Identifying Factors Which Influence Medication Adherence in a Cardiac Rehabilitation Population

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Department of Pharmacology and Toxicology
University of Toronto

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2018

Abstract
Nonadherence to cardiovascular disease medications is a health-related behaviour which increases adverse patient outcomes and healthcare costs. Identification of factors which impact adherence levels in those undergoing cardiac rehabilitation may reduce cardiovascular mortality rates. We hypothesized that use of a greater number of medications and use of acetylsalicylic acid (ASA), beta-blockers and statins would result in lower medication adherence levels. A Poisson regression showed that those who were adherent were taking 1.15 (95% CI, 1.03-1.28, p=0.014) times more medications than those who were nonadherent. An analysis of covariance found the combined use of ASA, beta-blockers and statins was associated with higher adherence levels ($F_{1,242}=5.76$, $p=0.017$). Furthermore, lower cardiopulmonary fitness levels, increased depressive symptoms and forgetfulness were all associated with lower medication adherence levels. These findings suggest that factors other than polypharmacy and medication class – such as cognitive function, depression, or fitness – may negatively influence adherence rates in this population.
Acknowledgments

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<th>Description</th>
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<tbody>
<tr>
<td>AEs</td>
<td>Adverse Events</td>
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<tr>
<td>AES</td>
<td>Apathy Evaluation Scale</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic Acid</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>β-AR</td>
<td>Beta-adrenergic receptor</td>
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<tr>
<td>β-blockers</td>
<td>Beta-blockers</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>Bpm</td>
<td>Beats per minute</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>COWAT</td>
<td>Controlled Oral Word Association Test</td>
</tr>
<tr>
<td>COX-1</td>
<td>Cyclooxygenase 1</td>
</tr>
<tr>
<td>COX-2</td>
<td>Cyclooxygenase 2</td>
</tr>
<tr>
<td>CR</td>
<td>Cardiac Rehabilitation</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>CVLT-II</td>
<td>California Verbal Learning Test 2nd Edition</td>
</tr>
<tr>
<td>CVRFs</td>
<td>Cardiovascular Risk Factors</td>
</tr>
<tr>
<td>df</td>
<td>Degrees of Freedom</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalized Anxiety Disorder</td>
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<tr>
<td>GAD-2</td>
<td>2-item Generalized Anxiety Disorder Scale</td>
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<tr>
<td>GPCOG</td>
<td>General Practitioner Assessment of Cognition</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>3-hydroxy-3-methylglutaryl-coenzyme A</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
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<tr>
<td>IHD</td>
<td>Ischaemic Heart Disease</td>
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<tr>
<td>MGL</td>
<td>Morisky-Green-Levine Medication Adherence Scale</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
</tr>
<tr>
<td>PHQ-2</td>
<td>Patient Health Questionnaire-2</td>
</tr>
<tr>
<td>PTCA</td>
<td>Percutaneous Transluminal Coronary Angioplasty</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic Curve</td>
</tr>
<tr>
<td>SCID-IV</td>
<td>Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders version IV</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>Trails B</td>
<td>Trail Making Test Part B</td>
</tr>
<tr>
<td>TRI</td>
<td>Toronto Rehabilitation Institute</td>
</tr>
<tr>
<td>VO2 peak</td>
<td>Peak oxygen consumption</td>
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1 Introduction

1.1 Statement of problem

Medication nonadherence is a significant risk factor for poorer outcomes in those with cardiovascular disease (CVD) or cardiovascular risk factors (CVRFs) (Munger et al. 2007). Studies indicate that one third to one half of CVD patients are nonadherent to their medication regimens (Dunbar-Jacob et al. 2000, LaFleur and Oderda 2004, Osterberg and Blaschke 2005). Nonadherence to medications has been shown to increase CVD mortality rates, hospitalizations and pose a significant burden on healthcare costs (Albert 2008, Baroletti and Dell’Orfano 2010, Ho et al. 2008, Jackevicius et al. 2008, Munger et al. 2007, Rasmussen et al. 2007, Simpson et al. 2006, Sokol et al. 2005). CVD itself is associated with significant health and economic burdens, and is responsible for up to 33% of deaths in Canada (Tarride et al. 2009). Interventions to prevent and treat CVD by ensuring adequate medication adherence can lower the rates of adverse events (AEs), result in significant cost savings and improved patient health outcomes (Albarqouni et al. 2017, Ferdinand et al. 2017).

Before a successful intervention can be implemented to improve medication adherence rates, the risk factors for nonadherence must first be identified. Medication nonadherence is multifactorial and several barriers exist which prevent patients from adhering to a regimen (Baroletti and Dell’Orfano 2010, Yap et al. 2016). The factors that most commonly contribute to medication nonadherence include communication barriers, complexity of a regimen, sociodemographic factors, healthcare coverage, comorbidities and AEs (Albert 2008, Baroletti and Dell’Orfano 2010, Ferdinand et al. 2017). The complexity of a regimen – relating to polypharmacy and frequency of dosing – has been widely studied in those with CVD and increased number of medications has frequently been associated with decreased adherence (Chapman et al. 2008, Gellad et al. 2011, Melloni et al. 2009, Stoehr et al. 2008). Furthermore,
adherence rates to commonly prescribed medications for those with CVD such as acetylsalicylic acid (ASA), beta-blockers (β-blockers) and statins are suboptimal, which can lead to poor patient prognoses (Albert 2008, Naderi et al. 2012).

Although there exists a large body of evidence as to which factors may contribute to medication nonadherence in a CVD population, no study to date has assessed barriers to medication adherence in those with CVD or CVRFs attending a cardiac rehabilitation (CR) program. Adherence rates and barriers to adherence in a CR population may differ from the general CVD population, as attendance to CR may itself be indicative of a more highly compliant population. The primary objective of CR programs are to provide tailored exercises and education sessions for those with CVD or CVRFs (Servey and Stephens 2016). Exercise-based CR improves daily functioning, reduces CVD risk and mortality rates (Anderson et al. 2016, Colbert et al. 2014, Servey and Stephens 2016). Furthermore, frequent exercise in those with CVD is associated with up to a 26% improvement in peak oxygen consumption (VO₂ peak) (Belardinelli et al. 2001). Recognition of which factors significantly impact medication adherence rates in those attending CR is essential to develop strategies to increase patient adherence and prevent poor clinical outcomes. As greater attendance of CR classes and increased medication adherence are both associated with lower mortality rates (Ferdinand et al. 2017, Servey and Stephens 2016), optimization of adherence in this population may provide patients with a substantial increase in overall health benefits in addition to those provided by CR (Bitton et al. 2013, Colbert et al. 2014).

Benefits to medication adherence rates have been observed in those who attend CR, but adherence levels are not routinely assessed throughout the course of CR (Servey and Stephens 2016). As predictors of medication nonadherence in CR patients remain unknown, assessment of adherence levels and barriers to adherence at multiple time points in the program can
provide information on which subgroups are at greater risk for worse health outcomes. This information may lead to the development of targeted interventions for specific individuals undergoing CR with low medication adherence levels.

1.2 Purpose of Study and Objective

Previous studies on medication adherence in those with CVD lack information on patients who are undergoing CR. Due to this lack of information, the objectives of this study were to determine which factors were associated with medication nonadherence in a population of CR participants with CVD or CVRFs. As polypharmacy has been consistently shown to be associated with decreased adherence rates (Chapman et al. 2008, Gellad et al. 2011, Gray et al. 2001, Stoehr et al. 2008, Turner et al. 2009), the primary objective was to determine if greater number of medication use was associated with lower medication adherence levels in those attending CR. This study also aimed to determine if the use of commonly prescribed CVD medications was associated with lower adherence rates. The presence of commonly diagnosed neuropsychiatric CVD comorbidities were also evaluated through the development of a novel screen to determine if comorbidity presence was associated with lower medication adherence.

1.3 Statement of Research Hypotheses and Rationale for Hypotheses

1.3.1 Primary Hypothesis

| Higher medication adherence levels in those with CVD and CVRFs will be associated with use of fewer medications at entry into CR. |

Rationale: There are several therapy-related factors that may influence medication adherence such as the complexity of the regimen, duration of the therapy, and frequency of dosing (Ferdinand et al. 2017). A commonly studied therapy-related factor is the complexity of the
regimen due to prescription of several medications. In several studies, use of a greater number of medications has been associated with lower adherence levels (Chapman et al. 2008, Gellad et al. 2011, Gray et al. 2001, Stoehr et al. 2008, Turner et al. 2009). While the definition of polypharmacy varies between studies, the use of five or more medications is most frequently used to define polypharmacy in elderly populations (Jörgensen et al. 2001, Jyrkkä et al. 2009, Kassab et al. 2013, Stoehr et al. 2008). Due to the varying diagnosis severities and comorbid illnesses of those attending CR, the number of medications prescribed may significantly differ between patients and result in differences in adherence levels. Therefore, it was hypothesized that use of fewer medications would be associated with greater medication adherence levels.

1.3.2 Secondary Hypothesis

CVD patients and those with CVRFs, who are taking ASA, β-blockers and statins will have lower levels of medication adherence than those not taking all three at entry into CR.

Rationale: Poor rates of adherence to ASA, β-blockers and statins have been demonstrated in those with CVD (Duffy et al. 2014, Naderi et al. 2012, Newby et al. 2006). Nonadherence to these medications is associated with increased risk of major cardiac AEs, subsequent CVD event occurrence, and increased hospitalizations (Breekveldt-Postma et al. 2008, Duffy et al. 2014, Glynn et al. 2010). As a result, it was hypothesized that use of all three of these medications would be associated with lower medication adherence levels in those attending a CR program. Identification of factors which influence lower adherence rates to these medications in those attending CR can significantly prevent and reduce CVD events (Wald and Law 2003).
1.3.3 Exploratory Hypotheses

1. CVD patients and those with CVRFs demonstrating greater symptoms of one or more neuropsychiatric comorbidities - depression, anxiety, apathy or cognitive impairment - will have lower medication adherence levels than those with fewer symptoms.

2. Higher medication adherence levels in those with CVD and CVRFs will be associated with significant improvements in VO$_2$ peak over the course of 3 months of CR.

3. Unintentional nonadherence due to forgetfulness in those with CVD and CVRFs will be associated with higher scores on the three items from the General Practitioner Assessment of Cognition (GPCOG) and poorer scores on the mini-trails B.

Rationale: Along with medication regimen complexity, other factors have been shown to influence adherence levels. Neuropsychiatric comorbidities such as depression, anxiety, apathy, or cognitive impairment have been associated with lower medication adherence levels (DiMatteo et al. 2000, Eurelings et al. 2014, Gehi et al. 2005, Shin and Liberzon 2010, Vlasnik et al. 2005). Furthermore, adherence to healthier lifestyles, such as increased physical activity, has been associated with improved medication adherence (Bitton et al. 2013). Lastly, unintentional nonadherence due to forgetfulness has been demonstrated to significantly impact medication adherence in those with CVD (Lowry et al. 2005, Molloy et al. 2014). However, none of the above factors and their relationship to medication adherence in a CR population have been assessed. As such, it was hypothesized that the presence of comorbidities, lower VO$_2$ peak levels and unintentional nonadherence would all be associated with lower medication adherence levels.
1.4 Review of Literature

1.4.1 Cardiovascular Disease

CVD is the leading cause of death worldwide, accounting for approximately one third of deaths (Naderi et al. 2012, Scott 2004). CVD poses a major economic burden as studies have shown that the annual costs associated with CVD in Canada to be over 20 billion dollars (Tarride et al. 2009). Along with its effects on the healthcare system, CVD negatively impacts ones’ quality of life (Ludt et al. 2011, Mozaffarian et al. 2016, Rumsfeld et al. 2013). Patient-reported health status has been shown to be an independent predictor of mortality, subsequent CVD events and hospitalization (Chan et al. 2009, Heidenreich et al. 2006, Mommersteeg et al. 2009, Rumsfeld et al. 2013).

CVD encompasses a class of diseases, which involve the heart or blood vessels, such as coronary artery disease, atrial fibrillation, heart failure, cerebrovascular accident, myocardial infarction (MI) or valvular heart disease (Ho et al. 2014, Mahmood et al. 2014); with the most predominant form being coronary artery disease. The major cause of CVD is known as atherosclerosis – the narrowing and inflammation of coronary arteries that supply blood to the heart (Ambrose et al. 2015, Scott 2004). Atherosclerotic plaques are composed of lipid deposits and inflammatory cells (Ambrose et al. 2015, Verheye et al. 2002). The build-up of fatty plaques inside the arterial wall results in insufficient blood flow and limited supply of oxygen to the heart (Ambrose et al. 2015). Restricted supply of oxygen to the heart may result in ischemia or MI. Restoring blood flow to the heart may require revascularization procedures, such as percutaneous transluminal coronary angioplasty or coronary artery bypass graft (Libby and Theroux 2005).

While genetics play a role in the development of atherosclerotic plaques, it is also largely influenced by the presence of several modifiable CVRFs such as smoking, diabetes,
hypertension and hyperlipidemia (Ambrose et al. 2015, Scott 2004). As such, other treatment options for those with CVD include pharmacotherapy or lifestyle modifications such as exercise or changes in diet (Libby and Theroux 2005, Scott 2004). Implementation of appropriate interventions to manage and treat CVD can aid in reducing the significant health and economic burdens posed by the disease.

1.4.2 Neuropsychiatric Comorbidities in CVD

Neuropsychiatric comorbidities in CVD are often underdiagnosed and subsequently undertreated. Comorbidities such as depression, anxiety, apathy and cognitive impairment are prevalent in those with CVD and have been shown to be risk factors for CVD (Bunevicius et al. 2013, Lichtman et al. 2008, Ligthart et al. 2012, Swardfager et al. 2011). While the prevalence of each comorbidity varies, early identification of these symptoms in those with CVD can aid in improving patient prognoses. Adequate assessment of each comorbidity is time-consuming due to the length of available screening tools and as such are not feasible in a busy CR setting. Therefore, the lengthy administration time of available scales may be a reason why these comorbidities remain undiagnosed. Furthermore, cardiologists often do not screen for these comorbidities as they believe it is not their responsibility, but the responsibility of a nurse or the family physician (Hare et al. 2014).

Symptoms of depression and apathy often overlap, however, the two are distinct disorders. Depression is characterized by feelings of sadness, sleep disturbance, fatigue, or impaired concentration (Hare et al. 2014); while apathy is defined primarily as a behavioural syndrome consisting of impaired motivation and diminished goal-oriented behaviour (Marin et al. 1991, Starkstein and Leentjens 2008). Mild forms of depression can be found in up to two-thirds of CVD patients and major depression can range anywhere from 15-20% (Hare et al. 2014).
The prevalence rates of depression also differ based on CVD severity, with higher rates of up to 40% being associated with increased disease severity (Hare et al. 2014, Rutledge et al. 2006). Furthermore, apathy has been shown to be a strong, independent risk factor for CVD, lending support to the vascular apathy hypothesis (Eurelings et al. 2014, Ligthart et al. 2012, van der Mast et al. 2008). The prevalence of apathy in CVD patients has been shown to be as high as 27% (van der Mast et al. 2008).

Anxiety is characterized by transient fear, uncertainty, phobias and panic disorders (Cohen et al. 2015, Tully et al. 2016). In those with CVD, the prevalence of generalized anxiety disorder (GAD) can be as high as 24% (Bankier et al. 2004) and anxiety is independently associated with increased CVD mortality and morbidity (Albert et al. 2005, Shin and Liberzon 2010, Smoller et al. 2007, Watkins et al. 2013). In approximately 50% of CVD patients, anxiety disorders are comorbid with depressive disorders, resulting in worse health outcomes such as increased rehospitalisation and mortality rates, compared to those with CVD alone (Barth et al. 2004, Frasure-Smith and Lespérance 2003, Hare et al. 2014, Khayyam-Nekouei et al. 2013, Tully et al. 2016).

Cognitive impairment, such as executive and memory dysfunction, can affect up to 35% of patients with CVD. Executive function has been shown to be the most commonly impaired domain in those with CVD (Haley et al. 2007, Rosano et al. 2005, Silbert et al. 2007, Vinkers et al. 2005). The presence of cognitive impairment in those with CVD or CVRFs can cause failure of recognition of early symptoms and seeking of timely medical attention, which can result in poorer outcomes such as increased hospital admissions and mortality rates (Chin and Goldman 1997, Ekman et al. 2001, Gifford et al. 2013, Howell et al. 2017, Patel et al. 2015).
While the prevalence of anxiety and depressive disorders are significantly higher in those with CVD than in the general population (Hare et al. 2014, Todaro et al. 2007, Tully et al. 2016), the use of different diagnostic tools across studies may account for the wide range in the prevalence of various comorbidities in CVD (Julian 2011, Radakovic et al. 2015, Thombs et al. 2006, Wulsin et al. 2005). To address this issue, it has been recommended that following a CVD event, patients should be screened for neuropsychiatric comorbidities at regular intervals and those who screen positive should undergo follow-up assessments (Cohen et al. 2015, Hare et al. 2014, Thombs et al. 2006).

1.4.3 Cardiac Rehabilitation

The prevalence of CVD events are reduced by up to 50% in those who are more physically active compared to those who are sedentary (Lee et al. 1997, Thompson et al. 2003, Williams 2001). As physical inactivity is a modifiable risk factor for CVD, exercise-based CR is strongly recommended for individuals immediately post a CVD event – prior to hospital discharge or during their first follow-up visit (Smith et al. 2011, Warburton et al. 2006). CR is a medically supervised program for individuals who have experienced a CVD event or those who have risk factors for developing CVD. The program is generally composed of prescribed exercises, education sessions, counselling and medical evaluations throughout the course of CR (Dalal et al. 2015). Immediate referral is essential as CR dropout rates are significantly lower when the program is started within 3 weeks of a CVD event compared to 6 to 12 months after an event (Oldridge 1982).

The recommendation for CR has been evaluated in multiple patient populations and has demonstrated that the benefits largely outweigh the risks (Clark et al. 2005, Hammill et al. 2010, Smith et al. 2011, Taylor et al. 2004, Thomas et al. 2007, Walther et al. 2008). Exercise-
based CR reduces CVD mortality, hospitalizations and improves quality of life (Anderson et al. 2016, Jolliffe et al. 2001, Thompson et al. 2003). In addition to the long-term benefits associated with CR, increased amounts of physical activity are associated with improvements in VO₂ peak – a reliable cardiopulmonary fitness measure (Belardinelli et al. 2001, Dugmore et al. 1999, Moholdt et al. 2012). Every 6% increase in VO₂ peak has been shown to be associated with a 4% lower risk of CVD mortality or hospitalization and a 7% lower risk of all-cause mortality (Swank et al. 2012).

1.4.4 Medication Adherence in CVD

The World Health Organization defines medication adherence as the extent to which a person’s medication taking behaviors, correspond with agreed recommendations from a healthcare provider (De Geest and Sabaté 2003). Medication taking behaviour is complex and to ensure adequate medication adherence rates, individuals must actively communicate with their healthcare professionals (Cutler and Everett 2010, Zelko et al. 2016). Adherence to medications is a responsibility shared by both the patient and the physician. The physician must emphasize the importance of adhering to medications and aim to simplify the regimen (Burnier 2006, Feldman et al. 1998, Frishman 2007, Osterberg and Blaschke 2005).

Medication nonadherence is often an unrecognized risk factor for CVD. Adherence to medications in those with CVD has been shown to be suboptimal, with studies reporting approximately 40-50% of patients having poor adherence to prescribed medications (DiMatteo et al. 2002, Ferdinand et al. 2017, Frishman 2007, Ho et al. 2006, Kronish and Ye 2013). Nonadherence is multi-factorial and is affected by healthcare coverage, patient beliefs, ethnicity, gender, motivation, polypharmacy and presence of comorbidities (Baroletti and Dell’Orfano 2010). Furthermore, poor medication adherence rates account for approximately
9% of acute CVD events (Chowdhury et al. 2013, DiMatteo et al. 2002, Molloy et al. 2014, Naderi et al. 2012) and increasing rates of nonadherence have been shown to lead to recurrent cardiac events, increased rehospitalisation and mortality rates (Al-Ganmi et al. 2016, Baroletti and Dell’Orfano 2010, Nieuwlaat et al. 2014, Poluzzi et al. 2011). Along with the potential to reduce CVD mortality rates, improved adherence to medications can also aid in reducing overall healthcare costs associated with CVD, as an annual reduction between $294 and $868 per patient has been shown between those with high and low adherence (Bitton et al. 2013).

1.4.5 Medication Adherence Measures

Evaluation of adherence levels can pose many difficulties as there is currently no gold standard assessment. Adherence must be determined on a situational basis as there are various factors which contribute to each individual’s medication taking behaviours (Lam and Fresco 2015, Vitolins et al. 2000). Measurements of adherence can be classified as objective or subjective. Subjective measures are among the most commonly used tools and include self-report questionnaires or clinician assessments. Objective measures include pill counts, biochemical measures, electronic monitoring, or secondary database analysis (Lam and Fresco 2015, Velligan et al. 2007, Vermeire et al. 2001). Different measures are used to identify different components of adherence and the choice of a method should be based on the ultimate goals of the clinician or researcher. Use of the appropriate tool to measure medication adherence is essential to determine the efficacy of the treatment and subsequent strategies to improve adherence (Lam and Fresco 2015). Studies have recommended the combination of methods to measure adherence as the strength of one method may compensate for weaknesses in another (Farmer 1999, Lam and Fresco 2015).
1.4.6 Factors which Influence Adherence

*Polypharmacy:* As the available number of medications increase, the number of prescribed drugs per patient increases as well. The average number of medications prescribed at discharge for heart failure patients increased from 6.8 from 1998-1999 to 7.5 from 2000-2001 (William H Frishman 2007, Masoudi et al. 2005). Nonadherence to multi-drug therapies has been shown to significantly increase for each added medication at discharge and increase in regimen complexity in those with an acute coronary syndrome (Melloni et al. 2009). Several studies highlight polypharmacy as a significant contributor to medication nonadherence (Chapman et al. 2008, Gellad et al. 2011, Gray et al. 2001, Stoehr et al. 2008, Turner et al. 2009). Furthermore, a lower total number of prescription drugs has been shown to be significantly associated with patients being classified as adherent (Stoehr et al. 2008).

In older adults, polypharmacy poses greater concerns to medication adherence as they may experience more difficulty in managing multi-drug regimens, finances and cognitive function (Marcum and Gellad 2012). It has been demonstrated that in older adults with a lower pill burden, their adherence to concomitant antihypertensive and lipid-lowering therapies was increased (Chapman et al. 2008). When patients are prescribed too many medications they are at an increased risk of experiencing an adverse drug reaction and drug-drug interactions, which can affect their adherence rates (Hajjar et al. 2007). Although the relationship between medication adherence and polypharmacy has been widely studied, this relationship has not been assessed in those with CVD or CVRFs in a CR setting.

*Gender/Ethnicity:* There are specific populations of people with CVD who have been shown to demonstrate lower medication adherence levels, including females and non-Caucasians (Ferdinand et al. 2017, Yap et al. 2016). Studies have shown that women are less adherent to
statins than men and that women are more likely to experience adverse drug reactions when taking CVD specific medications (Goldstein et al. 2016, Manteuffel et al. 2014, Zopf et al. 2008). Ethnic differences also contribute to the varying rates of medication adherence. Black race has been shown to be significantly associated with nonadherence. Black individuals report medication nonadherence 85-114% more than Caucasians, even after controlling for various factors (Gellad et al. 2007, Krousel-Wood et al. 2010, Marcum et al. 2013).

**Age:** While old age has been shown to be a predictor of nonadherence (Benner et al. 2002, Cárdenas-Valladolid et al. 2010, Jackevicius et al. 2002, Jackevicius et al. 2008), studies state that age per se may not be an important factor in medication adherence, but rather the interaction is impacted by several other factors that are prevalent in older populations (Hughes 2004, Vik et al. 2004, Yap et al. 2016). Factors associated with aging such as cognitive decline, polypharmacy and cost of medications are particularly important in elderly individuals who are retired (Holt et al. 2013, Kulkarni et al. 2008, Turner et al. 2012, Vik et al. 2004, Yap et al. 2016).

**Dosing Frequency:** Along with regimen complexity, frequency of dosing is an important factor to consider when assessing adherence levels. The use of once daily dosing has been shown to improve adherence to CVD medications (Claxton et al. 2001, William H Frishman 2007, Kripalani et al. 2007). Individuals who are prescribed twice daily medication regimens have shown up to a 23% lower rate of adherence than those taking once daily medications (Weeda et al. 2016).

**Unintentional Nonadherence:** The rates of intentional versus unintentional nonadherence are also important determinants of medication adherence levels. Intentional nonadherence is due to the patient’s choice to deviate from adhering to the regimen based on their beliefs, knowledge
and understanding of the treatment. However, unintentional nonadherence is due to forgetfulness and the presence of comorbidities, such as mental illness (Akeroyd et al. 2015, Lowry et al. 2005). In individuals who have experienced an acute CVD event, the rates of unintentional nonadherence and intentional nonadherence after 12 months were 53% and 15%, respectively (Molloy et al. 2014). Furthermore, 31% of patients taking an antihypertensive medication have reported their nonadherence as unintentional and only 9% report nonadherence as intentional (Lowry et al. 2005). These results demonstrate that unintentional nonadherence may be a critical factor which can impact the high rates of nonadherence in those with CVD.

**CR:** While the factors influencing medication adherence in those with CVD are widely studied, few studies focus on CVD patients who are in a CR program. A systematic review of 25 studies on both primary and secondary prevention of coronary artery disease reported that 22 of the studies did not control for the possibility that those who are more adherent to their medications may also be more adherent to healthier lifestyle behaviours. This was termed the “healthy adherer effect” and it was noted that higher medication adherence is most likely associated with a healthier diet and increased frequency of exercise (as those who participate in CR would undergo) (Bitton et al. 2013).

Furthermore, lack of implementation of CR and low participation rates may be factors contributing to the low medication adherence rates seen in those with CVD, as enrollment in a CR program has been shown to be independently associated with improved adherence to β-blockers and statins (Dalal et al. 2015, Shah et al. 2009). Adherence to medications can be improved through consistent attendance to CR classes, as those who are under the care of a cardiologist and receive counselling are more likely to adhere to their medications (Eagle et al. 2004, Jackevicius et al. 2002).
1.4.6.1 Neuropsychiatric Comorbidities and Medication Adherence

Depression, anxiety and apathy are important patient-centered factors which contribute to medication nonadherence and can affect the patients’ willingness and ability to follow through with a prescribed treatment (DiMatteo et al. 2000, Vlasnik et al. 2005). The association between depression and medication nonadherence has been demonstrated in various studies (Carney et al. 1995, DiMatteo et al. 2000, Gehi et al. 2005, Hare et al. 2014, Ziegelstein et al. 2000). Medication nonadherence in depressed CVD patients has been shown to be double that of non-depressed CVD patients (Gehi et al. 2005). Furthermore, the presence of apathetic symptoms may result in nonadherence to a healthy lifestyle and withdrawal from care, such as CR, involved in preventing CVD events (Eurelings et al. 2014). There have been contradicting results on the relationship between anxiety and medication adherence due to the heterogeneity of the studies and varying reports of effect sizes (DiMatteo et al. 2000).

However, it cannot be stated that anxiety has no impact on medication adherence. High stress is a factor contributing to nonadherence and there is overlap among the neurological pathways of the stress response and anxiety disorders (DiMatteo et al. 2000, Shin and Liberzon 2010, Vlasnik et al. 2005).

The ability of an individual to process and understand basic health information is known as health literacy. Health literacy has been shown to be impaired in those with abnormal cognitive function and was associated with higher all-cause mortality in those with heart failure (Peterson et al. 2011). Medication self-management skills are a component of health literacy and poorer management skills may be a result of cognitive impairment, which can decrease medication adherence (Howell et al. 2017). Assessing executive function and working memory has been suggested to identify older adults who may be at risk for medication nonadherence (Insel et al. 2006). Furthermore, misunderstanding of prescribing instructions, cognitive
decline associated with aging and forgetfulness are important factors that have been shown to contribute to nonadherence (Hayes et al. 2009, Vlasnik et al. 2005).

1.4.7 Pharmacotherapy Adherence in CVD

ASA, β-blockers and lipid-lowering agents (primarily statins) are three of the most commonly used medications in both the primary and secondary prevention of CVD (Bulpitt 2005, Stewart et al. 2017). Adherence to these medications are essential as each one treats factors aimed at decreasing and managing the prevalence of CVD. Adherence to ASA, β-blockers and statins as a primary preventative measure have been shown to be 72%, 44% and 57%, respectively and 65%, 62% and 76% as a secondary preventative measure (Duffy et al. 2014, Naderi et al. 2012). If these medications are adhered to completely, the combined use of all three can result in up to an 80% reduction and prevention of CVD events (Law, Wald, and Rudnicka 2003, Law, Wald, Morris, et al. 2003, Wald and Law 2003). However, along with suboptimal adherence rates being reported for each medication individually, studies have shown that adherence rates are less than 40% for the combined use of all three medications (Newby et al. 2006).

1.4.7.1 Acetylsalicylic Acid

ASA has been reported to be the most widely used drug in medicine (Ittaman et al. 2014, Ornelas et al. 2017, Vane and Botting 2003). In CVD populations, it is primarily used as a platelet inhibitor. ASA exerts its effects by irreversible inhibition of both cyclooxygenase 1 and 2 (COX-1 and COX-2), but is more selective for COX-1 (Ornelas et al. 2017). This inhibition occurs through acetylation of the hydroxyl groups of serine residues located in the active site of the enzymes (Ser529 in COX-1 and Ser516 in COX-2). COX-1 regulates basal levels of prostaglandins, while COX-2 is responsible for the release of prostaglandins after an
infection or injury (Ornelas et al. 2017). Prostaglandins are involved in mediating an inflammatory immune response and therefore, through the inhibition of COX enzymes ASA inhibits prostaglandin release. Furthermore, both COX-1 and COX-2 are expressed in platelets, which play a critical role in the clotting cascade and are recruited to the site of atherosclerotic plaque rupture (Ornelas et al. 2017, Scott 2004). ASA inhibits platelet aggregation – mediated through the reduction of thromboxane A\textsubscript{2} production – and subsequent clot formation, which are essential factors in both the primary and secondary prevention of CVD (Warner et al. 2011).

The standard dose of ASA is 325 mg/day, but doses normally range from 75-325 mg (Duffy et al. 2014). Studies have shown the effectiveness of ASA (even at low doses of 75-100 mg/day) in decreasing the risk of CVD events and reducing all-cause mortality (Antithrombotic Trialists’ Collaboration 2002, Seshasai et al. 2012). A recent meta-analysis of fourteen randomized control trials reported that ASA use for primary prevention was associated with significant reductions in major CVD events, MI, and stroke (Xie et al. 2014). However, low adherence rates to ASA have been demonstrated in those with CVD and after 12 months have been shown to drop by 18% (Duffy et al. 2014, Kulkarni et al. 2006). Low adherence rates to ASA may also be influenced by its availability as an over the counter drug, which can result in decreased patient’s perceptions of the benefits of this medication (Packard and Hilleman 2016). Furthermore, the most common AE associated with ASA use is gastrointestinal tract bleeding and studies have shown that greater than 3 episodes of gastrointestinal AEs are associated with increased ASA discontinuation (Biondi-Zoccai et al. 2006, Maulaz et al. 2005). As nonadherence to ASA can result in a three-fold higher risk of major cardiac AEs (Duffy et al. 2014), it is important to identify which factors impact ASA adherence to improve overall health outcomes and reduce healthcare costs.
1.4.7.2 β-blockers

Individuals with hypertension are at an increased risk for developing CVD and one of the most commonly used pharmacological interventions for treating hypertension are β-blockers. Although there are differences in the pharmacological and pharmacokinetic characteristics of different β-blockers, the general mechanism to reduce blood pressure (BP) is the same. β-blockers decrease BP by reducing cardiac output as a result of competitive antagonism at cardiac β-adrenergic receptors (β-AR) (Ripley and Saseen 2014). β-AR are G-protein coupled receptors and when activated result in increased levels of cyclic adenosine monophosphate (cAMP). This activation ultimately results in increased cytosolic calcium levels which causes increased cardiac myocyte contractility (Ladage et al. 2013). The binding of β-blockers to β-AR prevents endogenous catecholamines, such as norepinephrine and epinephrine, from binding. This inhibition of binding results in reduced levels of sympathetic nervous system activation, reduced myocyte contractility and lower heart rate (HR) (Figure I) (Shin and Johnson 2010). β-blockers can be selective for the β1 receptor or inhibit β1, β2 and α1 adrenergic receptors (DiNicolantonio et al. 2015, Ripley and Saseen 2014).

Although evidence demonstrates that effective treatment of hypertension is associated with reduced risk of cardiovascular death by 29%, all cause-mortality by 33% and reduces the risk of subsequent MI, lack of adherence to β-blockers remains a significant barrier to BP control (Al-Gobari et al. 2013, Breekveldt-Postma et al. 2008, Kramer et al. 2006). Low adherence rates may be influenced by AEs associated with β-blocker use such as fatigue, bradycardia, hypotension or depression (Andersson et al. 2014, Frishman 1988). However, discontinued use of β-blockers can increase the risk of MI or stroke and Kramer et al. demonstrated that adherence rates over the first year after an MI are only 45% (Breekveldt-Postma et al. 2008, Kramer et al. 2006). Furthermore, studies have shown that for every 20 mm
Hg increase in systolic BP and 10 mm Hg increase in diastolic BP, the risk of CVD increases by two-fold (Lewington et al. 2002). Persistent use of β-blockers must be encouraged in those with hypertension to ensure that patients are receiving the maximal health benefits possible.

**Figure I. Mechanism of action of β-blockers.** β-AR are coupled to Gs-proteins which activate adenyl cyclase when norepinephrine (NE) or epinephrine (Epi) are bound. Activation of adenyl cyclase results in formation of cAMP from adenosine triphosphate (ATP). Increased cAMP levels result in activation of protein kinase A (PKA) which phosphorylates L-type calcium channels. This causes increased calcium entry into the cell which increases contractility and HR. When β-blockers are bound however, NE or Epi cannot bind and therefore result in decreased HR and contractility, lowering BP.

### 1.4.7.3 Statins

Statins are competitive, irreversible inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase used to lower cholesterol levels and provide primary and secondary prevention against CVD (Figure II) (McFarland et al. 2014). HMG-CoA reductase is the rate-limiting step in cholesterol synthesis which catalyses the conversion of HMG-CoA to L-mevalonate and coenzyme A. The inhibition of HMG-CoA reductase prevents the endogenous production of cholesterol. Furthermore, statins increase the uptake and degradation of low
density lipoproteins (McFarland et al. 2014). Some of the most commonly prescribed statins include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. The lipophilicity of these statins differs and in turn can influence their ability to cross the blood brain barrier. Atorvastatin, fluvastatin, lovastatin, and simvastatin are lipophilic and can cross the blood brain barrier passively, while pravastatin and rosuvastatin are hydrophilic. These statins also differ with respect to other pharmacokinetic properties such as half-life, metabolism routes and bioavailability (McFarland et al. 2014). Due to the different characteristics of each statin, patient-level factors such as age, gender and the presence of comorbidities must be considered when administering this therapy (Pedro-Botet et al. 2015).

Two meta-analyses of randomized control trials published in 2010 and 2012, demonstrated that statin therapy significantly reduced CVD events when used for primary and secondary preventative measures (Baigent et al. 2010, Mihaylova et al. 2012, Pedro-Botet et al. 2015). Furthermore, a secondary analysis which aimed to assess the safety and efficacy of rosvastatin in elderly patients showed that rosvastatin use was associated with a 44% risk reduction in the incidence of MI, stroke, arterial revascularization, hospitalization for unstable angina, or CVD death (Glynn et al. 2010). In spite of the evidence highlighting the importance of statin use, those with CVD do not readily adhere to their treatment. A study comparing adherence to statins in those with a recent acute coronary syndrome, those with chronic coronary artery disease and those without coronary artery disease found two-year adherence rates to be only 40.1%, 36.1% and 25.4%, respectively (Jackevicius et al. 2002). These low adherence rates may be due to AEs associated with statin use such as myopathy and rhabdomyolysis, which have been shown to negatively contribute to adherence levels and can result in early treatment discontinuation (Birtcher 2015, Laufs et al. 2015). Emphasis of the
long-term benefits of statin adherence is critical to decrease rates of discontinuation and mortality rates.

**Figure II. Mechanism of action of statins.** Statins inhibit the conversion of HMG-CoA to L-mevalonate through competitive inhibition of HMG-CoA reductase. This inhibition results in a decrease in the downstream biosynthesis of cholesterol and other intermediate metabolites including isoprenoids (represented by three downward arrows).
2. Methods

2.1 Study Design

A cross-sectional study design was used for the primary and secondary hypotheses to assess the relationship between medication adherence, total number of medications and use of β-blockers, ASA and statins in patients with CVD or CVRFs. A prospective observational study design was used for the exploratory hypothesis assessing associations with change in VO₂ peak over the course of 3 months of CR and medication adherence. All study participants were recruited from the Toronto Rehabilitation Institute (TRI) CR program. The research ethics boards of TRI and Sunnybrook Health Sciences Centre approved this study. All participants who had indicated consent to research from TRI were screened at entry into CR using the novel screening tool outlined below and completed a medication adherence measure (Appendix A). A subset of participants were further consented to participate in the validation of the novel screen (Appendix B). Those who participated in the validation underwent neurocognitive assessments at baseline only and before or as close to the start of the CR as possible.

2.2 Cardiac Rehabilitation Program

Prior to beginning the 6 month CR program, patients undergo an initial assessment where cardiopulmonary fitness levels and depressive symptoms are assessed to determine a baseline measure of physical and mental health. Assessment of cardiopulmonary fitness levels and depressive symptoms are repeated at 3 months and 6 months into the program. Following the initial assessment, patients have the option to select a CR class once a week either in the morning, evening or afternoon. The class is a 90 minute session, with 60 minutes of exercise and a 30 minute education session. The 30 minute education session focuses on exercise safety,
risk factors, patient goals, nutrition and several other factors. The weekly classes are run in groups; however, each exercise session is different for each individual. Generally, the initial exercise prescription is to walk around an indoor track at the centre, however patients are expected to repeat exercises 4 times at home and maintain an exercise log every week to bring into the program. Half-way through the program, the patients undergo 4 group sessions with dietitians, and social workers or psychologists discussing mental health. The last education sessions are focused on self-management and adhering to their exercise routine once they have finished the CR program. Along with centre-based CR, TRI also provides a home-based CR program. For this program, patients have weekly telephone consults and submit exercise logs weekly by email to their supervisor. To assess their progress, they also come in to the centre for a few sessions on the track.

2.3 Inclusion/Exclusion Criteria

2.3.1 Inclusion

- Spoke and understood English
- Demonstrated evidence of CVD based on at least one of the following:
  - Previous hospitalization for acute MI
  - Coronary angiographic evidence of $\geq 50\%$ blockage in $\geq 1$ major coronary artery
  - Prior revascularization
- Demonstrated evidence of a CVD disorder including, but not limited to:
  - Congestive heart failure
  - Angina
  - Atrial fibrillation or other cardiac arrhythmias
- Cardiomyopathy
- Cardiomegaly
- Conduction deficit
- Valvular Heart Disease
- Cerebrovascular accident

- Demonstrated evidence of a CVRF including, but not limited to:
  - Hypertension
  - Hypercholesterolemia
  - Diabetes
  - Smoking history

- Stable CVD based on no hospitalization for cardiac events within four weeks prior to baseline assessment such as acute MI, unstable angina, congestive heart failure, ventricular arrhythmias or coronary revascularization

2.3.2 Exclusion

- Significant acute medical illness requiring recent hospitalization (≤ 4 weeks)

2.4 Demographics and Medical History

For everyone screened, concomitant medications, cardiac medical history and other relevant medical or surgical history were obtained through TRI’s electronic medical records. Cardiopulmonary and metabolic health indices (VO₂ peak, resting HR, maximum HR, BP, height, weight, body mass index (BMI), and body fat percentage) were also collected from TRI’s electronic medical records. In the validation population, detailed demographic and clinical characteristics including age, gender, ethnicity, employment status, total years of
education, smoking history, personal and family psychiatric history, and comorbidities independent of CVD were obtained through patient interviews.

### 2.5 Screen Development

The screening tool developed was designed to identify cognitive impairment, depression, anxiety and apathy in a CVD population before they began CR. The 5-word delayed recall from the Montreal Cognitive Assessment (MoCA) was used to assess verbal memory, which is a domain commonly impaired in those with CVD (Eggermont et al. 2012, Zheng et al. 2012). The word recall was given a score out of 5, with one point for each correctly remembered word. The mini-trails B sub-test of the MoCA was used to assess executive function, as it is the most commonly impaired domain in those with CVD (Gayda et al. 2017, Zheng et al. 2012). The mini-trails were scored out of 9, one point given for each correctly drawn line. Three items adapted from the six informant items of the GPCOG were also included as a subjective measure of cognitive function. The three questions refer to memory difficulties, handling financial matters and use of the right word when speaking. The GPCOG has been shown to be reliable and have a sensitivity and specificity of 85% and 86%, respectively in detecting cognitive impairments (Brodaty et al. 2002).

Depression was assessed using the Patient Health Questionnaire-2 (PHQ-2) which has been shown to be a validated screening tool for depression (Arroll et al. 2010, McManus et al. 2005). The PHQ-2 has shown a sensitivity and specificity of 100% and 77%, respectively among adults aged ≥65 years (Lakkis and Mahmassani 2015). The two questions refer to the patient’s feelings over the last two weeks and are scored on a 4-point Likert scale, with a maximum possible score of six. Previous studies have shown that a score ≥ 3 is the optimal cut-off for a positive screen of depression (Kroenke et al. 2003, Löwe et al. 2005).
Anxiety was assessed using the 2-item Generalized Anxiety Disorder Scale (GAD-2) which consists of the first two items of the 7-item GAD scale, as these two items reflect the core diagnostic criteria of GAD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Wild et al. 2014). The maximum possible score is six, with previous studies indicating the recommended cut-off as a score ≥ 3 to detect the presence of anxiety (Löwe et al. 2010).

Apathy questions on the screen were adapted by criteria developed by Robert et al. (Robert et al. 2009). These questions assessed for loss of or diminished motivation, loss of or diminished goal-directed behaviour and cognitive activity and loss of or diminished emotion over the past four weeks, which has caused clinically significant impairments in personal, social, occupational and other important areas of functioning. This is a 6-item screen and the maximum possible score is 14. Cut-offs were determined using the validation sample, as this screen has not been previously assessed for apathy cut-offs.

2.6 Screen Validation

Each section of the screen was validated using assessments from the neurocognitive battery based on the National Institute of Neurological Disorders and the Canadian Stroke Network for the study of vascular cognitive impairment. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to determine optimal cut-offs for each portion of the screen. The California Verbal Learning Test 2nd Edition (CVLT-II) was used to assess verbal memory. The Trail Making Test Part B (Trails B), Stroop Color-Word Interference Test and the Controlled Oral Word Association Test (COWAT) were used to measure executive function. The Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders version IV (SCID-IV) depression and GAD modules
were used to diagnose depression and anxiety. The Apathy Evaluation Scale (AES) was used to diagnose apathy.

2.6.1 Cognitive Impairment validation

To validate and develop a cut-off for the 5-word recall and the mini-trails B portion of the screen, the two scores were combined for a maximum score of 14. In order to determine an appropriate cut-off, verbal memory and executive function tests from the validation were used. Z-scores of tests assessing performance in the same cognitive domain can be summed into composite Z-scores to avoid multiple comparisons, as has been previously reported (Rej et al. 2016). For verbal memory, the Z-scores of the CVLT-II level of immediate recall trials 1-5, short delay free recall and long delay free recall were combined to create a standardized verbal memory Z-score. For executive function, Trails B, Stroop, and COWAT (F-A-S version) total word Z-scores were combined to create a standardized executive function Z-score. Impairment in either cognitive domain was defined by a Z-score ≤1 standard deviation below the mean. The ROC curve for the screen cognitive impairment validation is shown in Figure III.

2.6.1.1 CVLT-II

The CVLT-II word list includes 16 words that fall into four different categories: animals, ways of travelling, vegetables and furniture. The list of words is read to the participant and then they are asked to recall as many words as possible, in any order. To provide a measure of learning, this procedure is carried out five times to constitute the five learning trials. A distractor list is then read to the participant and again they are asked to recall as many words as possible, in any order. Following the distractor list, the participant is asked to recall as many words from the original list again. This is defined as the short-delay free recall and is a measure of short-term memory. After a 20 minute delay, the participant is asked to recall the
original word list again, which is defined as the long-delay free recall and is a measure of long-term memory. The test is then scored electronically and Z-scores for the performance over the five learning trials, short-delay free recall and long-delay free recall are provided in the final output. A higher Z-score reflects better performance on the test. The CVLT-II was chosen to assess verbal memory in this study as it has been shown to be sensitive to cognitive impairment in multiple domains in those with CVD (Alexander et al. 2003, Dickson et al. 2007, Hachinski et al. 2006, Rej et al. 2016).

2.6.1.2 Trails B

The Trails B test requires participants to use straight lines to alternate between connecting a series of numbers (in ascending order) and letters (in alphabetical order) as quickly as possible (e.g. 1-A-2-B). The least amount of time required to connect the series of numbers and letters correctly corresponds to a higher Z-score and better performance on the test. Trails B was chosen to assess executive function as it is widely used, easy to administer and has been previously used to assess cognition in coronary artery disease patients (MacPherson et al. 2017, Swardfager et al. 2010).

2.6.1.3 Stroop

The Stroop test requires the participant to read out three different cards, each with 24 items. Card one requires them to name the colours of rows of dots that are presented in four colours: red, blue, green and yellow. Card two requires them to name the colour (the same four colours as in card one) of various words written in rows. Card three requires them to name the colour of colour words printed in incongruent colours, providing a measure of interference (e.g. the word green printed in the colour red, the participant must say red). For cards two and three, participants are required to name the colours and not read the words. The least amount of
time required to read card three corresponds to a higher Z-score and better performance on the test. The Stroop test was chosen as it has a brief administration time, has demonstrated good psychometric properties and is a commonly used measure of executive function (Bayard et al. 2011).

### 2.6.1.4 COWAT

The COWAT test consists of three parts. Participants are given a letter and within one minute are asked to say out loud as many words as they can think of that begin with that letter. However, they are not permitted to say proper names such as the names of people or places, cannot repeat the same word and cannot say the same word again with a different ending. The participant is asked to provide words for three different letters: F, A, and S. The total words provided for all three letters are summed and the more words the participant provides corresponds to a higher Z-score. The FAS version is the most commonly used form of the test today and is a sensitive measure of executive function (Barry et al. 2008).

### 2.6.2 Depression Validation: SCID-IV Depression Module

The PHQ-2 was validated against the SCID-IV depression module which was used to assess the presence of depression or depressive symptoms. The SCID-IV depression module consists of nine questions, the first two questions refer to the participants’ mood over the last month and the next seven questions refer to their mood over the worst two weeks in the last month. The participant was rated as depressed if they had met at least five of the criteria, including a depressed mood almost every day or anhedonia. The ROC curve for the screen depression validation is shown in Figure IV.
2.6.3 Anxiety Validation: SCID-IV GAD Module

The GAD-2 was validated against the SCID-IV GAD module. The GAD module consists of seven questions each rated as absent/false, subthreshold, or threshold/true. The participant was classified as having GAD if they had met six of the criteria and were considered mild if they demonstrated a few symptoms in excess of the number required for diagnosis, moderate if they demonstrated symptoms or functional impairments between “mild” and “severe” or severe if they demonstrated many symptoms in excess of the number required for diagnosis. The ROC curve for the screen anxiety validation is shown in Figure V.

2.6.4 Apathy Validation: AES

The 6-item apathy questionnaire adapted from Robert et al. was validated using the AES self-version. The AES self-version is an 18-item questionnaire used to evaluate the behaviour, cognition, and emotional domains of apathy (Clarke et al. 2007, Clarke et al. 2011). The items are rated on a 4-point Likert scale from 1 (not at all characteristic) to 4 (very characteristic), with higher scores indicating higher levels of apathy (Marin et al. 1991). Participants who scored ≥37 were classified as apathetic (Clarke et al. 2007). The ROC curve for the screen apathy validation is shown in Figure VI.
Figure III. ROC curve (AUC =0.67) used to determine optimal cut-offs for the cognition portion of the screen. Using the two cut point method, as previously described (Swartz et al. 2017), optimal cut-offs to maximize sensitivity and specificity (98% and 80%, respectively) were <6 = high risk for cognitive impairment, 6-13 = intermediate risk, >13 = low risk.
Figure IV. ROC curve (AUC = 0.84) used to determine optimal cut-offs for the depression portion of the screen. Using the two cut point method, as previously described (Swartz et al. 2017), optimal cut-offs to maximize sensitivity and specificity (89% and 96%, respectively) were 0 = low risk for depression, 1-3 = intermediate risk, >3 = high risk.
Figure V. ROC curve (AUC = 0.79) used to determine optimal cut-offs for the anxiety portion of the screen. Using the two cut point method, as previously described (Swartz et al. 2017), optimal cut-offs to maximize sensitivity and specificity (86% and 94%, respectively) were 0 = low risk for anxiety, 1-3 = intermediate risk, >3 = high risk.
Figure VI. ROC curve (AUC =0.73) used to determine optimal cut-offs for the apathy portion of the screen. Using the two cut point method, as previously described (Swartz et al. 2017), optimal cut-offs to maximize sensitivity and specificity (88% and 92%, respectively) were <2 = low risk for apathy, 2-6 = intermediate risk, >6 = high risk.
2.7 The Four-Item Morisky-Green-Levine Medication Adherence Scale

The four-item Morisky-Green-Levine Medication Adherence Scale (MGL) is a widely used self-report medication adherence measure (Culig and Leppee 2014, Lam and Fresco 2015, Olowe and Ross 2017, Omar et al. 2018). This scale provides many advantages as it is easy to administer, easy to score, has a short administration time, identifies barriers to adherence, is adaptable for various groups of medications and various health conditions (Culig and Leppee 2014). The scale addresses factors such as forgetfulness in taking medications and reasons for cutting back due to the medications control of symptoms. A maximum score of 4 classifies participants as adherent and a score of <4 indicates nonadherence. These cut-offs were developed by Morisky et al. in an outpatient setting and continue to be used by subsequent studies assessing medication adherence in various populations (Mena-Vazquez et al. 2017, Morisky et al. 1986, Omar et al. 2018, Pan et al. 2017). For this study, the MGL was modified to include two additional questions: frequency of forgetting to take medications and the convenience of the regimen. Frequency of forgetting has been validated in previous studies as a part of the MGL. The convenience of a regimen has been used in several other medication adherence measures, such as the CULIG, and is an important barrier to assess in those attending CR (Beyhaghi et al. 2016, Culig and Leppee 2014, Olowe and Ross 2017, Omar et al. 2018, Wang et al. 2012).

2.8 Sample Size Calculation

Sample size was calculated based on the primary hypothesis that higher medication adherence levels will be associated with fewer medication use at entry into CR. Although no previous studies have examined medication adherence and polypharmacy in those attending CR, studies have reported differences in medication use in those who are adherent compared to
those who are nonadherent. Studies have shown that those who are nonadherent are 1.16 to 2.22 times more likely to be taking greater number of medications than those who are adherent (Gellad et al. 2007, Marcum et al. 2013, Stoehr et al. 2008). For this study, to detect a medium effect size, given that those with lower adherence levels will be 1.69 times more likely to be taking greater number of medications (Kassab et al. 2013, Marcum et al. 2013), with an alpha of 0.05, 261 participants were required for a power (1-β) of 80%.

2.9 Statistical Analyses

As previously reported, scores were dichotomized to categorize patients as adherent (MGL score =6) or nonadherent (MGL score 0-5) (Cruz et al. 2017, Hill-Briggs et al. 2005, Moise et al. 2018, Radwan et al. 2018). All data analyses were performed using IBM SPSS Statistics 24. Associations between demographic and clinical characteristics with medication adherence levels were found using analyses of variance (ANOVA) for continuous data and chi-square tests for categorical data. Continuous variables were reported as mean ± standard deviations. Categorical variables were reported as total number of people and percentage of study population. For all analyses a p-value of <0.05 was accepted as significant.

2.9.1 Testing Primary Hypothesis

The primary hypothesis to be tested was that higher medication adherence levels will be associated with use of fewer medications at entry into CR. To test this, differences in number of medications prescribed between those who were adherent and nonadherent were determined by a Poisson regression. Adherence was measured with the MGL and medication number was obtained through patient records at TRI. Medications which were prescribed as needed were included in the analyses as previous studies have noted their contribution to the complexity of a regimen (Dolce et al. 1991, Restrepo et al. 2008). Covariates were determined a prior based on
previous literature which suggested they may be potential confounders of the relationship being assessed. The covariates included in the regression – described below – were age, gender, VO2 peak and BMI. As differences in medication adherence have been demonstrated in those who use CVD medications for primary or secondary preventative measures, post-hoc analyses were conducted excluding individuals with only CVRFs (Kumbhani et al. 2013, Naderi et al. 2012). The post-hoc Poisson regression included the same covariates mentioned above.

2.9.2 Testing Secondary Hypothesis

The secondary hypothesis was that those taking ASA, β-blockers and statins will have lower levels of medication adherence than those not taking all three at entry into CR. To test this, differences in total MGL scores at baseline between the two groups who were taking all three or not taking all three medications, were determined by an analysis of covariance (ANCOVA). Medication adherence and use of medication were obtained in the same manner as the primary analysis. Covariates included in the primary analysis were also included in the secondary analysis. A post-hoc analysis excluding those with only CVRFs was also conducted, as in the primary analysis.

2.9.3 Testing Exploratory Hypotheses

2.9.3.1 First Exploratory Hypothesis

The first exploratory hypothesis was that those who demonstrate greater symptoms of one or more neuropsychiatric comorbidities - depression, anxiety, apathy or cognitive impairment - will have lower medication adherence levels than those with fewer symptoms. To test this, the differences in screen scores were determined by a one-way ANOVA. A post-hoc ANOVA was also conducted excluding those with only CVRFs.
2.9.3.2 Second Exploratory Hypothesis

The second exploratory hypothesis was that higher medication adherence levels will be associated with significant improvements in VO\(_2\) peak over the course of 3 months of CR. The changes in VO\(_2\) peak over the course of 3 months of CR were determined with a repeated measures analysis. A post-hoc repeated measures was also conducted excluding individuals with only CVRFs. The covariates included were age, gender and BMI.

2.9.3.3 Third Exploratory Hypothesis

The third exploratory hypothesis was that unintentional nonadherence due to forgetfulness will be associated with higher scores on the three items from the GPCOG and poorer scores on the mini-trails B. ANCOVAs were conducted to detect differences in GPCOG and mini-trails B scores between those who are unintentionally nonadherent or adherent. Post-hoc ANCOVAs were conducted excluding individuals with only CVRFs.

2.9.4 Selection of covariates

2.9.4.1 Age

Age has been shown to be a risk factor for medication nonadherence (Newby et al. 2006, Packard and Hilleman 2016). Although older individuals typically take more medications and can experience cognitive decline, there are discrepancies regarding old age and decreased medication adherence (Benner et al. 2002, Jackevicius et al. 2008, Krousel-Wood et al. 2009, Packard and Hilleman 2016, Tiv et al. 2012). A study assessing antihypertensive medication adherence found that low adherence was more common among participants aged 65-75 than those older than 75 (Krousel-Wood et al. 2009). However, when comparing old-old (mean age of 78 years) to young-old (mean age 66 years) participants,
young-old individuals had a higher rate of adherence (Park et al. 1992). These results demonstrate that age may be a potential confound when assessing medication adherence levels.

2.9.4.2 Gender

Gender is known to be a contributing factor to medication adherence. The factors associated with low adherence differ between men and women. Low adherence scores in men have been associated with reduced sexual functioning, and a BMI $\geq$ 25 kg/m$^2$. Low adherence scores in women have been associated with dissatisfaction with communication with their healthcare provider and depressive symptoms (Holt et al. 2013). A recent review in 2016 showed that women are less likely to adhere to statins than men (Goldstein et al. 2016). Furthermore, several studies have reported that men are more likely to adhere to their medication regimen than women (Chen et al. 2014, Granger et al. 2009, Manteuffel et al. 2014, O’Meara et al. 2007).

2.9.4.3 BMI

A high BMI, typically defined as BMI $> 30$ kg/m$^2$, is a well-known CVRF (Swardfager et al. 2010, Wilson et al. 2002). As obesity often precedes the development of several other CVRFs, adherence to a healthy diet, lifestyle, and pharmacological interventions is essential in those with a high BMI (Lichtenstein et al. 2006). Furthermore, obesity has been shown to be associated with medication nonadherence in Caucasians (Salas et al. 2008) and in men with a BMI of $\geq 25$ kg/m$^2$ (Holt et al. 2013). In addition to the direct effect obesity may have on medication adherence, studies have shown that patients with a higher BMI are more likely to be perceived as nonadherent by their physicians. This perception may influence physician prescribing and ultimately result in suboptimal care for obese individuals (Huizinga et al. 2010).
2.9.4.4 VO₂ Peak

Patients who adhere to their medications may be more likely to adhere to a healthier diet and exercise more frequently. Several studies which assess medication adherence, do not take this factor into account, termed the “healthy adherer” effect (Bitton et al. 2013). VO₂ peak is a measure of cardiopulmonary fitness and is a commonly used measure to determine the workload of physical exercise (Kashihara et al. 2009, Quinart et al. 2014). A recent study has shown that individuals taking more than two prescribed or over the counter medications were less physically fit, as measured by their VO₂ peak (Pannu et al. 2017). Furthermore, as several physiological changes occur in the cardiovascular system during exercise, inadequate medication adherence may result in increased AEs related to exercise and discourage individuals in maintaining a regular exercise routine (Guimarães et al. 2015).
3 Results

3.1 Participant Recruitment

The participant inclusion process for the study is show in Figure VII. For this study, 371 people were referred to TRI during the time research personnel were conducting the medication adherence assessment. Those who were unable to speak or understand English were excluded. Of the 346 participants to be screened, 83 were excluded as they did not show up to their appointment, were not referred to research personnel or did not complete the MGL due to time constraints. Ultimately, 263 participants completed the MGL.

Figure VII. Participant inclusion process for the study.
3.2 Demographics and Clinical Characteristics

3.2.1 Screening Population

Demographics and clinical characteristics of the 603 participants screened who did not complete the MGL and 263 participants who completed the MGL are shown in Table 1. Data are presented as means and standard deviations for continuous variables or total number of people and percentage of population for categorical variables.

Table 1: Demographic and clinical characteristics of all participants who completed the novel screen (n=866). 603 participants completed only the screen, while 263 completed both the screen and the MGL.

<table>
<thead>
<tr>
<th></th>
<th>MGL Sample (n=263) mean ± SD or n (%)</th>
<th>Screening Sample (n=603) mean ± SD or n (%)</th>
<th>Statistic (F or χ²)</th>
<th>p-value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socio-demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.8±11.1</td>
<td>63.0±12.6</td>
<td>0.05</td>
<td>0.82</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>195(75.3)</td>
<td>382(64.7)</td>
<td>9.19</td>
<td>*<em>0.002</em></td>
</tr>
<tr>
<td>Marital Status (% married)</td>
<td>163(62.0)</td>
<td>364(60.4)</td>
<td>0.20</td>
<td>0.66</td>
</tr>
<tr>
<td>Medical Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>111(42.2)</td>
<td>267(44.3)</td>
<td>0.32</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32(12.2)</td>
<td>64(10.6)</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>Depression</td>
<td>59(28.8)</td>
<td>131(29.7)</td>
<td>0.06</td>
<td>0.81</td>
</tr>
<tr>
<td>Cardiac History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>18(6.9)</td>
<td>51(8.6)</td>
<td>0.69</td>
<td>0.41</td>
</tr>
<tr>
<td>PTCA/Stent</td>
<td>91(35.1)</td>
<td>203(34.4)</td>
<td>0.04</td>
<td>0.84</td>
</tr>
<tr>
<td>CABG</td>
<td>44(16.7)</td>
<td>81(13.4)</td>
<td>1.61</td>
<td>0.20</td>
</tr>
<tr>
<td>MI</td>
<td>66(25.1)</td>
<td>153(25.4)</td>
<td>0.01</td>
<td>0.93</td>
</tr>
<tr>
<td>CVRF</td>
<td>20(7.6)</td>
<td>47(7.8)</td>
<td>0.01</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>MGL Sample (n=263) mean ± SD or n (%)</td>
<td>Screening Sample (n=603) mean ± SD or n (%)</td>
<td>Statistic (F or $\chi^2$)</td>
<td>p-value (significance at p&lt;0.05)*</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td><strong>Body Composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.2±6.2</td>
<td>28.6±5.9</td>
<td>1.73</td>
<td>0.19</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>32.2±9.5</td>
<td>34.5±42.3</td>
<td>0.70</td>
<td>0.40</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.1±9.4</td>
<td>168.4±9.7</td>
<td>5.43</td>
<td>0.02*</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>105.5±78.8</td>
<td>100.3±59.2</td>
<td>1.09</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Resting Physiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>75.4±14.2</td>
<td>76.2±14.4</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>Resting systolic BP (mm Hg)</td>
<td>121.3±17.5</td>
<td>122.1±17.4</td>
<td>0.43</td>
<td>0.51</td>
</tr>
<tr>
<td>Resting diastolic BP (mm Hg)</td>
<td>73.9±9.9</td>
<td>73.3±9.9</td>
<td>0.74</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Cardiopulmonary Fitness Parameters</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum HR (bpm)</td>
<td>128.4±23.7</td>
<td>127.8±23.8</td>
<td>0.09</td>
<td>0.76</td>
</tr>
<tr>
<td>Maximum systolic BP (mm Hg)</td>
<td>162.5±25.9</td>
<td>162.0±24.9</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>Maximum diastolic BP (mm Hg)</td>
<td>72.7±9.2</td>
<td>73.4±9.9</td>
<td>0.93</td>
<td>0.34</td>
</tr>
<tr>
<td>VO₂ peak (mL/kg/min)</td>
<td>21.5±6.5</td>
<td>20.9±6.6</td>
<td>1.21</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Concomitant Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>151(57.4)</td>
<td>312(51.7)</td>
<td>2.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>59(22.4)</td>
<td>107(17.7)</td>
<td>2.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Diuretics</td>
<td>51(19.4)</td>
<td>108(17.9)</td>
<td>0.27</td>
<td>0.61</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>140(53.2)</td>
<td>324(53.7)</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>Anti-diabetics</td>
<td>65(24.7)</td>
<td>137(22.7)</td>
<td>0.41</td>
<td>0.52</td>
</tr>
<tr>
<td>Statins</td>
<td>186(70.7)</td>
<td>387(64.2)</td>
<td>3.50</td>
<td>0.06</td>
</tr>
<tr>
<td>ASA</td>
<td>165(62.7)</td>
<td>313(51.9)</td>
<td>8.69</td>
<td>0.003*</td>
</tr>
<tr>
<td></td>
<td>MGL Sample (n=263) mean ± SD or n (%)</td>
<td>Screening Sample (n=603) mean ± SD or n (%)</td>
<td>Statistic (F or $\chi^2$)</td>
<td>p-value (significance at p&lt;0.05)*</td>
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<td>-----------------------</td>
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<td>--------------------------------------------</td>
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<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Screen Scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word Recall</td>
<td>3.5±1.3</td>
<td>3.9±1.2</td>
<td>26.06</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Mini-Trails B</td>
<td>8.0±2.7</td>
<td>8.3±1.7</td>
<td>4.59</td>
<td>0.03*</td>
</tr>
<tr>
<td>Three-item GPCOG</td>
<td>1.0±1.0</td>
<td>1.0±1.0</td>
<td>0.15</td>
<td>0.70</td>
</tr>
<tr>
<td>Depression</td>
<td>1.1±1.4</td>
<td>1.1±1.5</td>
<td>0.10</td>
<td>0.75</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.1±1.5</td>
<td>1.2±1.5</td>
<td>0.20</td>
<td>0.65</td>
</tr>
<tr>
<td>Apathy</td>
<td>2.9±2.8</td>
<td>2.7±2.7</td>
<td>0.89</td>
<td>0.35</td>
</tr>
<tr>
<td>Time to Complete (s)</td>
<td>347.4±113.1</td>
<td>304.2±108.9</td>
<td>23.82</td>
<td>&lt;0.005*</td>
</tr>
</tbody>
</table>

Abbreviations: SD: Standard deviation, IHD: Ischaemic Heart Disease, PTCA: Percutaneous Transluminal Coronary Angioplasty, CAGB: Coronary Artery Bypass Graft, MI: Myocardial Infarction, CVRF: Cardiovascular Risk Factor, BMI: Body Mass Index, bpm: beats per minute, HR: Heart Rate, BP: Blood Pressure, VO₂ peak: peak oxygen consumption, ASA: Acetylsalicylic Acid, GPCOG: General Practitioner Assessment of Cognition
3.2.2 Completed MGL

Demographics and clinical characteristics of the 263 participants who completed the MGL categorized as adherent or nonadherent are shown in Table 2, the distribution of MGL scores are shown in Figure VIII and the proportions of responses to MGL questions are show in Table 3. Data are presented as means and standard deviations for continuous variables or total number of people and percentage of population for categorical variables.

Table 2: Demographic and clinical characteristics of participants who completed the MGL (n=263). Participants were categorized into adherent or nonadherent groups.

<table>
<thead>
<tr>
<th></th>
<th>Nonadherent (n=141) mean ± SD or n (%)</th>
<th>Adherent (n=122) mean ± SD or n (%)</th>
<th>Statistic (F or χ²)</th>
<th>p-value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.3±11.9</td>
<td>64.4±9.9</td>
<td>5.0</td>
<td><strong>0.03</strong>*</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>104(74.8)</td>
<td>91(75.8)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td>Marital Status (% married)</td>
<td>83(58.9)</td>
<td>80(65.6)</td>
<td>1.25</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Medical Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>52(36.9)</td>
<td>59(48.4)</td>
<td>3.54</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16(11.3)</td>
<td>17(13.9)</td>
<td>0.40</td>
<td>0.53</td>
</tr>
<tr>
<td>Depression</td>
<td>39(34.5)</td>
<td>20(21.7)</td>
<td>4.04</td>
<td><strong>0.045</strong>*</td>
</tr>
<tr>
<td><strong>Cardiac History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>9(6.5)</td>
<td>9(7.5)</td>
<td>0.11</td>
<td>0.75</td>
</tr>
<tr>
<td>PTCA/Stent</td>
<td>43(30.9)</td>
<td>48(40.0)</td>
<td>2.32</td>
<td>0.13</td>
</tr>
<tr>
<td>CABG</td>
<td>23(16.3)</td>
<td>21(17.2)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Nonadherent (n=141) mean ± SD or n (%)</td>
<td>Adherent (n=122) mean ± SD or n (%)</td>
<td>Statistic (F or χ²)</td>
<td>p-value (significance at p&lt;0.05)*</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------</td>
<td>---------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Cardiac History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>30(21.3)</td>
<td>36(29.5)</td>
<td>2.36</td>
<td>0.13</td>
</tr>
<tr>
<td>CVRF</td>
<td>14(9.9)</td>
<td>6(4.9)</td>
<td>2.34</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Body Composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.5±5.8</td>
<td>28.7±6.6</td>
<td>0.93</td>
<td>0.34</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>33.2±9.2</td>
<td>31.0±9.6</td>
<td>3.34</td>
<td>0.07</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.2±8.0</td>
<td>170.0±10.9</td>
<td>0.03</td>
<td>0.87</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>99.4±13.3</td>
<td>112.7±115.2</td>
<td>1.78</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Resting Physiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>75.5±14.5</td>
<td>75.3±13.8</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>Resting systolic BP (mm Hg)</td>
<td>121.0±17.6</td>
<td>121.5±17.4</td>
<td>0.05</td>
<td>0.83</td>
</tr>
<tr>
<td>Resting diastolic BP (mm Hg)</td>
<td>74.4±10.3</td>
<td>73.4±9.5</td>
<td>0.74</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Cardiopulmonary Fitness Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum HR (bpm)</td>
<td>128.9±24.9</td>
<td>127.8±22.3</td>
<td>0.13</td>
<td>0.72</td>
</tr>
<tr>
<td>Maximum systolic BP (mm Hg)</td>
<td>163.3±26.2</td>
<td>161.6±25.6</td>
<td>0.29</td>
<td>0.59</td>
</tr>
<tr>
<td>Maximum diastolic BP (mm Hg)</td>
<td>73.0±9.4</td>
<td>72.3±9.0</td>
<td>0.39</td>
<td>0.53</td>
</tr>
<tr>
<td>VO₂ peak (mL/kg/min)</td>
<td>20.9±6.3</td>
<td>22.2±6.6</td>
<td>2.37</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Concomitant Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>75(56.4)</td>
<td>75(65.2)</td>
<td>2.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td>Nonadherent (n=141) mean ± SD or n (%)</td>
<td>Adherent (n=122) mean ± SD or n (%)</td>
<td>Statistic (F or χ²)</td>
<td>p-value (significance at p&lt;0.05)*</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------</td>
<td>-------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>33(24.8)</td>
<td>26(22.6)</td>
<td>0.17</td>
<td>0.68</td>
</tr>
<tr>
<td>Diuretics</td>
<td>28(21.1)</td>
<td>23(20.0)</td>
<td>0.04</td>
<td>0.84</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>71(53.4)</td>
<td>68(59.1)</td>
<td>0.83</td>
<td>0.36</td>
</tr>
<tr>
<td>Anti-diabetics</td>
<td>33(24.8)</td>
<td>32(27.8)</td>
<td>0.29</td>
<td>0.59</td>
</tr>
<tr>
<td>Statins</td>
<td>87(65.4)</td>
<td>97(84.3)</td>
<td>11.55</td>
<td>0.001*</td>
</tr>
<tr>
<td>ASA</td>
<td>80(60.2)</td>
<td>83(72.2)</td>
<td>3.96</td>
<td>0.047*</td>
</tr>
</tbody>
</table>

### Medication Adherence Scores

<table>
<thead>
<tr>
<th></th>
<th>Nonadherent (n=141) mean ± SD or n (%)</th>
<th>Adherent (n=122) mean ± SD or n (%)</th>
<th>Statistic (F or χ²)</th>
<th>p-value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGL</td>
<td>4.4±0.97</td>
<td>6.0±0.0</td>
<td>333.89</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Taking all three ASA, β-blockers, statins</td>
<td>46(34.6)</td>
<td>55(47.8)</td>
<td>4.48</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Abbreviations: SD: Standard deviation, IHD: Ischaemic Heart Disease, PTCA: Percutaneous Transluminal Coronary Angioplasty, CABG: Coronary Artery Bypass Graft, MI: Myocardial Infarction, CVRF: Cardiovascular Risk Factor, BMI: Body Mass Index, bpm: beats per minute, HR: Heart Rate, BP: Blood Pressure, VO₂ peak: peak oxygen consumption, ASA: Acetylsalicylic Acid, MGL: Morisky-Green-Levine Medication Adherence Scale
Table 3. Proportion of participants who responded yes to MGL questions.

<table>
<thead>
<tr>
<th>Question</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Forget to take medications?</td>
<td></td>
</tr>
<tr>
<td>How often?</td>
<td></td>
</tr>
<tr>
<td>• Never</td>
<td>203(77.2)</td>
</tr>
<tr>
<td>• Once in a while</td>
<td>45(17.1)</td>
</tr>
<tr>
<td>• Sometimes</td>
<td>13(4.9)</td>
</tr>
<tr>
<td>• Usually</td>
<td>2(0.8)</td>
</tr>
<tr>
<td></td>
<td>81(30.8)</td>
</tr>
<tr>
<td>2: Careless about taking medications?</td>
<td></td>
</tr>
<tr>
<td>• Due to convenience of regimen?</td>
<td>57(21.7)</td>
</tr>
<tr>
<td></td>
<td>41(15.6)</td>
</tr>
<tr>
<td>3: Stop taking medication when feeling better?</td>
<td>5(1.9)</td>
</tr>
<tr>
<td>4: Stop taking medication when feeling worse?</td>
<td>23(8.7)</td>
</tr>
</tbody>
</table>

Figure VIII. Distribution of MGL scores. Those who are adherent had an MGL score of 6 (122, 46%) and those who are nonadherent had a score of 0-5 (141, 54%).
3.3 Analyses to Test Hypotheses

3.3.1 Primary Hypothesis: Medication Adherence and Polypharmacy

Table 4: Coefficients of a Poisson regression detecting differences in total number of medications between those who are adherent or nonadherent. Covariates entered into the model included: gender, age, BMI and VO$_2$ peak.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wald Chi-Square</th>
<th>OR (95% CI)</th>
<th>df</th>
<th>p-value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>25.98</td>
<td>6.27 (3.10-12.70)</td>
<td>1</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Gender – male</td>
<td>29.46</td>
<td>1.48 (1.29-1.70)</td>
<td>1</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Age</td>
<td>1.59</td>
<td>1.00 (1.00-1.01)</td>
<td>1</td>
<td>0.208</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>0.00</td>
<td>1.00 (0.99-1.01)</td>
<td>1</td>
<td>0.970</td>
</tr>
<tr>
<td>VO$_2$ peak (mL/kg/min)</td>
<td>18.70</td>
<td>0.98 (0.97-0.99)</td>
<td>1</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Adherent</td>
<td>6.04</td>
<td>1.15 (1.03-1.28)</td>
<td>1</td>
<td>0.014*</td>
</tr>
</tbody>
</table>

Abbreviations: OR: odds ratio, CI: confidence interval, df: degrees of freedom, BMI: body mass index, VO$_2$: peak oxygen consumption

To compare the number of medications taken between those who are adherent or nonadherent, a Poisson regression was conducted with total medication number as the dependent variable and adherent or nonadherent as the factor. Gender, age, BMI and VO$_2$ peak were also added in the analysis as covariates. Females were the reference group for gender and nonadherence was the reference group for adherence level. As shown in Table 4, patients who were adherent were taking 1.15 (95% CI, 1.03-1.28, p=0.014) times more medications than those who were nonadherent. Figure IX represents the total number of medications taken in each group. Covariates including VO$_2$ peak and gender were also significantly associated with total number of medications taken. Males were taking significantly more medications than females and lower VO$_2$ peak values at baseline were associated with greater number of medications.
Figure IX. Total number of medications taken in the adherent and nonadherent groups.

The number of medications taken by those in the adherent group was significantly higher than those in the nonadherent group (p=0.014).

Post-hoc Analysis

In a post-hoc Poisson regression analysis controlling for the same covariates, when excluding individuals with only CVRFs, patients who were adherent were taking 1.17 (95% CI, 1.04-1.31, p=0.008) times more medications than those who were nonadherent.
3.3.2 Secondary Hypothesis: Medication adherence and use of ASA, β-blockers and statins

Table 5: Coefficients of an ANCOVA detecting differences in total MGL scores between those taking or not taking all three ASA, β-blockers and statins. Covariates entered into the model included: gender, age, BMI and VO₂ peak.

<table>
<thead>
<tr>
<th>Source</th>
<th>df error</th>
<th>F</th>
<th>p-value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>242</td>
<td>2.83</td>
<td>0.017*</td>
</tr>
<tr>
<td>Intercept</td>
<td>242</td>
<td>18.46</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Gender</td>
<td>242</td>
<td>0.60</td>
<td>0.441</td>
</tr>
<tr>
<td>Age</td>
<td>242</td>
<td>7.32</td>
<td>0.007*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>242</td>
<td>0.04</td>
<td>0.848</td>
</tr>
<tr>
<td>VO₂ peak (mL/kg/min)</td>
<td>242</td>
<td>2.54</td>
<td>0.112</td>
</tr>
<tr>
<td>Taking all three yes/no</td>
<td>242</td>
<td>5.76</td>
<td>0.017*</td>
</tr>
</tbody>
</table>

Abbreviations: df: degrees of freedom, BMI: body mass index, VO₂ peak: peak oxygen consumption

To compare the difference in total MGL scores between patients taking or not taking all three ASA, β-blockers and statins, an ANCOVA was conducted with total medication adherence score as the dependent variable and the use of all three or not as the factor. Gender, age, BMI and VO₂ peak were also added in the analysis as covariates. As shown in Table 5, patients taking all three medications differed significantly in their total MGL scores compared to those not taking all three (F₁, 242=5.76, p=0.017). The total medication adherence score of each group is represented in Figure X. Older age was also significantly associated with higher total medication adherence scores.
Figure X. MGL scores in those taking or not taking all three medications. Those taking all three medications had significantly higher MGL scores, indicating greater levels of medication adherence than those not taking all three (F1, 242=5.76, p=0.017).

Post-hoc Analysis

When excluding individuals with only CVRFs, the difference in the total medication adherence scores between the two groups remained significant in a post-hoc ANCOVA controlling for the same covariates (F1, 222=7.25, p=0.008).
3.3.3 Exploratory Hypotheses

3.3.3.1 Medication Adherence and Neuropsychiatric Comorbidities

Table 6: One-way ANOVA showing the differences in neuropsychiatric comorbidity screen scores between those who are adherent or nonadherent.

<table>
<thead>
<tr>
<th></th>
<th>Adherent (n=122) mean ± SD</th>
<th>Nonadherent (n=141) mean ± SD</th>
<th>F</th>
<th>p value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word Recall</td>
<td>3.3±1.4</td>
<td>3.6±1.3</td>
<td>4.62</td>
<td><strong>0.03</strong>*</td>
</tr>
<tr>
<td>Trails</td>
<td>7.8±2.9</td>
<td>8.1±2.6</td>
<td>0.64</td>
<td>0.42</td>
</tr>
<tr>
<td>GPCOG</td>
<td>0.9±1.0</td>
<td>1.1±1.0</td>
<td>2.66</td>
<td>0.10</td>
</tr>
<tr>
<td>Depression</td>
<td>0.8±1.3</td>
<td>1.3±1.5</td>
<td>7.11</td>
<td><strong>0.008</strong>*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.0±1.5</td>
<td>1.3±1.5</td>
<td>1.40</td>
<td>0.24</td>
</tr>
<tr>
<td>Apathy</td>
<td>3.2±3.2</td>
<td>3.8±3.4</td>
<td>1.83</td>
<td>0.18</td>
</tr>
<tr>
<td>Time to complete (s)</td>
<td>336.1±108.0</td>
<td>357.1±116.8</td>
<td>2.28</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Abbreviations: SD: standard deviation, GPCOG: General Practitioner Assessment of Cognition

As shown in Table 6, the significant between group differences were found in the depression and word recall portions of the screen. Those who were nonadherent had significantly higher scores on the depression questionnaire and recalled significantly more words.

Post-hoc Analysis

When excluding individuals with only CVRFs, the difference in depression screen scores between the two groups remained significant in a post-hoc ANOVA analysis ($F_{1, 241}=9.48$, $p=0.002$), however the word recall scores were no longer significantly different ($F_{1, 241}=2.93$, $p=0.088$).
3.3.3.2  Medication Adherence and VO\textsubscript{2} Peak

Table 7: Coefficients of a repeated measures showing the within-subject factors in VO\textsubscript{2} peak change over the course of 3 months of CR in those who are adherent or nonadherent. Covariates entered into the model included: gender, age and BMI.

<table>
<thead>
<tr>
<th>Source</th>
<th>df error</th>
<th>F</th>
<th>p-value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>1</td>
<td>15.18</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Time*Gender</td>
<td>1</td>
<td>4.32</td>
<td>0.041*</td>
</tr>
<tr>
<td>Time*Age</td>
<td>1</td>
<td>5.89</td>
<td>0.018*</td>
</tr>
<tr>
<td>Time* BMI (kg/m\textsuperscript{2})</td>
<td>1</td>
<td>5.65</td>
<td>0.020*</td>
</tr>
<tr>
<td>Time* Medication Adherence</td>
<td>2</td>
<td>0.13</td>
<td>0.718</td>
</tr>
</tbody>
</table>

Abbreviations: df: degrees of freedom, BMI: body mass index

In order to compare the improvements in VO\textsubscript{2} peak over time, a repeated measures was conducted with adherence levels as a between-subject factor. As shown in Table 7 and Figure XI, VO\textsubscript{2} peak significantly improved over the course of 3 months, but the group by time interaction was not significant (F\textsubscript{1,76}=0.13, p=0.718). However, there was a significant between group difference in improvements in VO\textsubscript{2} peak (F\textsubscript{1,76}=5.84, p=0.018). Subgroup analyses were also conducted to determine if VO\textsubscript{2} peak values improved in each group separately. In both adherent and nonadherent groups, VO\textsubscript{2} peak significantly improved over time (F\textsubscript{1,33}=4.82, p=0.035 and F\textsubscript{1,40}=10.08, p=0.003, respectively).
Both groups showed significant improvements in VO₂ peak over time.

**Post-hoc Analysis**

When excluding individuals with only CVRFs, the improvements in VO₂ peak over time remained significant ($F_{1,69}=16.43$, $p<0.005$). The between group difference also remained significant ($F_{1,69}=6.53$, $p=0.013$).
### Table 8: Coefficients of an ANCOVA detecting differences in the three-item GPCOG scores in those who are unintentionally nonadherent or adherent.

Covariates entered into the model included: gender, age, BMI and VO\textsubscript{2} peak.

<table>
<thead>
<tr>
<th>Source</th>
<th>df error</th>
<th>F</th>
<th>p-value (significance at p&lt;0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>241</td>
<td>2.06</td>
<td>0.071</td>
</tr>
<tr>
<td>Intercept</td>
<td>241</td>
<td>1.18</td>
<td>0.278</td>
</tr>
<tr>
<td>Gender</td>
<td>241</td>
<td>2.39</td>
<td>0.123</td>
</tr>
<tr>
<td>Age</td>
<td>241</td>
<td>0.48</td>
<td>0.489</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>241</td>
<td>0.03</td>
<td>0.874</td>
</tr>
<tr>
<td>VO\textsubscript{2} peak (mL/kg/min)</td>
<td>241</td>
<td>0.23</td>
<td>0.632</td>
</tr>
<tr>
<td>Unintentionally nonadherent yes/no</td>
<td>241</td>
<td>5.10</td>
<td>0.025*</td>
</tr>
</tbody>
</table>

Abbreviations: df: degrees of freedom, BMI: body mass index, VO\textsubscript{2} peak: peak oxygen consumption.

In order to compare GPCOG scores between those who forget to take their medication and those who do not, an ANCOVA was conducted with GPCOG scores as the dependent variable and unintentional nonadherence as assessed by question 1 on the MGL as the factor. Gender, age, BMI and VO\textsubscript{2} peak were also added in the analysis as covariates. As shown in Table 8, patients who are unintentionally nonadherent differed significantly in their GPCOG scores from those who are adherent (F\textsubscript{1,241}=5.10, p=0.025). GPCOG scores in each group are represented in Figure XII.
Patients who reported forgetting to take their medication demonstrated higher GPCOG scores (have had more memory difficulties in the past year, experienced difficulties in managing money or difficulties in finding the right word when speaking) than those who do not forget to take their medication ($F_{1, 241} = 5.10$, $p=0.025$).

**Post-hoc Analysis**

When excluding individuals with only CVRFs, the differences in GPCOG scores between the two groups remained significant in a post-hoc ANCOVA controlling for the same covariates ($F_{1, 221}=5.32$, $p=0.022$).
Table 9: Coefficients of an ANCOVA detecting differences in the mini-trails B scores in those who are unintentionally nonadherent or adherent. Covariates entered into the model included: gender, age, BMI and VO$_2$ peak.

<table>
<thead>
<tr>
<th>Source</th>
<th>df error</th>
<th>F</th>
<th>p-value (significance at p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>242</td>
<td>0.96</td>
<td>0.444</td>
</tr>
<tr>
<td>Intercept</td>
<td>242</td>
<td>23.46</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>Gender</td>
<td>242</td>
<td>0.09</td>
<td>0.769</td>
</tr>
<tr>
<td>Age</td>
<td>242</td>
<td>1.79</td>
<td>0.182</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>242</td>
<td>0.88</td>
<td>0.350</td>
</tr>
<tr>
<td>VO$_2$ peak (mL/kg/min)</td>
<td>242</td>
<td>0.01</td>
<td>0.929</td>
</tr>
<tr>
<td>Unintentionally nonadherent yes/no</td>
<td>242</td>
<td>1.25</td>
<td>0.264</td>
</tr>
</tbody>
</table>

Abbreviations: df: degrees of freedom, BMI: body mass index, VO$_2$ peak: peak oxygen consumption

In order to compare mini-trails B scores between those who forget to take their medication and those who do not, an ANCOVA was conducted with mini-trails B scores as the dependent variable and unintentional nonadherence as assessed by question 1 on the MGL as the factor. Gender, age, BMI and VO$_2$ peak were also added in the analysis as covariates. As shown in Table 9, patients who are unintentionally nonadherent did not significantly differ in their mini-trails B scores from those who are adherent (F$_{1, 242}$=1.25, p=0.264).

Post-hoc Analysis

When excluding individuals with only CVRFs, no significant differences were found in the mini-trails B scores between the two groups in a post-hoc ANCOVA controlling for the same covariates (F$_{1, 222}$=0.93, p=0.335).
4 Discussion

4.1 Study Findings and Interpretation

4.1.1 Primary and Secondary Hypotheses

The present study investigated factors associated medication adherence in CVD patients and those with CVRFs attending a CR program. While those attending CR may generally be an adherent group, the number of medications prescribed, and the types of medications may be barriers to adherence. Specifically, use of ASA, β-blockers and statins, which may be associated with low adherence, are common in this population. Based on previous studies that have found polypharmacy to be a predictor of lower medication adherence levels (Chapman et al. 2008, Gellad et al. 2011, Melloni et al. 2009, Stoehr et al. 2008), it was hypothesized that in this population being prescribed a greater number of medications would be associated with lower adherence scores. Unexpectedly, patients classified as adherent were taking significantly more medications than those who were nonadherent. Furthermore, in the post-hoc Poisson regression, those who were adherent and did not only have CVRFs, were taking significantly more medications than those who were nonadherent. The covariates gender and VO₂ peak were also significantly associated with total number of medications. Males were taking significantly more medications than females and those with a lower VO₂ peak at baseline were taking more medications.

The individual and combined use of ASA, β-blockers and statins has been shown to be associated with decreased adherence (Breekveldt-Postma et al. 2008, Duffy et al. 2014, Jackevicius et al. 2002, Newby et al. 2006), and as such it was hypothesized that those taking all three would have lower MGL scores. However, patients who were taking all three medications had significantly higher MGL scores than those not taking all three. Older age was also significantly associated with higher MGL scores.
4.1.2 Interpretation of Primary and Secondary Hypotheses

Although opposite to what was hypothesized, the findings that those taking more medications or taking all three ASA, β-blockers and statins demonstrated greater adherence levels, have significant implications. As previously mentioned, the majority of studies on medication adherence in CVD patients indicate polypharmacy to be associated with lower adherence. However, Gazmararian et al. also found that better adherence was associated with increased number of medications (Gazmararian et al. 2006). Studies have indicated that those who are taking more medications may have a more severe illness and thus are more focused in managing their health (George and Shalansky 2007). While the complexity of a regimen can cause difficulties in managing medication use, it may also increase adherence as several resources are available to aid patients in understanding the importance of adhering to a complicated regimen (Gazmararian et al. 2006, Yang et al. 2003). Furthermore, studies have shown that medication adherence is significantly higher in patients who have more physician visits and effective physician-patient communication (Balkrishnan 1998, Brown and Bussell 2011, Bultman and Svarstad 2000, Kerse et al. 2004). Those who are attending CR have more frequent interactions with health care providers which may add to their understanding of the importance of adherence.

Despite suboptimal adherence rates to common CVD medications, a meta-analysis showed that there are no significant differences in adherence levels between ASA, β-blockers or statins use (Naderi et al. 2012). This suggests that medication class differences may not be contributing to the low levels of adherence in CVD patients. In addition, the difference in the mean medication number between adherers and nonadherers, while statistically significant, may not represent a clinically significant difference. However, the difference in mean medication number between the two groups is similar to that of previous studies which report a

In this study, while approximately half of those in the adherent group were taking all three ASA, β-blockers and statins, 35% of nonadherers were also taking all three. To further improve adherence among those taking all three medications, studies have suggested the use of a polypill. The term polypill was introduced by Wald and Law in 2003 and it was suggested that everyone over the age of 55 with existing CVD be treated with a single pill containing ASA, three low-dose BP lowering medications, a statin and folic acid (Wald and Law 2003). Since then, various studies have aimed to assess the safety and efficacy of polypill use for both primary and secondary CVD prevention. The majority of studies have demonstrated that polypill use results in increased adherence, significant reductions in BP and cholesterol compared to placebo and approximate relative risk reductions in CVD, when combined with lifestyle modifications, of up to 70-80% (PILL Collaborative Group 2011, Indian Polycap Study et al. 2009, Thom et al. 2013, Thom et al. 2014, Wald et al. 2012, Yusuf et al. 2012, Yusuf et al. 2014). Concerns have been raised that polypill use may reduce individual efforts to maintaining a healthy lifestyle, but for those attending a CR program, it may provide substantial benefits as they are already engaged in consistent physical activity (Viera et al. 2011). The use of a polypill in nonadherers attending CR, may significantly improve their adherence rates.

Given the above results, for those attending a CR program, other factors influencing medication adherence aside from polypharmacy and medication class must be focused on. For example, clinicians in the program may want to focus on factors such as ethnicity, gender, age or cardiopulmonary fitness parameters when looking to identify groups at risk for nonadherence. A recent systematic review in 2016 showed that African-Americans perceived
hypertension to be episodic and symptomatic which resulted in irregular medication use (Buckley et al. 2016). Perceptions such as these likely play a role as to why CVD mortality rates are 15-23% higher in African-American individuals compared to Caucasians (Balfour et al. 2015). There are several other studies which have also reported on differences in medication adherence rates amongst different races (Gellad et al. 2007, Gerber et al. 2010, Manteuffel et al. 2014, Marcum et al. 2013, Monane et al. 1996, Trinacty et al. 2009). Our screen validation participants, which were representative of our total study population, were largely Caucasian. Furthermore, on average, those participating in the validation also had high incomes and high levels of education. These factors may be reasons why in this CR population, the results are opposite to what is widely reported in the literature. Therefore, it is necessary for cardiologists and CR supervisors to acknowledge differences in education, income and ethnic differences between patient-provider to aid in improving medication adherence (De Melo Ghisi et al. 2014, Di Chiara et al. 2015, Ghisi et al. 2014). Physicians should aim to educate and address patient concerns about taking multiple medications and aim to prescribe generics to reduce the possibility of individual financial burdens (Ferdinand et al. 2017).

In our study, there were no significant differences in total MGL scores between males and females. However, males were prescribed significantly more medications than females, which differs from the results reported by Manteuffel et al. (Manteuffel et al. 2014). They reported that the average number of medications females were using was significantly higher than that of males. The most important difference between their study and ours, is that our study was conducted in a CR population. A retrospective cohort study of 25,958 participants reported that females experienced significantly lower rates of referral to CR compared to males (Colbert et al. 2014). Our results are in concordance with this report as our population was 75% male. Furthermore, concerns about the teratogenicity of medications provides another
factor influencing physician prescription (Godfrey et al. 2012, Kusters et al. 2012). As many studies are biased towards male populations, this can influence physician behaviours, resulting in gender bias when prescribing and applying clinical guidelines (Ballantyne and Rogers 2011, Bierman 2007, Manteuffel et al. 2014). Studies have shown that women were less likely to be prescribed statins than men after an MI and when physicians are presented with patients with chest pain where the only difference is sex, males were more likely to receive appropriate treatment (Abuful et al. 2005, Buja et al. 2014, Kumbhani et al. 2013, Manteuffel et al. 2014, McSweeney et al. 2016). Based on the above studies and our results, it is evident that gender-based differences contribute significantly to medication prescribing and adherence.

The demographic characteristics of those who completed the MGL and the ANCOVA conducted for the secondary hypothesis, demonstrate that older age was associated with significantly higher total MGL scores. Simons et al. and Yang et al. both showed that older age was associated with lower risk of lipid-lowering agent discontinuation (Simons et al. 1996, Yang et al. 2003). An important point to consider when determining which individuals are at a high risk for nonadherence, is that the relationship between age and medication adherence cannot be viewed as linear. In a systematic review and meta-analysis, 10 out of 11 studies reported a u-shaped relationship between age and medication adherence. Younger participants, normally <50 years old, had a significantly higher relative risk for nonadherence than those aged 50-65 and those aged ≥70 had a higher risk for nonadherence than those aged 50-65 (Abraha et al. 2003, Avorn et al. 1998, Benner et al. 2004, Caspard et al. 2005, Donnelly et al. 2008, Hudson et al. 2007, Larsen et al. 2002, Mann et al. 2010, Vinker et al. 2008, Yang et al. 2003). Identifying if this u-shaped relationship between age and adherence is present in a CR setting will aid in implementing interventions to the appropriate group with low adherence.
4.1.3 Exploratory Hypotheses

Along with polypharmacy, neuropsychiatric comorbidities in CVD such as cognitive impairments, depression, anxiety, and apathy have been associated with lower adherence to medication (DiMatteo et al. 2000, Eurelings et al. 2014, Hare et al. 2014, Howell et al. 2017, Vlasnik et al. 2005). In the exploratory analyses, the relationship between test scores for the above comorbidities and medication adherence levels were assessed. It was hypothesized that greater symptoms of one or more comorbidities would be associated with lower medication adherence levels. Scores on the depression and word recall portions of the screen were the only ones significantly different between adherers and nonadherers. In keeping with the previous literature, those who were nonadherent demonstrated significantly higher depression screen scores than those who were adherent. However, when those with CVRFs were excluded, the significant difference in word recall scores was lost.

Improvements in VO\textsubscript{2} peak over the course of CR have been shown to decrease CVD mortality by up to 10% (Kavanagh et al. 2002, Kavanagh et al. 2003). As those who adhere to their medications are more likely to adhere to CR (Bitton et al. 2013), it was hypothesized that higher medication adherence levels would be associated with improvements in VO\textsubscript{2} peak over the course of 3 months in CR. Patients in both groups showed significant improvements in their VO\textsubscript{2} peak over time, but those who were adherent had significantly higher VO\textsubscript{2} peak values at baseline and 3 months.

Given that cognitive impairments can negatively impact medication adherence, it is not surprising that the rates of unintentional nonadherence due to forgetfulness in those with CVD are higher than the rates of intentional nonadherence (Lowry et al. 2005, Molloy et al. 2014). In this study, those who were unintentionally nonadherent as assessed by question 1 on the
MGL (Appendix A) had significantly higher scores on the GPCOG portion of the screen, but no significant differences in the mini-trails B scores. This indicated that those who were unintentionally nonadherent had difficulties in their memory over the past year, experienced difficulties in managing money or difficulties in finding the right word when speaking more so than those who were adherent.

To determine if those who only had CVRFs significantly impacted any group differences, sub-group analyses were conducted for all hypotheses excluding those with only CVRFs. When those who only had CVRFs and have not experienced any CVD event were removed from the analyses, all results remained significant.

4.1.4 Interpretation of Exploratory Hypotheses

Higher depression screen scores, lower VO$_2$ peak values and unintentional nonadherence due to forgetfulness were all associated with lower adherence levels. These three factors may be of importance for CR supervisors to assess as potential risk factors for not only decreased medication adherence, but decreased CR program adherence. Previous studies have demonstrated that major depressive disorder was associated with increased risk for non-completion of CR and improvements of depressive symptoms were associated with increased medication adherence (Bauer et al. 2012, Swardfager et al. 2011). Those with depression also showed significantly lower improvements in VO$_2$ peak compared to those without depression (Swardfager et al. 2011). To improve medication adherence in those attending CR who screen positive for depression, further assessments should be completed to determine appropriate treatment interventions.

While our results demonstrated that individuals in both groups showed significant improvements in VO$_2$ peak over time, adherers had significantly higher VO$_2$ peak values at all
time points. This may be indicative of lower CVD mortality rates in those who are adherent to their medications as studies have shown higher baseline fitness in CR patients is a predictor of lower CVD mortality rates. Moreover, increased attendance to CR classes is associated with significant improvements in VO₂ peak and as both group showed significant improvements, it is important to determine if the number of classes attended was significantly different between adherers and nonadherers (Alter et al. 2015, Dorn et al. 2001, Martin et al. 2013). Furthermore, a recent cohort study in 2015 showed that CR attendance was associated with improved behavioural health outcomes, such as increased visits to primary care physicians and higher medication adherence to statins (Alter et al. 2015).

The healthy adherer effect – consistent demonstration of healthy lifestyle behaviours – may be responsible for the improved outcomes found in those who attend more CR classes and for the higher VO₂ peak values of the adherent group (Bitton et al. 2013). Lower cardiopulmonary fitness levels are also associated with increased prevalence of comorbid illnesses such as hypertension or hypercholesterolemia in those with CVD (Martin et al. 2013). Pannu et al. also reported that individuals who were taking more than two prescribed medications had significantly lower VO₂ peak levels than those taking fewer medications (Pannu et al. 2017). In concordance with these results, we found that lower VO₂ peak values at baseline were associated with greater medication use, possibly to treat more comorbidities.

Factors such as forgetfulness, carelessness and sociodemographic characteristics may all contribute to the passive process of unintentional nonadherence (Akeroyd et al. 2015, Gadkari and McHorney 2012, Wroe 2002). In this study, unintentionally nonadherent participants were more likely to have more memory difficulties in the past year, experienced difficulties in managing money or difficulties in finding the right word when speaking than those who were adherent. This emphasizes that in this population, unintentional nonadherence
due to forgetfulness may be of particular importance over other circumstances out of one’s control, such as age or gender. The absence of significant between group differences in mini-trails B scores may be attributed to the fact that 86% of participants completed this assessment correctly. As this test was only a short screen and not a standard assessment of executive function, further assessments such as the full-length Trails B or Stroop test should be conducted in those who are unintentionally nonadherent to confirm the previously reported association between medication nonadherence and executive dysfunction (Insel et al. 2006, Silbert et al. 2007).

Lowry et al. reported that individuals who were unintentionally nonadherent, were more likely to have uncontrolled BP than those who were adherent (Lowry et al. 2005). Furthermore, Molloy et al. reported that unintentional nonadherence due to forgetfulness may be the primary form of nonadherence in the year following a CVD event (Molloy et al. 2014). Our results further support the suggestion that unintentional nonadherence is prevalent in those with CVD or CVRFs, undergoing CR. Approximately half of the participants in this study who were unintentionally nonadherent had hypertension. As uncontrolled BP is a well-known CVRF, this highlights the need for interventions to improve adherence in this population (Rapsomaniki et al. 2014). Different interventions are required to improve adherence in those who are intentionally or unintentionally nonadherent. For those who are intentionally nonadherent, the interventions may include addressing patient’s individual perceptions, involving them in decision making process and providing them with adequate information to weigh the pros and cons of the medication (Wroe 2002). Whereas for those who are unintentionally nonadherent, the interventions may include pill packaging, reminders, or education-based interventions (Lowry et al. 2005, Wroe 2002). Cardiologists or CR supervisors may want to consider regularly assessing unintentional nonadherence and apply
effective interventions before therapy discontinuation, as it may be contributing to decreased therapeutic benefit (Gadkari and McHorney 2012).

In all post-hoc analyses, when those with only CVRFs were excluded, the results remained significant. This may be an indication that the differences between medication adherence scores or number of medications taken were not driven by those who are in CR for primary preventative measures. A meta-analysis reported a significant difference in the percentage of people who were adherent to medications taken for primary or secondary CVD preventative measures (50% vs 66%, respectively) (Naderi et al. 2012). Those who only present with CVRFs may be less adherent to their medications as they may not be aware of the long-term benefits of treating asymptomatic conditions such as hypertension (Jackevicius et al. 2002). A recent systematic review showed that patients require a substantial CVD event risk reduction before they perceive that taking daily medication is worthwhile, which may be a factor influencing the decreased adherence in those taking medications for primary preventative purposes (Albarqouni et al. 2017). However, in our study, as a small number of participants had only CVRFs, it was difficult to compare adherence levels with those who had a CVD event. The small sample of CVRF participants may be why they did not drive any effects reported in the results.

4.2 Limitations and Recommendations for Future Studies

A limitation of this study is that medication adherence scores were only measured at baseline. This limited our ability to come to any conclusions about CR completion and medication adherence throughout the program. If medication adherence had been assessed at 3 and 6 months, as cardiopulmonary fitness measures are, further analyses could have been conducted. Future studies should aim to assess medication adherence throughout the course of
CR to determine which factors – such as smoking status, completion of CR, or nutritional status – positively or negatively influence medication taking behaviours (Alter et al. 2015, Heuberger and Caudell 2011, Shea et al. 1992). Along with only baseline measures of medication adherence, VO$_2$ peak values were only available for the 3 month time point in CR. To determine if VO$_2$ peak continues to improve in both adherers and nonadherers, it is necessary to further assess these values over the course of the full 6 month program. If nonadherers do not continue to show improvements in VO$_2$ peak after completion of the full program, this may identify a subgroup of individuals at higher risk for not receiving the optimal health benefits of CR (Alter et al. 2015).

Furthermore, this study did not exclude or categorize participants based on age or CVD diagnosis. While this allowed us to assess a more heterogeneous population, as is typically seen in CR, the results cannot be specified to a certain age group or type of CVD. Future studies should aim to replicate these results in CR participants grouped by age and diagnosis severity. Although we were able to include age, gender and VO$_2$ peak as covariates, we did not have information on the ethnicity of the participants. Including ethnicity as a covariate is essential as previously mentioned, several studies have shown that non-Caucasians are more likely to be nonadherent to their medications (Gellad et al. 2007, Gerber et al. 2010, Manteuffel et al. 2014, Marcum et al. 2013, Monane et al. 1996, Trinacty et al. 2009). As the ethnicity of the participants in each group was not known, identifying if the nonadherent group was largely non-Caucasian is important for future studies. Identification of ethnic and cultural differences regarding medication adherence among those in CR can provide clinicians with an opportunity to develop targeted interventions to improve adherence specifically for these populations.

Furthermore, the presence of a support system by either family or education from healthcare professionals has been shown to have a significant impact on improving adherence
rates. Factors such as knowledge of the illness, consistent medication taking routines, social support and adequate communication with physicians have all been shown to facilitate increased adherence rates (Chabot et al. 2003, Krousel-Wood et al. 2005, Mayberry and Osborn 2012, Morrison et al. 2000, Ogedegbe et al. 2004, Roter et al. 1998). In this study, the presence of a support system or ongoing education about medication adherence was not assessed for each individual. In the future, studies should aim to determine if those in CR adhere more readily to their medications given the presence of a support system and if this added support further improves CR adherence rates.

Other factors which have been shown to significantly impact adherence levels, are paying out of pocket due to lack of healthcare coverage and increased dosing frequency. The cost of medications poses the greatest burden on those with low incomes or elderly retired individuals and greater than once daily dosing is associated with decreased adherence levels (Albert 2008, Baroletti and Dell’Orfano 2010b, Claxton et al. 2001, Ferdinand et al. 2017, Jackevicius et al. 2008, Krousel-Wood et al. 2005, Soumerai et al. 2006, Weeda et al. 2016, Yap et al. 2016). Despite that in Ontario, those who are older than 65 years of age are insured, 13.2% of the total population younger than 65 are not enrolled in a public or private health insurance plan (Sutherland et al. 2017). Our lack of information on participant income, employment status, healthcare coverage and dosing frequency pose another limitation to this study and warrants further research for those attending CR. Another limitation is that our study was a single-centre study. This may influence the ability of these results to be generalizable to other populations. However, this study provides a basis for future studies to determine which factors influence medication adherence levels in other CR centres.

The use of the MGL as a self-report measure of medication adherence provides both limitations and strengths to this study. Self-report measures may be subject to recall bias,
overestimation of adherence, place blame on the patients for not adhering to the regimen and elicit socially acceptable responses. The patient’s mental health state may also influence their responses (Farmer 1999, Morisky et al. 2008, Svarstad et al. 1999). To address this limitation, the use of an objective measure such as a pill count or prescription refill records, in combination with the MGL, would provide a more comprehensive measurement of adherence (Lam and Fresco 2015). However, despite these limitations self-report measures are inexpensive, simple to use, provide real-time feedback, more useful in a busy clinical setting such as CR and can provide information regarding social or behavioural factors influencing adherence (Lam and Fresco 2015, Lavsa et al. 2011, Morisky et al. 2008, Nguyen et al. 2014).

Studies have also shown that there are significant correlations between self-report measures of medication adherence and pharmacy prescription records (Caskie and Willis 2004, Krousel-Wood et al. 2004).

Another important factor to consider is that adherence to medications is also dependent on the initial physician prescription. Patients have reported omitting approximately 19% of medications prescribed from their regimen, with increased medication omission associated with decreased physician-patient communication (Hulka et al. 1976, Kerse et al. 2004). Understanding the reasons for lack of prescription filling in those attending CR, is another factor which will ultimately contribute to improved medication adherence levels (Fischer et al. 2010).

Finally, this study is limited by the lack of information on AEs patients may have experienced due to the class of medication or due to nonadherence. Two adverse effects of β-blockers which may be particularly important in those attending CR are depression and bradycardia (Erdmann 2009, Ko et al. 2004, Rogers and Pies 2008). Although a meta-analysis demonstrated that use of β-blockers was not associated with a significant increase in depressive
symptoms compared to placebo, the potential for this AE may negatively impact medication adherence (Ko et al. 2002). Statins may cause muscle pain, fatigue and weakness and ASA may increase the risk of various gastrointestinal complications (Golomb and Evans 2008, Sostres et al. 2010). Nonadherence to CVD medications has also been shown to be associated with several AEs including higher all-cause and CVD mortality (Ho et al. 2008). Identification of AEs in future studies may provide useful information regarding their impact on medication adherence levels in those with CVD attending CR. CR centres should also consider implementing counselling programs directed at improving medication adherence and use of an appropriate polypill for those with low adherence levels, as both strategies have demonstrated favourable outcomes (Fonarow et al. 2001, Thom et al. 2013, Wald and Law 2003, Yusuf et al. 2014).

The term adherence itself is often used interchangeably with other terms such as compliance, but those terms define different aspects of medication taking behaviours. It has been proposed that the term adherence be further divided into three phases: initiation, implementation and discontinuation (Vrijens et al. 2012). Future studies conducted on medication adherence in CR centres should consider evaluating adherence levels in the context of those three phases to determine which phase is associated with greater nonadherence.

4.3 Conclusions

This study found that in those with CVD and CVRFs attending a CR program, polypharmacy was not associated with lower medication adherence levels. Similarly, those taking all three ASA, β-blockers and statins had higher medication adherence levels than those not taking all three. These results highlight that in a CR setting, the number or class of medications may not be the primary factors influencing medication adherence levels. In this
population, those who are using fewer numbers of medications, may be indicative of patients with pre-existing barriers to adherence. Instead, factors such as VO\textsubscript{2} peak, age, and gender were found to have significant associations with medication adherence and number of medications. However, the impact of factors such as ethnicity, presence of support systems and employment status on medication adherence in this population require further research (Gellad et al. 2007, Krousel-Wood et al. 2005, Marcum et al. 2013, Yap et al. 2016).

This study also found that higher depression screen scores and levels of unintentional nonadherence due to forgetfulness were associated with lower medication adherence levels. These results demonstrate a need for ongoing screening of neuropsychiatric comorbidities such as cognitive impairment and depression in this population, as has previously been suggested (Cohen et al. 2015, Hare et al. 2014, Thombs et al. 2006). It is important to understand that approaches to improving medication adherence are multifactorial and interventions should be tailored to each patient (Kolandaivelu et al. 2014). For those who demonstrate low adherence levels, CR centres should educate patients on the importance of adherence, ensure communication is ongoing between the patient and physician, discuss more affordable options if cost is an issue and aim to alleviate health disparities (Albert 2008, DiMatteo et al. 2012, Ferdinand et al. 2017). Continuous identification of which factors pose the greatest risk for decreased adherence levels in a CR population, will result in reduced healthcare costs per patient and improved outcomes, including increased attendance to CR classes.
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Appendices

Appendix A – Novel Screen and MGL
Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th></th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fold on lines, give to patient to complete

Executive

Turn over, give patient back page to complete, then complete memory recall

<table>
<thead>
<tr>
<th>Memory – Recall</th>
<th>Has to recall words WITH NO CUE</th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
</tr>
</thead>
</table>

SCORING

Cognition:
- Memory: # words remembered = _____ / 5
- Executive: # correct lines drawn = _____ / 9
- Qualitative: # yes = _____ / 3
- Anxiety: sum of 1 and 2 = _____ / 6

Depression: sum of 1 and 2: _____ / 6

Apathy: sum of 1 – 4: _____ / 12
- Is #5 yes? _____ / 1
- Is #6 no? _____ / 1

Front page

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**QUALITATIVE COGNITION**

a) In the past year have you had any difficulties with your memory?  
   Yes/No
   
   i. Has anyone commented on this?  
   Yes/No

b) Are you less able to manage money and financial matters than you were 5 years ago?  
   Yes/No

c) When speaking, do you have more difficulty in finding the right word, or do you tend to use the wrong words more often than you did 5 years ago?  
   Yes/No

**DEPRESSION**

Over the past two weeks, how often have you been bothered by the following problems?  

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several Days</th>
<th>More than half the days</th>
<th>Nearly everyday</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling down, depressed, or hopeless.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Little interest or pleasure in doing things.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**ANXIETY**

Over the past two weeks, how often have you been bothered by the following problems?  

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several Days</th>
<th>More than half the days</th>
<th>Nearly everyday</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious, or on edge.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**APATHY**

Circle the response that best describes your thoughts, feelings and actions during the past 4 weeks.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am less motivated.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. My interest in starting or participating in conversations or activities has decreased.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. My interest in the world around me has decreased.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. My reaction to sad or exciting events has decreased.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

If 1-4 answered 0, do not continue.

5. Lack of motivation or interest has made parts of my life, such as work or socializing, significantly more difficult?  
   Yes/No

6. Lack of motivation/interest began after I started a new medication, or right after a new medical condition?  
   Yes/No
Four-Item Morisky-Green-Levine Medication Adherence Scale

1. Do you ever forget to take your medicine?
   a. If so, how often do you forget to take your medicine?
      i. Never
      ii. Once in a while
      iii. Sometimes
      iv. Usually

2. Are you careless at times about taking your medicine?
   a. Is it due to the convenience of the regimen?

3. When you feel better, do you sometimes stop taking your medicine?

4. Sometimes, if you feel worse when you take the medicine, do you stop taking it?
Appendix B – Informed Consent Form
Validity, Feasibility, and Use of a Novel Screen for Cognitive Impairment, Depression, Anxiety, and Apathy Designed for Coronary Artery Disease and Related Disorders.

Subject Information and Consent

INFORMED CONSENT:

You are being invited to participate in a research study conducted at the Toronto Rehabilitation Institute and Sunnybrook Health Sciences Centre under the supervision of the above investigators. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Participation is completely voluntary and you are free to withdraw from the study at any time. A description of this study follows.

This form explains the purpose of this research study, provides information about the study procedures, possible risks and benefits, and the rights of participants. Please read this form carefully and ask any questions you may have. Please ask the study staff or one of the investigators to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

INTRODUCTION

You are being asked to consider participating in this study because you have coronary artery disease (CAD) and because you are taking part in the Toronto Rehabilitation Institute’s Cardiac Rehabilitation Program. In some people with heart disease, cognitive problems (difficulties thinking, reasoning, and remembering), mood symptoms, anxiety, and apathy (persistent lack of motivation) can develop. The knowledge from this study will help us develop
a simple test to identify patients who are likely to have these symptoms, so that they can be treated.

WHY IS THIS STUDY BEING DONE?

We have developed a brief (10 minute) screening test that quickly measures cognition, mood, anxiety, and apathy in people with heart disease. The purpose of this study is to show that this test can accurately identify individuals who are likely to have these four conditions. These symptoms all negatively affect the health outcomes of individuals with CAD, so identification in a short time span is important in CAD patients.

WHAT WILL HAPPEN DURING THIS STUDY?

If you agree to participate, you will be asked to undergo one assessment with a trained researcher that will take approximately 1 hour. This will include tests of memory and thinking speed, and a screening interview for mood and anxiety. You will be asked to complete a few simple questionnaires assessing your mood and anxiety levels. For the cognitive tests you will be asked to complete a few verbal tasks such as memorizing a list of words, and a few visual tasks such as reproducing a few shapes on paper. This study will not interfere with any of the usual care received in cardiac rehabilitation or from your family physician.

With your permission, we would notify your Toronto Rehabilitation team if the results of this interview suggest you might benefit from the resources that are already in place to assist patients showing signs of depression, anxiety or cognitive impairment. These resources include the opportunity to make appointments with a psychologist on staff at Toronto Rehabilitation Institute, or referral to Sunnybrook Health Sciences Centre.

If you agree to participate in this study, we would ask to review information that you have provided to the rehab team including demographic information (age, gender and diagnoses), medications you are using, and the results of your stress tests in the past year. If the results from our assessment show clinical abnormalities, with your permission, we will contact your physician at Toronto Rehabilitation Institute.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

It is anticipated that about 350 people recruited from the Toronto Rehabilitation Institute will participate in this study conducted with Sunnybrook Health Sciences Centre. The entire study is expected to take about 3 years to complete and the results should be known in 3½ years.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you decide to participate in this study you will be asked to do the following:

Attend 1 visit at Sunnybrook Health Sciences Centre (2075 Bayview Avenue, Room EG04). The visit will last approximately 1 hour. During the visit you will be asked to complete a number of tests and questionnaires.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?
There are no medical risks to you from participating in this study, as this is an observational study and does not involve a medical intervention but taking part in this study may make you feel uncomfortable.  
*Cognitive testing:* You may experience mental stress as a result of memory or timed tasks.

**WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?**

You may or may not benefit directly from participation in this study. Your participation may or may not help other people with heart disease in the future. Knowledge gained from this study may be helpful in the future recognition and management of depressive, anxiety or cognitive symptoms resulting from heart disease. As mentioned, the results may suggest that you would benefit from existing Toronto Rehabilitation Institute resources. The study results will be published, and if you wish, we will be happy to forward to you a copy of any publication(s) that may arise from this work.

**CAN PARTICIPATION IN THIS STUDY END EARLY?**

You can choose to end your participation at any time. If you withdraw voluntarily from the study, the information about you that was collected before you left the study will still be used. No new information about you will be collected without your permission.

**WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?**

Participation in this study will not involve any additional costs to you.

**ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?**

You will not be paid to participate in this study. However you will be reimbursed for travel costs or parking expenses when you come for a study visit.

**DO THE INVESTIGATORS HAVE ANY CONFLICTS OF INTEREST?**

There are no conflicts of interest to declare related to this study.
WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice (voluntary). You have the right to choose not to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, your choice will not have any effect on your current or future medical treatment.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study (Principal Investigator) Dr. Lanctôt, Department of Psychiatry at [redacted]. If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call Dr. Philip C. Hébert, Chair of the Sunnybrook Research Ethics Board at [redacted].

4. You have the right to have any information about you and your health that is collected, used or disclosed for this research study to be handled in a confidential manner.

If you decide to participate in this study, the investigator(s) and study staff will look at your personal health information and collect only the information they need for this study. “Personal health information” is health information about you that could identify you because it includes information such as your:

- name,
- address,
- telephone number,
- date of birth,
- new and existing medical records, or
- the types, dates and results of various tests and procedures.

The following people may come to the hospital to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines:

Representatives of the Sunnybrook Research Ethics Board, who oversees the ethical conduct of this research study.

Access to your personal health information will take place under the supervision of the Principal Investigator. In addition, any study data about you that is sent outside of the hospital will have a code and will not contain your name or address, or any information that directly
identifies you. “Study data” is information about you that is collected for the research study, but that does not directly identify you. Study data that is sent outside of the hospital will be used for the research purposes explained in this consent form.

The investigator(s), study staff and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

When the results of this study are published, your identity will not be disclosed. The Principal Investigator will keep any personal information about you in a secure and confidential location for 10 years and then destroyed as required by institutional policy.

5. By signing this consent form, you do not give up any of your legal rights.

6. You have the right to receive a copy of this signed and dated informed consent form before participating in this study. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff.

7. You have the right to access, review and request changes to your personal health information.

8. You have the right to be informed of the results of this study once the entire study is complete.
DOCUMENTATION OF INFORMED CONSENT
Full Study Title: Validity, Feasibility, and Use of a Novel Screen for Cognitive Impairment, Depression, Anxiety, and Apathy Designed for Coronary Artery Disease and Related Disorders

Name of Participant: ________________________________________

Participant/Substitute decision-maker
By signing this form, I confirm that:
• This research study has been fully explained to me and all of my questions answered to my satisfaction
• I understand the requirements of participating in this research study
• I have been informed of the risks and benefits, if any, of participating in this research study
• I have been informed of any alternatives to participating in this research study
• I have been informed of the rights of research participants
• I have read each page of this form
• I authorize access to my personal health information, medical record and research study data as explained in this form
• I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study

Name of participant/Substitute decision-maker (print)  Signature  Date

_______________________  ________________________  _____________________

Person obtaining consent
By signing this form, I confirm that:
• This study and its purpose has been explained to the participant named above
• All questions asked by the participant have been answered
• I will give a copy of this signed and dated document to the participant

Name of Person obtaining consent (print)  Signature  Date

_______________________  ________________________  _____________________

Statement of Investigator
I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

Name of Investigator (print)  Signature  Date

_______________________  ________________________  _____________________
Neuropsychopharmacology

Validity, Feasibility and Use of a Novel Screen for Cognitive Impairment, Depression, Anxiety, and Apathy Designed for Coronary Artery Disease and Related Disorders

Patient Number: _____________  Date: ________________  Visit Number: __________

Informed Consent Checklist/Note

Consent version # / date: __________________________

Consent signed and dated by subject prior to any study related procedures:  □ YES  □ NO

Date/Time signed: ______________________________________

Was a copy of the consent given to the subject?  □ YES  □ NO

Did subject demonstrate comprehension of consent form contents?  □ YES  □ NO

Comments:  
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Consent obtained by:  
__________________________________________  ______________________________  __________
Print name  Signature  Date