be caused by interstitial lung oedema.

ICAF-beta trial records peak \( \dot{V}O_2 \) however this is not an inclusion criteria or a primary end point for the study. York Teaching Hospital NHS trust perioperative service also does not use peak \( \dot{V}O_2 \) as part of the risk stratification tool. Peak \( \dot{V}O_2 \) is seen as predictive for complications in a CHF and surgical populations (Wijeysundera et al., 2018, Sarullo et al., 2010, Mancini et al. 1991, Guimaraes et al., 2010). Although establishing a true maximal test is more difficult it may be beneficial if peak \( \dot{V}O_2 \) is used in the ICAF-beta study as a secondary end point.

Chapter 3 has discussed the choice of beta-blocking agent in section “study drug”. There is no clear evidence to guide the choice of drug in a cohort of patients without a formal diagnosis of CHF or without RCRI tool risk factors. This study has used a beta 1 selective beta-blocker. Following guidelines one would suggest bisoprolol or atenolol is preferable (Jørgensen et al., 2018). However, if the study is proposing that a raised \( VE/\dot{V}CO_2 \) is a surrogate marker of CHF then perhaps the study should use carvedilol. It is thought that intra and postoperative hypertension is strongly associated with poorer outcomes and raised mortality post-operatively (Sessler et al., 2019) therefore the study drug of choice should perhaps be the most cardiac selective and one with the least hypotensive effects. Or perhaps a drug with the most favourable ancillary properties, eg carvedilol, should be chosen where there is no clear drug of choice based on receptor affinity.
Study limitations

The main limitation of the ICAF-beta study is that there has not been sufficient recruitment to present a complete data set for analysis. The study prediction for recruitment was approximately 20%. The treatment duration time was reduced from 10 days to 7 days to increase recruitment. This was approved by the Research and Development department and study sponsor.

The ICAF-beta trial does not measure pulmonary function tests. Pulmonary function tests have a cardiac element to their interpretation (Lizak et al., 2009). However, one main criteria for grading airway obstruction, FEV₁ : FVC, is unchanged in even severe CHF (Lizak et al., 2009). Therefore, in the ICAF-beta cohort it is impossible to attribute a raised VE/\(\dot{V}\)CO₂ to cardiac dysfunction alone. Lung function is a confounding factor as it raises VE/\(\dot{V}\)CO₂ but is not amenable to the drug treatment. Wasserman et al.,(1999) advocate conducting spirometry before conducting an exercise test. Lung function is assessed on Wasserman panel 7 and via flow volume loops during exercise which is recorded in York teaching hospital CPET data (Balady et al., 2010).

There is missing data for NT-Pro BNP. 15 of 18 patients had a NT-Pro BNP taken. NT-Pro BNP levels are artificially raised by exercise (Krupicka, 2010). As such patients who had completed a CPET before phlebotomy were invited to come back to hospital the next day to have blood taken and enrolled on the trial. The patients declined this as it meant an extra visit to hospital solely for the drug trial. An
improved trial design would be for all patients to have blood taken before CPET however this is not practical in a busy perioperative assessment clinic.

During routine pre-assessment the patient for major surgery involves a screening test for anaemia. If the patient is found to have an iron deficient anaemia they are referred for iron transfusion. Iron transfusions is a confounding factor in this trial as patients who have received an iron transfusion will theoretically have an improved oxygen carrying capacity and thus improved CPET variables (Wasserman et al., 1999). Iron transfusion rate are not collected as part of the study and are not adjusted for in analysis. Furthermore, Beattie et al., (2010) conducted a retrospective review of non-cardiac surgery patients. They used a composite of major cardiac complications and mortality in beta-blocker naive compared to patients who were chronically beta-blocked with decreasing levels of haemoglobin. Complications and MACE was increased in beta-blocked patients with more than 35% drop in haemoglobin concentration, and beta-blocked patients may not tolerate surgical anaemia (Beattie et al., 2010). This result suggests that patients who are anaemic rely on their HR to continue to deliver oxygen to tissues. By blunting this response they may be unable to mount a response to post-operative complications. Based on this result patients who were anaemic and those who were at high risk of bleeding should potentially be excluded from the study as the risk benefit ratio may be more weighted towards risk.
Chapter 6. Conclusions

To conclude, this thesis comprised of two parts: a systematic review and meta-analysis and the ICAF-beta trial. Firstly, the major finding from the systematic review and meta-analysis that there is a disparity between a statistically significant improvement in ejection fraction and no statistically significant improvement in CPET variables associated with the administration of de novo beta-blockade. This finding must be viewed with the overall trend that all CPET variables were improving but their significance did not reach statistical significance. This is either because there is a true disparity between measurable cardiac function and CPET variables. In which case, other variables should be analysed to assess whether they are better markers for the improvement seen with beta-blockade. Or that the meta-analysis failed to detect in a statistically significant way the trend to improvements in all the measured variables as the included studies samples were small and heterogeneous.

Secondly, the ICAF-beta study is still in recruitment so has been unable to answer the primary research question of whether administering bisoprolol (2.5mg OM) to patients with objective evidence of impaired VE/\(\dot{V}CO_2\) (value 34 or greater) on CPET improves cardiac function. This thesis has however, made recommendations, based on national guidelines and primary research, for future directions primary research into the high risk surgical patient may take once the results of ICAF-beta are shown.

Thirdly, the current evidence base has critically appraised and the following conclusions were discussed. Overall, larger prospective studies, which focus on postoperative outcomes, with the administration of beta-blockade need be conducted
in populations which should improve with beta-blocking agents. Starting beta-blocking agents in all high risk patients is clearly the wrong way to manage these patients as the risk of stroke and increased mortality rates have been described. Starting patients on beta-blockade the day of surgery is also unadvisable and against current guidelines. Targeting treatment to those who will benefit from it is the priority; however, how to target therapy is unknown. The issue may be even more complex and require more individualised prescribing based not only on the patients known co-morbidities but on their blood results and risk of bleeding during surgery.

In broad terms, the current guidelines suggest that there is a stronger indication to start treatment when a patient has more risk factors. The RCRI tool can be used to quantify the risk factors. However, all risk factors are weighted equally and it is known there is a clear benefit of starting beta-blockers for patients with CHF but not one for IHD. ASA grade is suggested by the ESC for the grading of beta-blocker use. These seem too blunt a tool to target therapy adequately. The ability to target which cohort of patients is likely to benefit from beta-blockade and then which beta-blocking agent to choose is logically linked. Ie if one targets only patients with demonstrable CHF then carvidelol may be preferred but if treatment is targeted to those with high preoperative risk scores then no agent may be superior.

The ICAF-beta study hypothesises that ventilator inefficiency is one way to target treatment. This is attractive as it is measurable and this thesis meta-analysis suggests it may respond to beta-blockade. It also is associated with mortality in a CHF population and a surgical population. However, this study is incomplete and thus cannot report whether in this pre-surgical high risk population beta-blockade can
improve ventilatory inefficiency. Furthermore, it will not be able to answer whether any change in VE/V\textsubscript{\textit{CO}_2} translates into any mortality benefit.

This study is also unique in that it does not target therapy to those who are traditionally seen as high risk (eg confirmed history of CHF or a high score on RCRI tool etc.) as patients are enrolled based on their CPET risk. This means that the study is starting treatment in patients who can be apparently healthy. If ICAF-beta is able to show a demonstrable improvement in ventilatory efficiency with a short, cheap and generally well tolerated treatment it is an exciting prospect for improving perioperative management. If it fails to demonstrate an improvement then future work should focus on targeting therapy to a cohort which will benefit from beta-blockade eg those with demonstrable myocardial dysfunction due to tachycardia seen on CPET.
References:


Balady G, Arena R, Sietsema K et al., (2010) Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease and Interdisciplinary Council on Quality of Care and Outcomes Research on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on

Beattie S, Hare G (2014) Beta-blockers are the old BLACK, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie,* 61 (9), 787-793.


with magnetic resonance myocardial tagging. *American Heart Journal* 143(4), 676-673


Cardiology/American Heart Association Task Force on Practice Guidelines.  
*Circulation*. 130, 2215–2245


Guimaraes, G. d’Avila V, Silvia M et al. (2010) A cutoff point for peak oxygen consumption in the prognosis of heart failure patients with beta-blocker therapy. *Int J Cardiology*, 145 (1), 75-78


O’Connor C, Whellan D, Lee K. et al. (2009) Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure: HF-ACTION Randomized Controlled Trial. JAMA, 301(14), 1439-1450


Volterrani M, Cice G, Caminiti G et al. Effect of Carvedilol, Ivabradine or their combination on exercise capacity in patients with Heart Failure (the CARVIVA HF trial), *International Journal of Cardiology*, 151(2), 218-224


List of Appendices and Tables

Appendix 1

Search strategy for ICAF-beta literature search.

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### Appendix 2

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<td>(beta-block* OR b-AR* OR b-block* OR beta-adrenergic OR b-adrenergic).ti,ab</td>
<td>62073</td>
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<td>3</td>
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<td>(bisoprolol OR atenolol OR nebivolol OR metoprolol OR carvedilol).ti,ab</td>
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<tr>
<td>4</td>
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<td>(1 OR 2 OR 3)121230</td>
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<td>5</td>
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<td>60921</td>
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<td>6</td>
<td>Medline</td>
<td>(&quot;cardiopulmonary exercise test*&quot; OR &quot;cardio-pulmonary exercise test*&quot; OR CPET OR CPX).ti,ab</td>
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<td>7</td>
<td>Medline</td>
<td>(treadmill OR ergometer* OR &quot;fitness test*&quot; OR &quot;stress test*&quot; OR &quot;exercise test*&quot; OR &quot;exercise capacity&quot; OR cycle OR bicycle OR anaerobic OR &quot;aerobic exercise&quot;).ti,ab</td>
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<td>9</td>
<td>Medline</td>
<td>(4 AND 8)</td>
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<td>10</td>
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<td>exp &quot;CLINICAL TRIALS AS TOPIC&quot;/</td>
<td>327143</td>
</tr>
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<td>11</td>
<td>Medline</td>
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<td>Medline</td>
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<td>Medline</td>
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<td>14</td>
<td>Medline</td>
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<td>Medline</td>
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<td>Medline</td>
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<td>[DT 1990-2018]</td>
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Appendix 3

Systematic review consort diagram.
Appendix 4

Revised Cochrane Risk of Bias tool for randomised trials (RoB 2.0).

Appendix 5

The Risk of Bias in non-randomised studies of interventions (ROBINS-1) assessment tool used for before and after comparison trials.
Appendix 6

Funnel plots for the primary outcomes

VE/VCO₂
Peak VO₂

AT

EF
### Appendix 7

Table of study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Intervention</th>
<th>Population</th>
<th>Sample size</th>
<th>Assessment of exercise capacity</th>
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<tr>
<td>Witte et al., 2005</td>
<td>Before and after comparison study</td>
<td>Carvedilol and Bisoprolol. 12 months</td>
<td>CHF</td>
<td>35</td>
<td>CPET- Treadmill. Bruce protocol. Echo.</td>
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<td>Nodari et al., 2003</td>
<td>Prospective randomised parallel trial</td>
<td>Atenolol and Nebivolol. 6 months</td>
<td>CHF with HT</td>
<td>26 (13 patients per group)</td>
<td>CPET- Cycle ergometer. 20w ramped protocol. Echo. Pulmonary artery catheterisation</td>
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<td>Vanhees et al., 2000</td>
<td>Randomised double blind cross over study</td>
<td>Bisoprolol and Atenolol. 3 weeks</td>
<td>Healthy men</td>
<td>12</td>
<td>CPET- Cycle ergometer. 20w ramped protocol. Cardiac output calculations</td>
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<tr>
<td>Volterrani et al., 2011</td>
<td>Prospective randomised, open, blinded endpoint study</td>
<td>Carvedilol, Ivabradine or dual therapy 12 weeks</td>
<td>CHF</td>
<td>121 (38,41,42 per group)</td>
<td>CPET- protocol not published. Echo. Muscle power. 6MWT.</td>
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<td>West et al., 2015</td>
<td>Interventional cohort study</td>
<td>Bisoprolol 1 week</td>
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<td>48 (28 denovo Bisoprolol, 20 chronic Bisoprolol)</td>
<td>CPET- Cycle ergometer ramped protocol.</td>
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<td>Issa et al., 2006</td>
<td>Before and after comparison study</td>
<td>Bisoprolol 3 months</td>
<td>CHF</td>
<td>14</td>
<td>CPET- Treadmill. Naughton protocol. Echo.</td>
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<td>Dubach et al., 2002</td>
<td>Double blind randomised control trial</td>
<td>Bisoprolol 12 months</td>
<td>CHF</td>
<td>28 (13 Bisoprolol group and 15 placebo group)</td>
<td>CPET- Cycle ergometer. Ramped protocol. MRI.</td>
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<td>Before and after comparison study</td>
<td>Carvedilol 12 months</td>
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<td>Metoprolol or Carvediolol</td>
<td>CHF</td>
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<td>Intervention</td>
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<td>Carvedilol 14 weeks</td>
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<td>Atenolol</td>
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<td>43 (23 atenolol group and 20 placebo group)</td>
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<td>Randomised double blind placebo control trial</td>
<td>6 months</td>
<td>Metoprolol</td>
<td>CHF</td>
<td>52 (26 per group)</td>
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<tr>
<td>Broch et al., 2016</td>
<td>Randomised double blind placebo control trial</td>
<td>6 months</td>
<td>Metoprolol</td>
<td>Asymptomatic moderate to severe aortic regurgitation</td>
<td>72 (36 per group)</td>
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<tr>
<td>Terzi et al., 2003</td>
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<td>CHF</td>
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<tr>
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<td>Bisoprolol</td>
<td>Healthy subjects</td>
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<td>Randomised double blind multicentre parallel group placebo control trial.</td>
<td>6 months</td>
<td>Nebivolol</td>
<td>CHF</td>
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<td>Bisoprolol</td>
<td>CHF</td>
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Radionuclide ventriculography. Thermodilution. 6MWT.
CPET - Cycle ergometer. Radionuclide ventriculography. Right heart catheterisation and thermodilution. 6MWT.
CPET - Cycle ergometer. Stepped submaximal endurance protocol to exhaustion or 90mins. Interval stepped maximal test.
CPET - semi reclined cycle ergometer. Ramped protocol. Echo. 6MWT.
CPET - cycle ergometer and treadmill. Cardiac MRI.
CPET - treadmill. Stepped protocol. Echo.
CPET - 30w Ramped protocol. Chemo and metaboreflex sensitivity testing.
CPET cycle ergometer. 20W per 2 minutes. Echo. 6MWT
Cycle Ergometer 0.5W per kg
| blind placebo controlled study | secondary to congenital heart disease | increase per 2 mins. Echo, Cardiac MRI |
### Appendix 8

Table of baseline and post treatment primary end points.

<table>
<thead>
<tr>
<th>Study</th>
<th>VE/(\dot{V}CO_2) baseline (mean +/- SD)</th>
<th>VE/(\dot{V}CO_2) post treatment (mean +/- SD)</th>
<th>Peak (\dot{VO}_2) baseline (mean ml/kg/min +/- SD)</th>
<th>Peak (\dot{VO}_2) post treatment (mean ml/kg/min +/- SD)</th>
<th>AT baseline (mean ml/kg/min +/- SD)</th>
<th>AT post treatment (mean ml/kg/min +/- SD)</th>
<th>EF baseline (mean % +/- SD)</th>
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<td>Issa et al., 2006 bisoprolol</td>
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<td>Metra et al., 2000 metoprolol</td>
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<tr>
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### Appendix 9

Table of excluded meta-analysis data and reasons for exclusion

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<th>Study</th>
<th>VE/VCO₂ baseline (mean +/- SD)</th>
<th>VE/VCO₂ post treatment (mean +/- SD)</th>
<th>Peak VO₂ baseline (mean ml/kg/min +/- SD)</th>
<th>Peak VO₂ post treatment (mean ml/kg/min +/- SD)</th>
<th>AT baseline (mean ml/kg/min +/- SD)</th>
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<td>Vanhees et al., 2000 Bisoprolol</td>
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<td>No sig change</td>
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</table>
Appendix 10

Cohort diagram for study

Patient information sheet and covering letter sent by post to patients due to attend CPET clinic who are:
55 years old or over and scheduled to have major intra-abdominal surgery

On arrival at clinic, patient asked whether they have received the study information and whether they have any questions.

If a patient declines they will not be considered for the study and normal pre-assessment clinic procedures will follow

Initial screening through normal pre-assessment clinic procedures:
Medical history
Cardiac review

Patient ineligible at any stage then no longer considered for study and normal clinical procedures will follow

Routine bloods collected prior to CPET testing (as per normal clinic procedures)

CPET testing

Patient ineligible at any stage during the screening procedures then no longer considered for study and normal clinical procedures will follow

Patient review by study delegation- eligibility to enter the study confirmed

Patient consents to enter the study

Echocardiogram

Blood sample sent to Laboratory

Prescribed 2.5mgs bisoprolol daily for a minimum of 10 days

After a minimum of 10 days repeat CPET, BNP and Echocardiogram.

Continue medication as agreed with cardiologist and proceed to planned surgery

Patient withdrawn if:
- Surgery takes place before 7 days
- Medication not tolerated or stopped
- Admitted for surgery without a repeat CPET being performed
ICA F-B ETA
Improving cardiac function in high-risk surgical patients: exercise testing, biomarkers and beta-blockade

ISRCTN: 95679074

STATISTICAL ANALYSIS PLAN
Draft v0.5

York Trials Unit
Department of Health Sciences
University of York

Version date: 21/05/2019
Authors: Ada Keding, Alex Mitchell
Chief Investigator: Dr Jonathan Wilson
**Definition of terms/acronyms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>AV</td>
<td>Aortic Valve</td>
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<tr>
<td>BNP</td>
<td>Beta-natuirietic peptide</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>CPD</td>
<td>Core Patient Database</td>
</tr>
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<td>CPET</td>
<td>Cardio-pulmonary exercise testing</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>LA</td>
<td>Left atrial</td>
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<tr>
<td>LV</td>
<td>Left ventricular</td>
</tr>
<tr>
<td>LVOT</td>
<td>Left ventricular outflow tract</td>
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<td>NT-proBNP</td>
<td>N terminal pro beta-natuirietic peptide</td>
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<td>Pulmonary Artery</td>
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<td>PIS</td>
<td>Patient Information Sheet</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious adverse reaction</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>TDI</td>
<td>Tissue Doppler Imaging</td>
</tr>
<tr>
<td>TR</td>
<td>Tricuspid Regurgitation</td>
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<td>SUSAR</td>
<td>Suspected unexpected serious adverse reaction</td>
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<tr>
<td>VE/VCO₂</td>
<td>Ventilatory efficiency for carbon dioxide</td>
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<tr>
<td>VO₂/HR</td>
<td>Volume of oxygen per heart beat (Oxygen Pulse)</td>
</tr>
<tr>
<td>VO₂/Watt</td>
<td>Volume of oxygen per Watt (Oxygen Workrate)</td>
</tr>
</tbody>
</table>
**Document Scope**
This statistical analysis plan (SAP) covers the reporting of the study progress and planned analyses addressing the study aim of the ICAF-BETA study. Any further post-hoc or other exploratory analyses using the study data are not covered by this SAP.

**The ICAF-Beta Study**

**Aim**
To investigate whether patients who are due to undergo major surgery and with objective evidence of impaired VE/CO₂ (value greater than 34) on CPET have better cardiac function after being administered bisoprolol. This will determine whether bisoprolol has the potential to reduce surgical risk for patients.

**Design**
ICAF-BETA is a prospective proof-of-concept case series study. Consenting patients 55 years of age or older with impaired VE/CO₂ (value greater than 34) were prescribed bisoprolol before scheduled major intra-abdominal surgery. Cardiac function and other outcomes were measured and compared before (at routine pre-assessment for surgery) and after (after a minimum of 7 days) the introduction of bisoprolol. Full details of the study design and procedures are given in the study protocol (latest version: v7.0, dated 23/01/2019).

**Treatment**
The study IMP was bisoprolol, a cardio-selective beta-blocker, licensed for the treatment of heart failure. Participants were prescribed 2.5mgs daily for a minimum of 7 days.

**Sample size**
Internal data from 14 patients with VE/VCO₂ >34 who have had CPET before and after beta blockade with bisoprolol for varying reasons showed a mean reduction in VE/VCO₂ of 4 (SD 7.9), from 42 to 38. VE/VCO₂ was reduced to 34 or less for six out of the 14 patients, thus placing them in a lower risk group for post-operative mortality than previously. In order to observe a difference of the same magnitude with 90% power at the 5% significance level, 43 patients with before-and-after observations would be required. Allowing for 10% dropout, the study aimed to recruit 48 patients, however recruitment would be closed once 43 patients successfully completed the study.
Outcomes

Primary outcome
The primary outcome was the ventilatory equivalent for CO₂ (VE/VCO₂), measured at anaerobic threshold or nadir. VE/VCO₂ was measured before and after introduction of bisoprolol. A reduced VE/VCO₂ is an improved outcome.

Secondary outcomes
The secondary outcomes were:
- NT-proBNP (ng/L, normal range 0-399 ng/L)
- Echocardiographic measures of systolic and diastolic function
  - ECG rate (BPM)
  - ECG rhythm (categorical) Sinus rhythm (normal), Atrial fibrillation, LBBB, RBBB, other ECG abnormality (abnormal)
  - LV dimensions (ml)
  - LV volumes (ml)
  - LA volume (ml)
  - Ejection fraction (%)
  - Right size (ml)
  - LVOT velocity (m/s⁻¹)
  - AV velocity (m/s⁻¹)
  - A and E Velocity (m/s⁻¹)
  - TDI septal and lateral E/E
  - TR Velocity (m/s⁻¹)
  - Est PA Pressure (mmHg)
- Anaerobic threshold (mLO₂/Kg/min, abnormal classed as below 11mLkg⁻¹min⁻¹)
- Evidence of myocardial abnormality on CPET
  - VO2/HR response Panel 2 either: normal/ normal shape low values/ flat low curve/ descending These are both a subjective assessment of whether the shape is normal or abnormal. This is categorical. I think this should be recorded as Binary normal or abnormal (but please ask Dr Davies for a final answer on that)
  - VO2/Watt response Panel 3 either: normal/ reduced gradient/ infection

All secondary outcomes were measured before and after introduction of bisoprolol.

Other collected data

The following variables were collected at baseline:
- Demographics
  - Age
  - Gender
- Physical Examination
  - Weight(kg)
  - Height(m)
  - Heart rate (bpm)
  - Sitting blood pressure (mmHg)
- Concomitant Medication
Clinical risk factors for major adverse cardiac events
- History of ischaemic heart disease
- History of cerebrovascular disease
- Renal insufficiency
- History of chronic heart failure

Adverse Events
- Adverse events were defined using the GCP definitions and local SOP definitions
- For any adverse event, seriousness, intensity, expectedness and probability of relatedness to IMP were recorded

Compliance
- Number of days on medication
- Regular IMP use (yes/no)
- Missed doses (yes/no)
- Side effects (yes/no, details reported as adverse events)

Follow-up

Visit 1 - Pre-assessment
Patient assessments before prescription of bisoprolol took place at their routine pre-assessment appointment before surgery. Assessments included routine CPET and blood sample testing as well as an echocardiogram.

Interim safety assessment
Three to six days following prescription of bisoprolol, patients were contacted by phone by a member of a research team to check on their progress and collect any adverse events. If not arranged at the pre-assessment visit, an appointment for the follow-up visit was made at this time.

Visit 2 / 3 - Follow-up
At the follow-up visit ten or more days following bisoprolol prescription (or on admission to surgery if not feasible earlier), repeat tests of CPET, BNP and echocardiogram were conducted. Patients who underwent surgery early were followed up if they had completed at least 7 days on bisoprolol or were withdrawn from the study otherwise.

End of study
Patients concluded their involvement in the study once the second echocardiogram, BNP blood sample and CPET had all been obtained. There was no long-term follow-up for study purposes. However, patients were asked for consent to allow the research team to access their surgical outcomes and any cardiology follow-up as available. This information may help to inform a subsequent trial.
### Data collection schedule

#### Table 1: Data collection schedule

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<th>Days since bisoprolol started (Day 0)</th>
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<th>Phone Call</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>End of Study</th>
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<tr>
<td>Screening / Pre-assessment</td>
<td>&lt;Day 0</td>
<td>Day 3-6</td>
<td>Day 7-20</td>
<td>only if missing visit 2 data</td>
<td>after last follow-up</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Risk factors for major cardiac events</td>
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<td>(•)</td>
<td>(•)</td>
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<td>Cardio-pulmonary exercise measures</td>
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<td>Echocardiographic measures</td>
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<td>(•)</td>
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<td>(•)</td>
<td>(•)</td>
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<td>Post-surgery Notes</td>
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<td>Cardiac Follow-up Notes</td>
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Data

**Standard Operating Procedures (SOPs)**

In accordance with Trust SOP Data Management (R&D/S29; Version 3.0, 22 August 2017) a Data Management Plan (DMP) has been produced, which outlines all activities relating to management of study data including collection and storage. This document provides a comprehensive list of all applicable SOPs to the management of study data. Completion of the CRF for this study is undertaken in line with the Trust SOP on Case Report Form (CRF) Design and Completion (R&D/S81) Version 2.0 24th August 2017.

The statistical analysis will be conducted in line with York Trials Unit SOPs, specifically S01 (Statistical Considerations Version 5.0) and SG02 (Statistical Reporting Guidance Version 3.0). Appropriate YTU standard forms apply. Any assumptions made during the processing and merging of data as well as for the analysis will be documented (internal document reference numbers in bracket) using a Trial Assumptions Form (F23). In the event of necessary changes or additions to analyses detailed here, these will be documented on a Statistical Analysis Plan Departure Form (F24). The statistical analysis will be signed off using a Primary Analysis Sign-off Form (F16).

**Case Report Forms (CRFs)**

Completion of the CRF for this study is undertaken in line with the Trust SOP on Case Report Form (CRF) Design and Completion (R&D/S81) Version 2.0 24th August 2017.

**Management of datasets and data verification**

In accordance with Trust SOP Data Management (R&D/S29; Version 3.0, 22 August 2017) a Data Management Plan (DMP) has been produced, which outlines all activities relating to management of study data including collection, validation and storage. This document provides a comprehensive list of all applicable SOPs to the management of study data.

Management Data: A patient tracking Excel document was used to allow GP letter and cardiology letters to be sent in a timely manner and to plan the patient appointments. This contains the patient hospital number but no further details and is kept on a protected folder which requires permission access on the Hospital Trust Q Drive. This data set will not be used for the statistical analysis.

CRF Data: Participants were anonymised using a sequential BIS study participation ID number, starting with BIS001 as the first patient. This number was given to the patient at the first visit. Data were transferred from the CRF or CPD to either a password protected Excel sheet or a password protected SPSS file by M Williams and J Mann will transfer the data from the source or CRF. This will be overseen by Dr Davies and Dr Wilson. The match between CRF fields and variable names will be recorded by means of xxx. Pharmacovigilance Data: Data relating to all serious and non-serious adverse events were entered on an Excel spreadsheet and have undergone validation.

At the end of the study, a copy of the CRF data and Pharmacovigilance data will be transferred to the statistician, who will carry out further consistency and validity checks. Any resulting queries will be raised with the study team, and revised data will be transferred to the statistician as necessary. Analyses will be conducted on the final hard locked data set.
Analysis

Study progression
The numbers of patients screened, eligible and consenting will be presented. Reasons for ineligibility will be tabulated. Of those consented, the number of patients with complete and incomplete initial and follow-up assessments will be presented and the total number available for analysis given. The number of patients withdrawn from the study will be tabulated by reason. The progression of patients through the study will be illustrated using a flow diagram.

Baseline data
Participant baseline data will be summarised descriptively for all consented patients and patients included in the primary analysis. Continuous measures will be reported as means and standard deviations; categorical data will be reported as counts and percentages.

Treatment
For patients who were prescribed bisprolol, the average number of days between pre- and post-assessments will be presented (mean, median, SD). Details of compliance and cases of early discontinuation will be given.

Primary analysis
VE/VCO₂ before and after bisoprolol will be analysed using a paired t-test. The assumption that the change in VE/VCO₂ is normally distributed will be assessed graphically using a histogram and a Q-Q plot. If the assumption of normality does not hold, the primary outcome will be analysed non-parametrically using the Wilcoxon signed-rank test. The average difference between pre- and post-assessments will be presented together with 95% confidence interval and the associated p-value of the statistical test. The proportion of patients with a reduction of VE/VCO₂ to 34 or below will be presented.

Analysis of secondary outcomes

Pre/Post Comparisons
Secondary outcomes will be presented descriptively at available time points, as well as any change between pre- and post-bisoprolol treatment, including 95% CIs.
Differences for the following continuous outcomes will be analysed as in the primary analysis, using paired t-test or appropriate non-parametric test depending on the distribution of the outcome differences:
- NT-proBNP
- Echocardiographic measures of systolic and diastolic function as detailed in the Outcomes section)
- Anaerobic threshold

Differences in proportions of the following binary categorical outcomes will be analysed using McNemar’s test:
- Normal vs abnormal CPET based on VO₂/HR response
- Normal vs abnormal CPET based on VO₂/Watt response

There will be no formal adjustment for multiple comparisons, however the statistical report will highlight the inflated Type-I error for secondary outcome comparisons, and interpretation will focus on confidence intervals instead.
Associations between Outcomes
Analysis of correlation between a change in EF (echo) and change in VE/VCO2 and markers of diastolic heart failure and Ve/vco2. To assess whether improved cardiac ejection fraction is associated with improved ventilator efficiency.
The Pearson correlation coefficient will be calculated between Pro-nt-BNP and VE/VCO2. The assumption that the relationship between Pro-nt-BNP and VE/VCO2 is linear will be assessed graphically using a scatter plot.

Sensitivity analyses
There are no planned sensitivity analyses.

Adverse events
Adverse events were assessed by the CI or a delegated medically qualified doctor for intensity, causality, expectedness and seriousness. All AEs and SAEs were recorded regardless of their suspected causal relationship to the study intervention.
The total number of adverse events and the number of patients with at least one adverse event will be reported. The number of adverse events per participant will be reported using the median, range and IQR. The number of AEs, SAEs, SARs and SUSARs will also be reported.
The number of adverse events that are mild, moderate or severe in terms of intensity will be tabulated. Causality, expectedness and seriousness will be presented in a similar manner.

Analysis Software
Analyses will be conducted using the latest version of SPSS and verified using Stata.

SAP Revisions

<table>
<thead>
<tr>
<th>Amendment/addition to SAP and reason for change</th>
<th>New version number, name and date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First complete draft</td>
<td>Version 1.0 (xx/05/2019)</td>
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Roles and responsibilities

Non-signatory names and contributions

Murray Williams has been part of the research team for the study and has contributed to the details of this SAP. As part of his own research degree, he will conduct some of the analyses for this study under the supervision of the statistics team, who will independently verify all analyses.

Alex Mitchell is a trainee statistician at York Trials Unit who will undertake some of the data analyses for this study as well as the supervision of Murray Williams, both under the supervision of Ada Keding.

Murray Williams is conducting a masters by thesis at the University of York and HYMS. This comprises of a systematic review and meta-analysis of studies which conduct breath to breath CPET before and after de novo beta-blockade. This is in all patient cohorts. This will act of increasing the background knowledge on de novo beta-blockade to test the theoretical premise of the trial. As the ICAF0-beta is ongoing at the end of the thesis period, baseline variables of the first year of recruitment will be reported in the thesis. No statistical analysis will be done as part of the thesis and no interim analysis will be conducted.

Signatures

<table>
<thead>
<tr>
<th>Name</th>
<th>Study Role</th>
<th>Signature</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Jonathan Wilson</td>
<td>Chief Investigator</td>
<td></td>
<td></td>
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<tr>
<td>Ada Keding</td>
<td>Statistician</td>
<td></td>
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<tr>
<td>Mia Porteous</td>
<td>Study co-ordinator</td>
<td></td>
<td></td>
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</tbody>
</table>

References

None.
Suggested tables and figures

Figure 1 – Patient Flow Diagram

Assessed for Eligibility (n = x)

Excluded (n = x)
- Reason 1 (n=x)
- Reason 2 (n=x)
- ...

Consented and entered into study (n = x)

Pre-IMP Assessment (n = x)
- CPET (n = x)
- BNP (n = x)
- Echocardiogram (n = x)

Withdrawn from study (n=x)
- Early surgery (n=x)
- Patient withdrew (n=x)
- Clinician withdrew patient (n=x)

Post-IMP Assessment (n = x)
- CPET (n = x)
- BNP (n = x)
- Echocardiogram (n = x)

Analysis
- Included in analysis (n = x)
- Excluded from analysis (n = x)
Table 1 – Reasons for Exclusion

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<th>N (%)</th>
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<td>Not aged 55 or over</td>
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<td>Not scheduled for major intra-abdominal surgery</td>
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<tr>
<td>Not presenting for routine CPET</td>
<td></td>
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<tr>
<td>Does not consent to GP being informed</td>
<td></td>
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<tr>
<td>Not presenting for routine CPET</td>
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</tr>
<tr>
<td>Does not consent to GP being informed</td>
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<tr>
<td>Not available for the study duration</td>
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<tr>
<td>VE/VCO2 &lt;= 34 on CPET</td>
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<tr>
<td>Does not have one or more risk factors</td>
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<td>Refused or unable to give informed consent</td>
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<tr>
<td>Current / within 1 month BB</td>
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<tr>
<td>Participation in another research study</td>
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<td>Unable to read and speak English</td>
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<td>BB contra-indicated</td>
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<td>Other</td>
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Table 2 – Baseline Characteristics

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<th>Ineligible participants</th>
<th>Participants in the study</th>
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<td>Female, n (%)</td>
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Table 3 – Outcome Comparisons

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<td>AV velocity (ml/s)</td>
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<td>A and E Velocity (ml/s)</td>
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