Evaluating Pre-existing Cognitive Impairment and Anticholinergic Burden as Predictors of Post-operative Delirium following TAVI (Transcatheter Aortic Valve Implantation)

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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Abstract

Post-operative delirium (POD) is common following Transcatheter Aortic Valve Implantation (TAVI) and is associated with adverse health outcomes. We hypothesized that cognitive impairment and anticholinergic burden may exacerbate risk of POD in TAVI due to their effects on cholinergic pathways underlying delirium. Cognitive deficits were screened using the Mini-Cog test before TAVI and anticholinergic burden assessed using the Anticholinergic Cognitive Burden (ACB) scale. Logistic regression adjusted for age, history of stroke, atrial fibrillation, diabetes and anesthesia found that neither the Mini-Cog (OR: 6.62, p=0.09) nor the ACB scale (OR: 1.62, p=0.17) were significant independent predictors of POD when assessed individually. When assessed together, patients screening positive on the Mini-Cog and with a high ACB scale score (OR 6.94, p=0.01) predicted increased risk of POD in a significant model ($\chi^2 (6) =29.1, p<0.01$). This suggests that cognitive deficits and anticholinergic burden may exert their deleterious effects on POD through a common pathway and pre-screening of risk can potentially reduce risk for POD.
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1. Chapter 1: Introduction

1.1 Statement of Problem

Patients undergoing a cardiac intervention are at risk for peri-procedural complications including post-operative delirium (POD) and cerebrovascular events. (Newman et al., 2006). Transcatheter Aortic Valve Implantation (TAVI) is a less invasive method used to treat severe aortic stenosis compared to surgical valve replacement in patients who are deemed inoperable or at high risk of surgical complications due to advanced age and associated comorbidities (Kappetein et al., 2013; Ponikowski et al., 2016). Delirium is a common complication after elective vascular surgery in the elderly with high rates of incidence observed after open aortic surgery (Raats, Steunenberg, de Lange, & van der Laan, 2016; Raats, van Eijsden, Crolla, Steyerberg, & van der Laan, 2015). Several factors including advanced age, comorbidity and cognitive impairment have been suggested as predisposing factors for delirium after elective cardiac surgery (Raats et al., 2016; Veliz-Reissmuller, Aguero Torres, van der Linden, Lindblom, & Eriksdotter Jonhagen, 2007). TAVI patients are also at high risk of peri-procedural complications including POD (Eeles et al., 2010; Tse, Bowering, et al., 2015). The development of delirium following cardiac intervention is associated with poor outcomes in the perioperative period that can lead to longer hospital length of stay and drive healthcare costs (Eeles et al., 2010; Steiner, 2011); thereby warranting the need to identify TAVI patients with high risk of delirium.

Pre-existing cognitive impairment has been associated with poor outcomes following cardiac interventions including TAVI (Millar, Asbury, & Murray, 2001; Stroobant & Vingerhoets, 2009; Tse, Schwarz, Bowering, Moore, & Barr, 2015). Studies in elective surgery patients have also shown that patients who develop delirium post-surgery have lower scores on tests
evaluating executive functioning and verbal knowledge prior to procedure (Fong, Hshieh, et al., 2015). Similarly, polypharmacy has been indicated as a factor precipitating delirium in the elderly (Hein et al., 2014). In particular, prescription medications with anticholinergic properties have been indicated in the development of neuropsychological disorders including delirium (Clegg & Young, 2011; Naja et al., 2016; Young & Inouye, 2007). The pathophysiology of delirium is complex and multiple neurotransmitter pathways have been implicated, which complicates optimal management (Alagiakrishnan et al., 2007; Tremblay & Gold, 2016). Deficits in the cholinergic system have been postulated as a possible mechanism underlying the pathophysiology of delirium. Polypharmacy in an elderly population can have deleterious effects on cholinergic and dopaminergic pathways (Brown, 2000; L. Tune, Carr, Hoag, & Cooper, 1992; L. E. Tune et al., 1981); therefore, this may be a particular risk factor in delirium. Consistent with this, rates of delirium have been associated with an intake of larger numbers of anticholinergic medications in patients undergoing cardiac surgery that impair central cholinergic function and thereby lead to delirium (L. E. Tune et al., 1981).

Anticholinergic burden is driven mainly by the cumulative effects of less potent anticholinergic medicines including oral anticoagulants, diuretics and opioids (Magin et al., 2016; Mintzer & Burns, 2000). TAVI patients often present with multiple co-morbidities and polypharmacy which puts them at a high risk of developing delirium (Eeles et al., 2010; Tse, Bowering, et al., 2015). While cognitive impairment has been studied as a risk factor for delirium in TAVI (Tse, Bowering, et al., 2015; Tse, Schwarz, et al., 2015), the possible contribution of anticholinergic medication, which may also be particularly important in this elderly population (Magin et al., 2016) has not been investigated in the context of POD in TAVI.

Current clinical practices do not screen for geriatric specific risk factors that can have important prognostic significance in improving outcomes post TAVI. Therefore, it is important to
determine the risks associated with pre-disposing factors like pre-existing cognitive impairment in addition to the possible contribution of potentially modifiable, precipitating risk factors like anticholinergic burden in the context of POD in TAVI. This study will assess the importance of cognitive impairment as a risk factor in TAVI in addition to reinforcing the need to identify at-risk patients requiring further care.

1.2 Purpose of the Study and Objective

TAVI is an increasingly preferred procedure in treating severe aortic stenosis as it has been shown to substantially reduce mortality and improve quality of life and functional status (Grimaldi et al., 2013; Krane et al., 2010) compared to surgical valve replacement and medical therapy (Ak et al., 2017). However, TAVI has also been associated with poor in-hospital outcomes that may be exacerbated by pre-existing co-morbidities that are not accounted for during TAVI risk assessments in this already at-risk population (Reardon et al., 2017; Sardar et al., 2017; Zack et al., 2017). Pre-existing cognitive impairment, an important consideration prior to cardiac intervention (Rosengart et al., 2005; Silbert, Scott, Evered, Lewis, & Maruff, 2007) is a risk factor for poor peri-procedural outcomes like delirium. A prospective study evaluating predictors of delirium in elderly elective surgery patients found that subtle pre-operative cognitive deficits are associated with an increased risk of POD (Lowery, Wesnes, & Ballard, 2007). While risks associated with more advanced stages of vascular dementia or Alzheimer’s disease (AD) are more easily identified, patients with subtle cognitive deficits or those with mild cognitive impairment (MCI) are under-recognized and may still be at risk of poorer post procedural outcomes. The primary objective of this study is to identify risk factors associated with POD in patients undergoing a TAVI. In particular, this study will focus on identifying pre-existing cognitive impairment as a pre-disposing risk factor for delirium post TAVI using the
Mini-Cog test. The Mini-Cog is a brief, easy to administer screening tool to detect cognitive impairment in older adults (Neville, 2015). It has previously been used to detect cognitive impairment in elderly non-cardiac surgery and heart failure patients (Agarwal, Kazim, Xu, Borson, & Taffet, 2016; Heng et al., 2016; Trowbridge et al., 2016) and informed about perioperative morbidity, post-hospitalization risk and mortality (Heng et al., 2016; Patel et al., 2015; Trowbridge et al., 2016). Therefore, the Mini-Cog may be a useful tool to detect cognitive deficits in a similar elderly population referred for TAVI. In this study, it was used as a screening tool to investigate cognitive impairment as a predictor of POD in TAVI patients. Deficits in cholinergic function have been postulated to cause POD following elective surgery (Hshieh, Fong, Marcantonio, & Inouye, 2008; Pratico et al., 2005; Trzepacz, 1996) and anticholinergic burden has been correlated with the prevalence of both delirium symptoms and mortality in the elderly (Naja et al., 2016). Elderly patients referred for TAVI present with and are treated for multiple comorbidities and cardiovascular risk factors with medications that have anticholinergic properties which may affect cognitive function (G. Grande et al., 2017; Lopez-Alvarez et al., 2015; Pfistermeister, Tumena, Gassmann, Maas, & Fromm, 2017) and subsequently increase risk of delirium following TAVI. However, the effect of concomitant medication with anticholinergic properties haven’t been studied as a factor precipitating delirium in this population. This study will investigate anticholinergic burden of concomitant medications as an individual risk factor for POD in TAVI and also in conjunction with pre-TAVI cognitive deficits as a risk factor precipitating POD in TAVI.

1.3 Statement of Research Hypotheses and Rationale for Hypotheses

1.3.1 Primary Hypothesis: Cognitive impairment on the Mini-Cog test will predict increased risk of POD in TAVI.
**Rationale:** Risk factors including advanced age, co-morbidities and cognitive impairment have been associated with POD in severe aortic stenosis patients referred for a TAVI procedure (Eide et al., 2015, 2016; Tse, Bowering, et al., 2015). However, routine clinical practices that evaluate TAVI risk assessments do not include screening for and subsequent management of geriatric specific risk factors like mild cognitive impairment that may be an important predictor of outcomes in the elderly and multi-morbid TAVI patient population. This study proposed that a simple screening tool for cognitive impairment in the elderly like the Mini-Cog test has the potential to inform health care practitioners who are at high risk for POD pre-operatively. The risk of POD was investigated in patients that screened positive (words recalled: 0/3 OR words recalled: (1-2)/3 and abnormal clock drawing task) compared to those who screened negative (words recalled: 3/3 OR words recalled: (1-2)/3 and normal clock drawing task) on the Mini-Cog test prior to TAVI.

1.3.2 **Secondary Hypothesis:** Higher anticholinergic burden measured using the Anticholinergic Cognitive Burden (ACB) scale will predict increased risk of POD in TAVI.

**Rationale:** Changes in the cholinergic system in the aging brain include decline in release and synthesis of acetylcholine (Dumas & Newhouse, 2011; van der Mast, 1998). In a healthy brain, these aging related reductions in cholinergic brain receptors are compensated for by increases in cholinergic system. However, compared to younger adults, the elderly are more susceptible to anticholinergic intoxication due to these changes (Han et al., 2001). The use of anticholinergic drugs has been associated with an increased frequency of delirium in the elderly in the past (Rojo-Sanchis et al., 2016). However, the effect of anticholinergic burden has not been studied as a risk factor for POD in elderly TAVI patients, who may be at risk of anticholinergic
intoxication. In this study, it is hypothesized that patients with a higher score on the ACB scale will predict an increased risk of POD in TAVI.

1.3.3 Exploratory Hypothesis: Cognitive impairment on the Mini-Cog test in conjunction with a higher anticholinergic burden measured using the Anticholinergic Cognitive Burden (ACB) scale will predict increased risk of POD in TAVI.

Rationale: Based on the cholinergic deficiency hypothesis in the aged brain, dysfunction of cholinergic neurons may be important in both cognitive dysfunction and delirium pathophysiology (Hshieh et al., 2008). Underlying cognitive deficits and a higher anticholinergic burden may exacerbate risk of POD in the elderly TAVI population but have not been previously studied. Therefore, in this study we hypothesized that elderly TAVI patients who have cognitive deficits as screened using the Mini-Cog test and are also at risk of higher anticholinergic burden with high score on the ACB scale will be susceptible to higher risk of POD.

1.4 Review of Literature

1.4.1 Transcatheter aortic valve implantation (TAVI)

Aortic valve stenosis or the stiffening of the aortic valve is one of the most prevalent cardiovascular diseases after arterial hypertension and coronary artery disease in the Western population (Arora, Misenheimer, & Ramaraj, 2017; Iung & Vahanian, 2011). It is the most common valvular heart disease affecting over 7% of the population over the age of 65 (Gohlke-Barwolf et al., 2013). Aortic stenosis progresses with age due to degenerative calcification of the aortic valve and restricts blood flow from the left ventricle to the aorta, forcing the heart to work harder to pump blood through the valve and build pressure in the left ventricle (Gohlke-
Barwolf et al., 2013). During the asymptomatic latent period, left ventricular hypertrophy and atrial augmentation of preload compensate for the increase in afterload caused by aortic stenosis (Grimard, Safford, & Burns, 2016). However, with disease progression, these compensatory mechanisms become inadequate, leading to symptoms of shortness of breath, fatigue, heart failure, angina, or syncope (Grimard et al., 2016). Severe aortic stenosis (SAS) is defined in patients on a stress echocardiography, when the mean aortic pressure gradient is greater than 40 mmHg with a valve area less than 1.0 cm$^2$ at any flow rate and peak aortic velocity greater than 4.0 m/s (Vahanian & Otto, 2010). It is characterized by severe functional limitations, major adverse events leading to poor quality of life and excess mortality (Gohlke-Barwolf et al., 2013; Horstkotte & Loogen, 1988). Aortic stenosis is a progressive disease with a poor prognosis and mortality rate of 50% at 2 years if left untreated i.e without valve replacement (Arora et al., 2017; Kolh, Lahaye, Gerard, & Limet, 1999). Patients with hemodynamically severe stenosis that decline a surgical intervention only have an 18 percent five-year probability of survival (Horstkotte & Loogen, 1988).

Surgical aortic valve replacement (SAVR) is considered the gold standard treatment for severe aortic stenosis to reduce clinical symptoms as well as mortality and no medical therapy has shown its efficacy in improving outcomes (Arora et al., 2017; Marquis-Gravel, Redfors, Leon, & Genereux, 2016). However, preoperative morbidity may contribute to an unacceptable surgical risk during SAVR (Panayiotides & Nikolaides, 2014). Transcatheter aortic valve implantation (TAVI) is used to treat SAS patients who are deemed inoperable due to high surgical risk for advanced age and associated comorbidities (Kappetein et al., 2013; Ponikowski et al., 2016). TAVI has become an increasingly preferred alternative to SAVR in the elderly due to its reduced mortality rate and improved quality of life and functional status (Grimaldi et
al., 2013; Krane et al., 2010; Rosengart et al., 2005), compared to both surgery and medical therapy (Ak et al., 2017).

In recent years, TAVI has played a ground-breaking role in the treatment of elderly or high-risk surgical patients with SAS. It is a key and reliable innovation that has evolved from a complex procedure to a safe and effective therapy (Kilic & Yilmaz, 2017). TAVI has been shown to sustain favorable valve hemodynamic and patient symptoms for up to 5 years and although initially administered in patients at highest risk, currently, TAVI treatment is shifting to intermediate and even low risk patients and is not restricted to severely symptomatic patients only (Kilic & Yilmaz, 2017; Sardar et al., 2017).

While in some instances, both SAVR and TAVI can be performed with similar clinical efficacy and in-hospital outcomes of mortality and morbidity, there are different patterns of adverse events associated with each procedure (Reardon et al., 2017; Sardar et al., 2017; Zack et al., 2017). While surgery is associated with higher rates of acute kidney injury, atrial fibrillation, and major bleeding events leading to transfusion requirements, TAVI has been associated with higher rates of vascular complications and the need for pacemaker implantation (Enezate et al., 2017; Reardon et al., 2017; Sardar et al., 2017; Zack et al., 2017). Compared to SAVR, TAVI is a cost-effective treatment for high-risk aortic stenosis patients who are ineligible for surgery but its long-term outcomes may substantially affect the procedure’s cost-effectiveness (Fairbairn et al., 2013; Kularatna, Byrnes, Mervin, & Scuffham, 2016). As a fairly new procedure, there is constant research on innovating the TAVI procedure while exploring its short and long-term outcomes and benefits; and despite the safety and reliability of the procedure, TAVI patients are at some risk of post-procedural complications. Post procedural complications such as delirium, cerebrovascular events, transient ischemic attack, bleeding
events and acute kidney injuries are key determinants of post procedural management of TAVI patients and resource allocation; and therefore have important implications to inform reimbursement decisions of TAVI (Kaier et al., 2017; Kularatna et al., 2016).

1.4.2 Post-operative delirium (POD)

Delirium is defined by the International Classification of Disease-10 as an etiologically non-specific organic cerebral syndrome characterized by acute and fluctuating neurologic disturbances in inattention, levels of consciousness, perception, memory and thinking (Chaput & Bryson, 2012; Steiner, 2011). POD develops typically 1–4 days following a surgical intervention and is a common neuropsychiatric condition associated with adverse health outcomes including increased morbidity, impaired functional recovery and increased length of hospital stay that drive increased health care costs (Eeles et al., 2010; Steiner, 2011). The incidence of delirium has a negative impact on the quality of life and is an independent risk factor for in-hospital mortality (Abelha et al., 2013). It reflects a change from baseline cognition and has also been associated with long-term complications including dementia, institutionalization, and death (Eeles et al., 2010; van Meenen, van Meenen, de Rooij, & ter Riet, 2014; van Zyl & Seitz, 2006). Recent studies have shown that delirium strongly predicts future new-onset dementia, as well as accelerating existing dementia (Maclullich et al., 2013). Despite the range of poor outcomes, delirium is one of the foremost unmet medical needs in healthcare (Maclullich et al., 2013). The rates of delirium recognition are low, resulting in inadequate management. In recent years, there has been considerable growth in delirium research with increased recognition of the importance of delirium and increased interest from policymakers and educational and audit programmes (Khan et al., 2012; Maclullich et al., 2013).
The incidence of delirium is characterized by several factors including pre-existing medical co-morbidities, inflicted brain injuries and side-effects of medical management. Some of the risk factors identified for the development of delirium include advanced age, preoperative cognitive deficits and surgery (Bakker, Osse, Tulen, Kappetein, & Bogers, 2012; Inouye, 2006; Leslie, Marcantonio, Zhang, Leo-Summers, & Inouye, 2008; Smulter, Lingehall, Gustafson, Olofsson, & Engstrom, 2013). Older patients are particularly prone to delirium affecting 15% to 70% of elderly medical and surgical patients (Avidan et al., 2014; van Zyl & Seitz, 2006). POD is more common in patients older than age 65 years with an estimated incidence between 25% and 50% after cardiac surgery (Maniar et al., 2016). Despite efforts to identify risk of POD and designing delirium prevention strategies in the past decade (Zaal, Devlin, Peelen, & Slooter, 2015), it remains under recognized in many clinical settings. As elderly frail patients increasingly undergo major procedures, it is estimated that the incidence of POD is likely to increase substantially during the next decade (Zaal et al., 2015). POD following cardiac surgery has also been associated with increased morbidity, longer hospital length of stay, and greater mortality (Ely et al., 2004; Gottesman et al., 2010), the negative outcomes of which have resulted in increased annual health care costs estimated at $150 billion annually.

**1.4.3 POD in TAVI**

One of the commonly explored outcomes in TAVI is the incidence of POD, which can be a major risk factor for postoperative morbidity and mortality (Eide et al., 2016). Studies have found that POD may be prevalent in as high as 50 percent of patients over the age of 80 following TAVI (Eide et al., 2016; Tse, Bowering, et al., 2015). Major postoperative complications and delirium are individually associated with adverse events and poorer outcomes in the perioperative period and can also demonstrate a combined effect (Gleason et
al., 2015). At the population level, delirium is the most frequently occurring post-procedural complication and has profound effects on patient prognosis compared to any other major complications (Gleason et al., 2015). About one third of patients undergoing TAVI experience POD (Maniar et al., 2016) with a slightly lower incidence ranging between 12 to 18% in transfemoral TAVI (TF-TAVI) (Maniar et al., 2016; Tse, Bowering, et al., 2015; Tse, Schwarz, et al., 2015). POD is associated with increased morbidity and mortality (Maniar et al., 2016) and in patients undergoing TF-TAVI, it has been shown to be a predictor of mortality independent of increasing age and other complications (Maniar et al., 2016). POD has been associated with an almost 3 times higher rate of readmission and mortality during the first few months post procedure. In addition, up to 80 percent of patients who experienced delirium have been documented to have a hospital readmission within a month of discharge and 64% of delirious patients had a readmission within 3 months of discharge after TAVI (Eide et al., 2016)(van der Mast, 1998). Given the high incidence of POD and the significant negative consequences associated with it, including worsening medical and cognitive outcomes, it is of imminent need to identify factors that contribute to an increased risk of POD in TAVI to minimize the incidence of POD and improve patient outcomes.

1.4.4 Risk Factors of POD

Poor long-term survival is often attributable to patient factors rather than to procedural factors (Levi et al., 2017). Predictors of long-term adverse outcomes after TAVI have been studied previously and there is evidence that long term mortality is largely related to non-cardiac causes and high-risk patient characteristics rather than TAVI procedural features (Eide et al., 2015; Rojo-Sanchis et al., 2016). Review of literature investigating pre-operative risk factors for delirium in patients undergoing elective cardiac surgery identified some key risk factors in
delirium including age, pre-existing neurologic conditions, and the type of cardiac surgery, such as valve procedure (Lin, Chen, & Wang, 2012; Tse, Schwarz, et al., 2015). Non-transfemoral access i.e transapical or transaortic access to the aortic valve has been identified as a predictor of delirium after TAVI (Abawi et al., 2016; Tse, Schwarz, et al., 2015). Age is a key predictor of POD in elective cardiac and general surgery as well as TAVI (Galyfos, Geropapas, Sianou, Sigala, & Filis, 2017; Gernhardt et al., 2017; Guenther et al., 2013; Pinho, Cruz, Santos, & Abelha, 2016; Thorsteinsdottir, Sveinsdottir, & Snaedal, 2015). Increasing age is associated with higher rates of comorbidities, with more advanced aortic, carotid or intracerebral atherosclerosis, which increases the risk of cerebral hypoperfusion and embolization and make the elderly prone to post procedural complications (Bucerius et al., 2004).

A history of cerebrovascular disease is also one of the strongest predictors of delirium. Pre-existing cardiovascular diseases and injuries are largely associated with poorer outcomes as well as higher readmission rates in TAVI patients over the age of 80 (Eide et al., 2016). A previous history of stroke is one of the predisposing factors of delirium in both non cardiac (Guo et al., 2016; Shi, Wang, Chen, & Gu, 2010) and cardiac (Koster, Hensens, Schuurmans, & van der Palen, 2011; Lin et al., 2012; Rolfson et al., 1999; Tse, Schwarz, et al., 2015) surgery patients including TAVI (Abawi et al., 2016). Pre-existing cerebral infarcts due to a previous stroke contribute to the vulnerability of the central nervous system implicated in the pathogenesis of POD. Cardiac arrhythmia and atrial fibrillation are also common and major risks for POD (Jodati et al., 2013; Kazmierski et al., 2010; Kazmierski et al., 2006; Lin et al., 2012; Saeki et al., 1998). Studies investigating the association between atrial fibrillation with neuroimaging measures of cerebrovascular disease and AD found that atrial fibrillation was associated with higher rates of cerebral infarcts and silent cerebral embolic lesions (Anselmino et al., 2013; Graff-Radford et al., 2016). These small lesions can cause delirium when they
affect the thalamus or the caudate nucleus bilaterally due to disrupted connections with the frontal lobe following a surgery (Otomo, Maekawa, Goto, Baba, & Yoshitake, 2013). In addition, insults to the brain, such as ischemia and immunological stressors can decrease the level of cerebral neuronal density and lead to an imbalance between cholinergic and other neurotransmitter neurotransmitters pathways that may account for an increased predisposition to delirium (Lin et al., 2012 77).

Generalized atherosclerosis increases the risk of cerebral embolization, particularly during intraoperative aortic manipulation (Borger et al., 2001) and therefore may be a risk for poor outcomes in TAVI. Traditional cardiovascular risk factors including hypertension, diabetes and dyslipidemia that are associated with atherosclerotic disease burden are also associated with severe aortic stenosis (Yan et al., 2017). In a large population-based observational study of 1.12 million individuals over the age of 65 followed for a median of 13 years, cardiovascular risk factors were found to have independent and dose-response associations with incident aortic stenosis and together accounted for approximately one-third of the incidence of severe AS (Yan et al., 2017). Hypertension (Kumar, Jayant, Arya, Magoon, & Sharma, 2017; Li et al., 2013; Okusaga et al., 2013; Zou et al., 2014), diabetes (Li et al., 2013; Tiwari et al., 2012) and dyslipidemia (Zou et al., 2014) are commonly present in many TAVI patients and have been associated with cognitive impairment and risk of delirium. Several studies have identified pre-operative diabetes mellitus as an independent predictor for postoperative delirium in the elderly after cardiac and non-cardiac surgery (Bucerius et al., 2005; Bucerius et al., 2003; Gandhi et al., 2005; Gao, Yang, Li, Shi, & Fu, 2008; Nikolic, Putnik, Lazovic, & Vranes, 2012; Smulter et al., 2013; Sockalingam et al., 2005; M. C. Tan et al., 2008). Delirium may be the result of post-operative hypoglycemic episodes or diabetic ketoacidosis, neither of which are uncommon in patients with diabetes (Boland et al., 2001; Kitabchi et al., 2001; Lewis, 1999). Moreover,
patients suffering from co-morbid psychiatric disorders are more likely to experience hypoglycemic delirium (Balhara, 2011).

Elderly TAVI patients present with a plethora of co-morbidities including cognitive impairment that put them at a high risk of developing delirium (Eeles et al., 2010; Tse, Schwarz, et al., 2015). Aging is also related to neurochemical changes in the brain including a deficiency in the cholinergic pathway that predispose patients to delirium (Lin et al., 2012). Cognitive impairment is prevalent in 20-40% of patients with severe aortic stenosis patients undergoing a TAVI (Auffret et al., 2016; Ghanem et al., 2013; Schoenenberger et al., 2016; Tse, Bowering, et al., 2015) and has been identified as a risk factor for POD (Tse, Bowering, et al., 2015). Cognitive dysfunction has been studied extensively as a risk factor for other cardiac surgeries including coronary artery bypass grafting surgery in coronary artery disease patients with results confirming the importance of patient's pre-existing cognitive and emotional states in influencing outcomes post-surgery (Millar et al., 2001; Rosengart et al., 2005; Silbert et al., 2007). Subjective memory complaints and mild cognitive impairment predict delirium after cardiac surgery suggesting that cognitive evaluation should be incorporated in pre-operative assessments (Ryan et al., 2013; Veliz-Reissmuller et al., 2007).

Polypharmacy and the use of medication with anticholinergic properties have been indicated in the development of neuropsychological disorders including delirium in the elderly (Clegg & Young, 2011; Hein et al., 2014; Naja et al., 2016; Young & Inouye, 2007). Cholinergic medications have been explored in patients at risk for vascular cognitive impairment (Birks & Flicker, 2007) and a recent study has shown that increased anticholinergic burden due to concomitant medications was associated with poorer performance in tests of attention, processing speed, and executive function in patients with coronary artery disease (Lanctot et al.,
The prevalence of POD is also exacerbated in patients who are receiving higher doses concomitant medication with anticholinergic properties (L. E. Tune, 2000). A recent study on the incidence of delirium in hospitalized patient found a significant correlation between delirium and anticholinergic treatment and also documented longer hospital duration of stay in these patients (Ruiz Bajo, Roche Bueno, Seral Moral, & Martin Martinez, 2013).

Medications used during intraoperative procedure also pay a role in POD. Drugs of general anesthesia generally appear to be safe, but the brain mediation of general anesthesia during surgery is not clear yet. Surgical and anesthesiological procedures use drugs that suppress cholinergic cells to achieve a state of unconsciousness and avoid the occurrence of intraoperative memory (Pratico et al.). However, in some instances, anesthetics and drugs administered during anesthesia, can interfere with cholinergic signal pathways with severe, unfavourable, additional effects including POD (Pratico et al., 2005). Muscarinic acetylcholine receptors in the central nervous system play a role in the pathogenesis of POD and can also lead to post-operative cognitive dysfunction. Inhalation anesthetics may produce a number of changes affecting the central nervous system such as headaches, emergence excitement and POD which are related to physiological changes in the aging brain (Ancelin, De Roquefeuil, & Ritchie, 2000; Pratico et al., 2005). This is consistent with the report in geriatric patients who are more prone to delirium due to decline in cholinergic transmitters (Freyle & Levy, 2004; Pratico et al., 2005).

### 1.4.5 Pathophysiology of POD

The pathophysiology of delirium is complex and multiple neurotransmitter pathways have been implicated (Alagiakrishnan & Wiens, 2004; Maclullich et al., 2013; Maclullich, Ferguson, Miller, de Rooij, & Cunningham, 2008) Although the exact mechanisms behind delirium are
not well characterized, POD is often the consequence of an existing medical condition (Kazmierski et al., 2010; Kazmierski et al., 2006). As already mentioned, predisposing and precipitating risk factors of delirium that have been identified include advanced age and cognitive impairment (Abawi et al., 2016; O'Neal & Shaw, 2016; Raats et al., 2016).

Several potential pathways that have been implicated in delirium include neurotransmitter interference, global cognitive disorder, and neuroinflammation. To date, central cholinergic deficiency and abnormalities in acetylcholine neurotransmission are the leading hypothesised mechanisms to cause delirium and cognitive dysfunction (Hsieh et al., 2008). Acetylcholine plays a key role in conscious awareness, attention and working memory by acting as a modulator of signal-to-noise ratio in the sensory and cognitive input in the basal and rostral forebrain (Terry & Buccafusco, 2003). Disruption of function in these cholinergic pathways can result in core symptoms of delirium and cognitive decline including inattention, disorganized thinking, and perceptual disturbances (Terry & Buccafusco, 2003). Dysfunction of cholinergic neurons and neuronal loss leading to low levels of acetylcholine has been implicated in both dementia and delirium (Boustani, Campbell, Munger, Maidment, & Fox, 2008).

1.4.5.1 Cholinergic deficiency hypothesis

Several morphological changes including decrease in brain volume and weight, reduced number and volume of neurons, and compromised neurotransmitter function have been described in a normal aging brain (van der Mast, 1998). Cholinergic deficits are implicated in aging and MCI (Richter et al., 2017). Changes in the cholinergic system in the elderly include decline in release and synthesis of acetylcholine which is related to cognitive decline both in normal aging and in AD (Dumas & Newhouse, 2011; van der Mast, 1998). The cholinergic hypothesis of geriatric memory dysfunction was proposed by Bartus et al. in 1982 stating that
functional disturbances in cholinergic activity of healthy elderly adults and demented patients play a key role in memory loss and related cognitive problems and therefore restoration of cholinergic function may reduce the severity of the cognitive loss (Bartus, Dean, Beer, & Lippa, 1982). There has been extensive clinical research based on this hypothesis using cognitive enhancers to modulate cholinergic functioning with modest benefits in AD patients (Di Santo, Prinelli, Adorni, Caltagirone, & Musicco, 2013; Hansen et al., 2008; C. C. Tan et al., 2014).

The cholinergic system is involved in multiple domains of cognitive function including attention, working memory, inhibition of irrelevant information, and learning (Dumas & Newhouse, 2011). Recent imaging findings investigating the role of the cholinergic system found that it modulates stimulus-specific processing of bottom-up sensory information in sensory cortical areas (Bentley, Husain, & Dolan, 2004; Furey, Pietrini, & Haxby, 2000). It also influences brain regions such as the hippocampus and frontal lobe involved in memory processing. Cholinergic enhancement can augment the selectivity of perceptual processing during encoding, thereby simplifying processing demands during memory maintenance and reducing the need for prefrontal participation to enhance memory performance (Dumas et al., 2010; Furey et al., 2000; Sperling et al., 2002; Thiel, 2003). The cholinergic system is involved in modulating initial processes like attention necessary for encoding memory and modulating frontal and posterior activation patterns in response to cognitive demands, a system that is sensitive to age and disease (Dumas & Newhouse, 2011).

The cholinergic deficiency hypothesis has been extensively studied in AD and has been identified as a major neurochemical abnormality in AD pathology (Rakonczay, Horvath, Juhasz, & Kalman, 2005). In a normal aging brain, age related changes in sensory and
executive function processes are compensated by increases in cholinergic system activity. Functional compensation involves recruitment of additional frontal regions to maintain adequate performance on tasks that are postulated to be modulated by cholinergic functioning. Healthy older adults with intact cholinergic functioning benefit from the recruitment of frontal networks and attentional processes to help compensate for decreasing sensory inputs (Dumas & Newhouse, 2011). However, disease-related changes in cholinergic system activity will lead to the disruption of this ability and older adults with neurodegenerative conditions are no longer able to recruit cholinergic inputs for cognitive compensation. This results in a loss of control processes of attention in addition to affecting working and long term memory (Dumas & Newhouse, 2011). Furthermore, normal biological aging brains have intact cognitive reserve capacities and are more likely to respond to cholinergic manipulations, whereas pathologic aging processes with neuronal or synaptic loss have lower cognitive reserve capacity leading to reduced responsiveness to cholinergic stimulation and hence, diminished cognitive performance (Dumas & Newhouse, 2011).

In elderly patients with MCI and AD, benefits of cholinergic enhancing drugs (e.g., acetylcholinesterase inhibitors) are only seen early in the disease state with improvement or stabilization of cognitive performance. However, with increasing neuronal degeneration, the ability of pro-cholinergic drugs to maintain or enhance performance is lost (Dumas & Newhouse, 2011). Neuronal integrity is compromised in MCI patients and therefore they are more susceptible to anticholinergic intoxication because of aging-related reductions in cholinergic brain receptors (Han et al., 2001). Moreover, metabolizing capacity of hepatic enzymes is also compromised in the elderly and the concurrent use of several medications with anticholinergic property put this population at higher risk for poor outcomes.
1.4.5.2 Cholinergic deficiency in POD

As already mentioned, one of the leading hypothesis for the neurobiology and molecular mechanism of POD is identified as ‘the central cholinergic deficiency’ (Inouye, 2006). It is postulated that reduced cholinergic activity in the brain may lead to the incidence of delirium (Hshieh et al., 2008). A large proportion of patients with delirium (up to two-thirds) have underlying dementia and, conversely, dementia is a significant risk factor for delirium (Fong, Davis, Growdon, Albuquerque, & Inouye, 2015; Inouye, 2006). Delirium itself may also lead to long-term cognitive impairment and dementia in addition to its underlying etiologies (J. C. Jackson, Gordon, Hart, Hopkins, & Ely, 2004; Kiely et al., 2006). Since both AD and delirium patients exhibit cholinergic deficits, several clinical and epidemiologic studies have interrelated the two pathologies with implications that acetylcholine deficiency is a potential common pathway in both syndromes (Hshieh et al., 2008). Dysfunction of cholinergic neurons play an important role in delirium pathophysiology and therefore, elderly patients are at higher risk of developing POD, due to age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems (van der Mast, 1998).

A review on the pathophysiology of delirium suggest that an imbalance of cholinergic and noradrenergic systems underlies delirium caused by anticholinergic drugs (van der Mast, 1998). In animal studies, delirium has been demonstrated through both the administration of anticholinergic drugs as well as selective removal of cholinergic neurons (Field, Gossen, & Cunningham, 2012). In humans, anticholinergic compounds and their metabolites can cross the blood-brain barrier and induce delirium through competitive antagonism of postsynaptic muscarinic receptors (Hshieh et al., 2008; Leentjens & van der Mast, 2005). Drugs with anticholinergic properties have been implicated in delirium development in both medical and
surgical patients (Han et al., 2001; Khan et al., 2012). In a study on elderly medical in-patients, exposure to anticholinergic medications was independently and specifically associated with a subsequent increase in delirium symptom severity (Han et al., 2001). The use of medications with anticholinergic activity have also been related to an increased cumulative risk of cognitive impairment and mortality (Fox et al., 2011). However, there are conflicting results of clinical and epidemiological studies on the anticholinergic-delirium association. While some studies document a significant association between use of anticholinergic medications and delirium (Flacker et al., 1998; Trzepacz, 1996; L. E. Tune, 2000, 2001; L. E. Tune et al., 1981), others reject the hypothesis of central or peripheral anticholinergic activity as an important mechanism of delirium (Marcantonio et al., 1994; Moorey, Zaidman, & Jackson, 2016; Watne et al., 2014).

Figure 1: A schematic representation of the ‘the central cholinergic deficiency’ hypothesis that may be a possible mechanism underlying the pathophysiology of delirium. We hypothesize that cognitive impairment may predict an increased risk of delirium due to reduced cholinergic activity in those with pre-existing pathology. Anticholinergic burden may augment the increased risk of delirium through the postulated anticholinergic-delirium association.
1.4.6 Management of POD

1.4.6.1 Pharmacotherapy for POD

Research evidence on effectiveness of delirium treatment interventions is sparse and inconsistent due to variability in intervention design and methodological challenges. A number of pharmacotherapy and non-pharmaceutical therapy have been investigated for POD treatment with some evidence suggesting benefit of pharmacologic interventions. However, it is necessary to develop high-quality clinical trials to evaluate all risks and benefits before such interventions can be implemented in the clinical environment as part of future delirium prevention and treatment strategies (Khan, Gutteridge, & Campbell, 2015).

Despite the high prevalence and poor outcomes of POD in the elderly, there is still no pharmacological intervention approved for the prevention and treatment of POD (Khan et al., 2015). A systematic review on the pharmacotherapy of POD found no difference in delirium duration and severity between use of typical antipsychotics e.g. haloperidol and either morphine or ondansetron (Khan et al., 2015; Wang et al., 2012). Compared to placebo, the second generation antipsychotic risperidone reduced the conversion of sub-syndromal delirium to delirium in one study but simple enhancement of cholinergic neurotransmission using cholinergic or acetylcholinesterase inhibitor rivastigmine had no impact on delirium incidence or duration (Gamberini et al., 2009; T. A. Jackson et al., 2017; Khan et al., 2015). Drugs like haloperidol, olanzapine, ketamine and monitored anesthesia have been documented to have some improvement in delirium outcomes although no conclusive recommendations could be drawn from these studies for clinical practice due to poor quality of evidence (Hudetz et al., 2009; Kalisvaart et al., 2005; Khan et al., 2015; Larsen et al., 2010). A systematic review evaluating the efficacy and safety of first and second-generation antipsychotics, cholinergic
enhancers, antiepileptic agent, inhaled anesthetic, injectable sedatives and benzodiazepine targeting either prevention or management of delirium found no differences in efficacy or safety among the evaluated treatment methods (first and second generation antipsychotics) and neither cholinesterase inhibitors nor pro-cholinergic drugs were effective in preventing delirium (Campbell et al., 2009). A meta-analysis of 5 studies on the prophylactic use of antipsychotic medication to reduce risk of POD in elderly patients found a 50% reduction in the relative risk of POD with antipsychotic use compared to placebo suggesting benefit in perioperative use of antipsychotics to reduce incidence of delirium (Teslyar et al., 2013). However, a more recent systematic review and meta-analysis did not support the use of antipsychotics for prevention or treatment of delirium in their analysis (Neufeld, Yue, Robinson, Inouye, & Needham, 2016). Another literature review on prevention of POD in the elderly using pharmacological agents found that the incidence of POD was reduced using antipsychotics in 8 studies, statins in 2 studies and melatonin, dexamethasone, gabapentin, and diazepam in one study each although the conclusions were questionable due to study designs, methodological issues, and authors' interpretations of results (Tremblay & Gold, 2016).

1.4.6.2 Prevention of POD

Over time, only limited success has been availed by studies targeting treatment development for POD. Surgical and patient factors play key roles in predicting who will subsequently develop delirium and therefore prevention is much more effective than treatment in the management of delirium (Chaput & Bryson, 2012). A greater emphasis on the development of risk identification and stratification strategies for POD can improve patient outcomes by offering avenues for targeted prevention and treatment efforts (McCoy, Hart, & Perlis, 2017). TAVI patients with greater preoperative cardiac and neurologic burdens may be pre-disposed to
higher risk of delirium post TAVI. A multifactorial risk model should be applied to identify patients at an increased risk of developing delirium following elective cardiac intervention (Koster et al., 2011).

In current clinical practice, surgical risk prior to TAVI is evaluated using both the European System for Cardiac Operative Risk Evaluation score (EuroScore) II and Society of Thoracic Surgeons (STS) score (Nashef et al., 2012; Shahian et al., 2009). A high surgical risk is defined with cut-off values of 6% and 10% for the EuroSCORE II and the STS score respectively (Kuwaki et al., 2015). The STS score was developed analysing 101,661 cardiac procedures from January 2002 to December 2006 in order to predict a mortality score for cardiac procedures. This includes mortality scores for procedures like heart valve surgery combined with CABG as well as individual risk scores for major morbidities, composite major morbidity or mortality, and short and prolonged length of stay post-surgery (Shahian et al., 2009). The EuroScore II is also a validated risk prediction model for contemporary cardiac surgery practice primarily used for combined AVR and CABG cases (Chalmers et al., 2013). While these traditional risk scores account for a number of risk factors contributing to cardiac surgical mortality including but not limited to age, gender, symptomatic disease status, previous cardiac surgery, recent myocardial infarction, cardiovascular risk factors diabetes and hypertension, renal dysfunction, mobility and procedure urgency (Nashef et al., 2012; Roques et al., 1999; Shahian et al., 2009), measures of geriatric specific risk factors such as cognitive impairment are not included in these risk analyses. As already mentioned, these risk scores were primarily derived for assessing risk of cardiovascular surgeries and may not be optimal for the risk assessment of elderly TAVI patients (Stortecky et al., 2012). A prospective cohort study has recently highlighted the need for development of improved risk prediction models using
multidimensional geriatric assessments including the risks associated with cognitive impairment in TAVI (Stortecky et al., 2012).

1.5 Summary of Background

Cognitive deficits are critical in a geriatric population and are predictive of functional decline (Jefferson et al., 2006), poorer quality of life (Newman et al., 2001) and increased mortality (Gale, Martyn, & Cooper, 1996; Stortecky et al., 2012). Cognitive impairment is also a risk factor for the development of delirium in TAVI patients but is under-recognized. POD has a complex etiology with multifactorial dysfunction of neurotransmitter pathways. In particular, compromised cholinergic function of the elderly brain makes it susceptible to neurological insults and injuries that may be exacerbated by the increased use of prescription medications with anticholinergic properties. Anticholinergic drugs are common in elderly patients and have also been indicated in the development of neuropsychological disorders including POD (Clegg & Young, 2011; Naja et al., 2016; Young & Inouye, 2007).

_Therefore, this study proposed to use the Mini-Cog as a screening tool to identify patients with cognitive impairment or dementia before TAVI with the hypothesis that patients screening positive on the Mini-Cog will be at higher risk of POD. We also hypothesized that patients with a higher anticholinergic burden will be at higher risk of POD. Therefore, we suggest that while identification of predisposing factors like cognitive impairment may be used for risk evaluation in TAVI, careful consideration of precipitating factors like concomitant medication use contributing to anticholinergic burden prior to procedure may also help to reduce risk of POD and improve survival and quality of life post TAVI._
2. **Chapter 2: Methods**

2.1 **Study Design**

A prospective observational study design was used to assess outcomes of TAVI in severe aortic stenosis patients referred to the Sunnybrook Structural Heart Clinic for TAVI. Consecutive patients referred for TAVI were screened for cognitive impairment using the Mini-Cog test as part of their clinical assessment prior to TAVI. Clinic charts for TAVI patients were reviewed to record co-morbidities, concomitant medication use and post-operative outcomes e.g. delirium, cerebrovascular events, vascular complications and death. Data from this study were collected and included as part of the study protocol “Screening for And MAnaging Risk factors in TAVI: an Interdisciplinary Endeavor (SMARTIE)” approved by the research ethics board (REB) at Sunnybrook Health Sciences Centre (Appendix: REB Approval).

2.2 **Subjects**

Patients with a diagnosis of severe symptomatic aortic stenosis SAS (aortic valve area < 1 cm\(^2\) or mean gradient across the aortic valve ≥40 mmHg or peak aortic jet velocity >4.0m/sec) who were eligible for and had undergone a TAVI between September 2015 and December 2016 were included in this study.

2.3 **Patient Characteristics and Clinical Outcomes**

Prior to TAVI, patient charts were reviewed to collect data on demographics including age, gender and surgical risk score. Pre-procedural medical history of comorbidities and concomitant medication use were recorded from physician’s notes from patient’s pre-
assessment visit(s). TAVI procedural details including the route of valve access (transfemoral, transapical or transaortic implantation), type of anesthesia protocol used (general anesthesia vs conscious sedation) was noted. Some of the anesthetic medications used in both general anesthesia and conscious sedation in this patient cohort were opioid anesthetics fentanyl and remifentanil. In addition to opioids, patients undergoing TAVI in conscious sedation were more likely to receive midazolam from the benzodiazepine family and dexmedetomidine, an α2-adrenergic receptors agonist that causes sedation and analgesia while keeping psychomotor function preserved. On the contrary, patients undergoing TAVI under GA commonly received propofol, muscle relaxants, rocuronium and succinylcholine and an inhaled anaesthetic, sevoflurane. Following TAVI, charts were reviewed to record peri-procedural outcomes from patient’s hospital discharge summary as noted by attending physician or nurse practitioner including incidence of POD, stroke or transient ischemic attack (TIA). Outcomes including all cause morbidity: vascular complications, permanent pacemaker implantation, acute kidney injury, major bleeding, systemic inflammation and neuropsychiatric symptoms; hospital length of stay, number of readmissions and mortality was also recorded up to 6 months post TAVI.

2.3.1 Mini-Cog test

Patients were screened for cognitive deficits prior to TAVI using the Mini-Cog test as part of TAVI clinical assessment. The Mini-Cog test is a brief instrument that can be used as a screening tool to detect cognitive impairment in older adults although it should not be substituted for a complete diagnostic work up for cognitive impairment (Borson, Scanlan, Brush, Vitaliano, & Dokmak, 2000). It consists of two components, an un-cued three-item recall test for memory and a simply scored clock drawing test. A maximum of 3 points were allocated for all words recalled correctly. A normal clock has all of the following elements: all
numbers 1 to 12 are present in the correct order and direction, numbers are evenly spaced in the circle, and the two hands point to 11 and 2 to indicate time 10 past 11. All of the elements need to be present to earn 2 points on the clock drawing task. If any of these elements are missing, the clock is scored as abnormal (Borson et al., 2000). Patients were scored positive for cognitive impairment if they recalled 1-2 out of 3 words and had an abnormal clock or if they recalled 0 words. Patients who recalled all 3 words or 1-2 words and drew a normal clock were scored negative for cognitive impairment on the Mini-Cog test. In other words patients scoring less than 3 on the Mini-Cog were considered impaired. The Mini-Cog was chosen to detect cognitive impairment in this population as it has been shown to be a quick and well accepted test to administer in elderly patients (McCarten, Anderson, Kuskowski, McPherson, & Borson, 2011). Moreover, a study on the acceptability of the Mini-Cog test has shown that it may be administered successfully by relatively untrained raters as a first-stage dementia screen (Scanlan & Borson, 2001), making it ideal to be used by cardiac staff at the TAVI clinic at Sunnybrook.

2.3.2 Anticholinergic Burden

Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden (ACB) scale. ACB score was calculated using the sum of score contributed by each concomitant medication used with either no (score of 0), possible (score of 1) or definite (score of 2 or 3) anticholinergic properties (Boustani et al., 2008). Drugs with anticholinergic properties identified by the ACB scale has been associated with worse cognitive and functional performance in elderly patients (Pasina et al., 2013) and with increased rates of hospitalization and all-cause mortality in institutionalized older adults with cardiovascular disease (Vetrano et al., 2016). The ACB scale has also been successfully used to assess anticholinergic exposure in coronary disease patients.
with high cardiovascular risk burden and polypharmacy (Lanctot et al., 2014). Elderly TAVI patients are at risk of cognitive deficits and also present with high cardiovascular burden. Therefore the ACB scale may be a useful tool to assess anticholinergic burden in this population.

### 2.3.3 Post-operative Delirium

Delirium was assessed in the perioperative period using the Intensive Care Delirium Screening Checklist (ICDSC). The ICDSC is a validated tool to screen delirium in cardiac surgery patients with high sensitivity and specificity (Nishimura et al., 2016). The checklist is scored by a qualified attending physician or nurse practitioner in the Intensive Care Unit (ICU) as part of patient’s clinical care. The list contains 8 items: Altered Level of Consciousness, Inattention, Disorientation, Hallucination/delusions/psychosis, Psychomotor agitation or retardation, Inappropriate speech or mood, Sleep wake/cycle, Symptom fluctuation. One point is allotted for an abnormality in each item on the list and a total score ≥ 4 is classified as positive for delirium.

### 2.4 Sample Size Calculation

Sample size of this study was calculated based on a previous cohort study looking at the incidence of POD in TAVI, that reported delirium in 12% of TF-TAVI patients and identified pre-existing cognitive impairment as a risk factor (OR:6.5). Based on these assumptions, G*Power 3.1.9.2 (Faul, Erdfelder, Buchner, & Lang) was used to calculate a sample size of 81 patients that will allow the Mini-Cog to predict risk of POD with an α of 0.05 for the power of 0.8 in a logistic regression model. The TAVI population presents with a number of comorbidities and concomitant medication use that may be associated with cognitive
impairment and POD. This calculation was based assuming a moderate association (R = 0.50 i.e. $R^2=0.25$) between any covariates added to the model. A sample size of 90 patients was included in this study that will allow for addition of maximum 8 covariates in the regression models.

2.5 Statistical analysis

Data analyses were performed using IBM SPSS Statistics 24. Continuous variables were reported as mean ± standard deviation. Associations between demographic data and clinical characteristics and outcomes between 2 groups were reported using bivariate chi-square analysis for categorical data. For continuous variables, t-tests and Mann-Whitney tests were used to assess group differences for parametric and non-parametric data respectively. All analyses were 2-tailed and a p-value < 0.05 was accepted as significant.

2.5.1 Analyses to test hypotheses

Patients were dichotomized as either positive or negative for POD. Multivariable logistic regression models were then employed to identify independent predictors of delirium accounting for covariates. Continuous variables were entered in the model in their numeric mode rather than being categorized. Linearity of continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure (Box & Tidwell, 1962). Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable. Co-linearity between variables vs POD was also reviewed and considered. For variables with obvious co-linearity, only one of the variables was selected on the basis of its assumed higher clinical (Smulter et al., 2013) or study relevance. For
instance, in this study total anticholinergic burden was preferred rather than total number of
drugs as it was one of our variables of interest and directly related to the study hypotheses.
Covariates entered in the model were selected a priori based on established risk factors for
POD in TAVI and vascular surgery. Independent risk factors were presented as odds ratio and
95% confidence interval and a significance of p<0.05 was set for the final model. The model fit
of the prediction model was assessed by computing the Hosmer-Lemeshow goodness-of-fit test
where p>0.05 refers to a good fit model.

2.5.2 Co-variates

Age: Several studies have identified age is a predictor of POD in TAVI (Abawi et al., 2016;
Soundhar et al., 2017; Tse, Schwarz, et al., 2015). An aging brain involves morphological
changes including decrease in brain volume, reduced number of neurons, and compromised
neurotransmitter function (van der Mast, 1998) that make geriatric patients more prone to
delirium.

History of stroke: A previous history of stroke is one of the predisposing factors of delirium in
cardiac (Koster et al., 2011; Lin et al., 2012; Rolfson et al., 1999; Tse, Schwarz, et al., 2015)
surgery patients and TAVI (Abawi et al., 2016). Pre-existing brain lesions and its underlying
pathology contribute to neurologic burden that pre-dispose patients to a greater risk of POD.

Atrial fibrillation: Predictors of POD in TAVI suggest higher odds of developing delirium in
patients with pre-existing atrial fibrillation (Abawi et al., 2016; Eide et al., 2015). Atrial
fibrillation is associated with higher rates of cerebral infarcts and silent cerebral embolic lesions
(Anselmino et al., 2013; Graff-Radford et al., 2016), which in turn increase risk of POD
(Otomo et al., 2013).
Diabetes: Diabetes is an independent predictor of delirium following cardiac surgery (Bucerius et al., 2004; Nikolic et al., 2012; Smulter et al., 2013; Sockalingam et al., 2005; M. C. Tan et al., 2008) and therefore diabetic patients undergoing TAVI may also be at increased risk of POD.

Anesthesia: Both general anesthesia (GA) and local anesthesia with conscious sedation (SA) have been used to successfully treat TAVI patients with similar short and long-term mortality outcomes in the past (Bergmann et al., 2011; Mayr, Michel, Bleiziffer, Tassani, & Martin, 2015). However, the use of sedation and fast-track anesthesia weaning protocols have been documented to decrease the incidence of delirium in cardiac surgical patients (Lin et al., 2012) and compared to general anesthesia, locoregional anesthesia was associated with a significantly shorter procedure time and a reduction in hospital length of stay in TAVI patients (Maas, Pieters, Van de Velde, & Rex, 2016; Toppen et al., 2017). Use of anesthesia may affect delirium outcomes in TAVI and was therefore adjusted for as a covariate in these analyses.

2.5.3 Post-hoc analyses

Clinical and TAVI procedural characteristics that were significantly different between the two groups (POD vs non-POD) were used to adjust regression models in post hoc analyses. Post hoc power analysis was also conducted.
3. Chapter 3: Results

3.1 Chart review: Overview of clinical characteristics and outcomes

A total of 186 patients had TAVI between September 2015 and December 2016. Of those, 90 patients were screened using the Mini-Cog test prior to TAVI and therefore 90 charts were reviewed for inclusion in this study (Figure 2).

![Consolidated flow diagram for TAVI patients included in this study](image-url)
As seen in Table 1, the average age of patients was over 80 years and the majority of patients were male. STS-PROM (Society of Thoracic Surgeons Predicted Risk of Mortality) risk score for mortality was available in 68 patients with an average score 7.6±5.2. The Mini-Cog test used during TAVI pre-assessment clinic visit identified 31 patients screening positive for cognitive deficits. A total of 7 (7.8%) patients experienced POD in this cohort.

A large number of patients had an atherosclerotic disease burden including history of coronary artery disease (CAD), and cerebrovascular risk factors hypertension, diabetes and hyperlipidemia. Patient characteristics were mostly similar between patients with and without POD although a significantly higher number of patients with a previous history of stroke experienced POD. On average, patients were on 9.7±4.2 number of medications and polypharmacy (total number of medication use) was correlated with the total anticholinergic burden (r=0.58, p<0.01). Anticholinergic burden assessed by the ACB scale showed that 20 percent of patients were not on any medication with anticholinergic properties, 42.2 percent were on one medication with possible anticholinergic property (ACB=1), while some 37.8 percent were on either at least one definite anticholinergic or on more than one possible or definite anticholinergic medication (ACB≥2). Comparison of groups with and without POD showed that anticholinergic burden was higher among patients experiencing POD compared to those that did not. A significantly higher number of patients receiving general anesthesia experienced POD compared to those receiving local anesthesia with conscious sedation during TAVI. All patients in this cohort underwent their TAVI procedures using a transfemoral access to the valve. Clinical characteristics and TAVI procedural details are shown in Table 1.
Table 1: Summary of clinical characteristics in patients with and without POD

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=90)</th>
<th>POD (n=7)</th>
<th>No POD (n=83)</th>
<th>Chi square or t-score</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>83±6</td>
<td>84.3±6.0</td>
<td>83.2±6.0</td>
<td>-0.47</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Gender (Male)</strong></td>
<td>55 (61.1)</td>
<td>6 (85.7)</td>
<td>49 (59.0)</td>
<td>1.93</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Mini-Cog (+ve screen)</strong></td>
<td>31 (34.4)</td>
<td>4 (57.1)</td>
<td>27 (32.5)</td>
<td>1.73</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**Comorbidities**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>All patients (n=90)</th>
<th>POD (n=7)</th>
<th>No POD (n=83)</th>
<th>Chi square or t-score</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>31 (34.4)</td>
<td>4 (57.1)</td>
<td>27 (32.5)</td>
<td>1.73</td>
<td>0.19</td>
</tr>
<tr>
<td>CAD</td>
<td>59 (65.6)</td>
<td>5 (71.4)</td>
<td>54 (65.1)</td>
<td>0.12</td>
<td>0.73</td>
</tr>
<tr>
<td>CHF</td>
<td>25 (27.8)</td>
<td>4 (57.1)</td>
<td>21 (25.3)</td>
<td>3.26</td>
<td>0.07</td>
</tr>
<tr>
<td>PVD</td>
<td>9 (10.0)</td>
<td>0 (0.0)</td>
<td>9 (10.8)</td>
<td>0.84</td>
<td>0.36</td>
</tr>
<tr>
<td>History of stroke</td>
<td>14 (15.6)</td>
<td>3 (42.9)</td>
<td>11 (13.3)</td>
<td>4.31</td>
<td>0.04*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (21.1)</td>
<td>3 (42.9)</td>
<td>16 (19.3)</td>
<td>2.16</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77 (85.6)</td>
<td>5 (71.4)</td>
<td>72 (86.7)</td>
<td>1.23</td>
<td>0.27</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>60 (66.7)</td>
<td>4 (57.1)</td>
<td>64 (77.1)</td>
<td>1.39</td>
<td>0.24</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (7.8)</td>
<td>0 (0.0)</td>
<td>7 (8.4)</td>
<td>0.64</td>
<td>0.42</td>
</tr>
<tr>
<td>Renal disease</td>
<td>26 (28.9)</td>
<td>1 (14.3)</td>
<td>25 (30.1)</td>
<td>0.79</td>
<td>0.38</td>
</tr>
<tr>
<td>Liver disease</td>
<td>6 (6.7)</td>
<td>0 (0.0)</td>
<td>5 (6.0)</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>Lung disorder</td>
<td>9 (10.0)</td>
<td>0 (0.0)</td>
<td>9 (10.8)</td>
<td>0.84</td>
<td>0.36</td>
</tr>
<tr>
<td>Frailty</td>
<td>9 (10.0)</td>
<td>2 (28.6)</td>
<td>7 (8.4)</td>
<td>2.91</td>
<td>0.09</td>
</tr>
<tr>
<td>History of surgery (non-cardiac)</td>
<td>27 (30.0)</td>
<td>3 (42.9)</td>
<td>24 (28.9)</td>
<td>0.60</td>
<td>0.44</td>
</tr>
<tr>
<td>Cancer</td>
<td>17 (18.9)</td>
<td>0 (0.0)</td>
<td>17 (20.5)</td>
<td>1.77</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**Concomitant medication use (pre-TAVI)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>All patients (n=90)</th>
<th>POD (n=7)</th>
<th>No POD (n=83)</th>
<th>Chi square or t-score</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmic</td>
<td>8 (8.9)</td>
<td>1 (14.3)</td>
<td>7 (8.4)</td>
<td>0.27</td>
<td>0.60</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>50 (55.6)</td>
<td>5 (71.4)</td>
<td>45 (54.2)</td>
<td>0.78</td>
<td>0.38</td>
</tr>
<tr>
<td>Ca channel blocker</td>
<td>32 (35.6)</td>
<td>2 (28.6)</td>
<td>30 (36.1)</td>
<td>0.16</td>
<td>0.69</td>
</tr>
<tr>
<td>Medication</td>
<td>All patients (n=90)</td>
<td>POD (n=7)</td>
<td>No POD (n=83)</td>
<td>Chi square or t-score</td>
<td>p*</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>----</td>
</tr>
<tr>
<td>Diuretic</td>
<td>71 (78.9)</td>
<td>7 (100.0)</td>
<td>64 (77.1)</td>
<td>2.03</td>
<td>0.15</td>
</tr>
<tr>
<td>Anti-hypertensive</td>
<td>60 (66.7)</td>
<td>5 (71.4)</td>
<td>55 (66.3)</td>
<td>0.08</td>
<td>0.78</td>
</tr>
<tr>
<td>Anti-diabetic</td>
<td>21 (23.3)</td>
<td>3 (42.9)</td>
<td>18 (21.7)</td>
<td>1.62</td>
<td>0.20</td>
</tr>
<tr>
<td>Platelet inhibitor</td>
<td>65 (72.2)</td>
<td>6 (85.7)</td>
<td>64 (71.1)</td>
<td>0.69</td>
<td>0.41</td>
</tr>
<tr>
<td>Lipid lowering agent</td>
<td>75 (83.3)</td>
<td>6 (85.7)</td>
<td>69 (83.1)</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>13 (14.4)</td>
<td>3 (42.9)</td>
<td>10 (12.0)</td>
<td>4.96</td>
<td>0.03*</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>1 (1.1)</td>
<td>1 (14.3)</td>
<td>0 (0.0)</td>
<td>11.99</td>
<td>0.00*</td>
</tr>
<tr>
<td>Cholinesterase inhibitor</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>0.27</td>
<td>0.60</td>
</tr>
<tr>
<td>ACB scale</td>
<td>1.5±1.3</td>
<td>2.7±1.7</td>
<td>1.4±1.2</td>
<td>-2.68</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

|                         |                     |           |               |                       |     |
| TAVI characteristics     |                     |           |               |                       |     |
| Anesthesia               | Conscious sedation  | 66 (73.3) | 2 (28.6)      | 64 (77.1)             | 7.78| 0.01*|
|                         | General anesthesia  | 24 (26.7) | 5 (71.4)      | 19 (22.9)             |     |     |
| Valve access             | Trans-femoral       | 90 (100)  | 7 (7.8)       | 83 (92.2)             | -   | -   |
|                         | Transapical or transaortic | 0 (0.0) | 0 (0.0) | 0 (0.0) | - | - |

ACB: Anticholinergic Cognitive Burden, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, POD: Post-operative delirium, PVD: Peripheral Vascular Disease, TAVI: Transcatheter Aortic Valve Implantation
*p significance: p<0.5
3.2 POD and TAVI outcomes

Post-operative delirium was associated with higher rates of stroke, and mortality at 1 month and 6 months. Table 2 shows the difference between TAVI outcomes in patients with and without POD.

**Table 2: POD and TAVI outcomes**

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=90)</th>
<th>POD (n=7)</th>
<th>No POD (n=83)</th>
<th>X² or U test score</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA</td>
<td>7 (7.8)</td>
<td>4 (57.1)</td>
<td>3.6</td>
<td>25.80</td>
<td>0.00*</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>15 (16.7)</td>
<td>3 (42.9)</td>
<td>14.5</td>
<td>3.75</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>3.0 (2.0-6.8)</td>
<td>7.0 (2.0-12.0)</td>
<td>3.0 (2.0-6.0)</td>
<td>231.00</td>
<td>0.41</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-0.3)</td>
<td>238.50</td>
<td>0.33</td>
</tr>
<tr>
<td>All cause morbidity^</td>
<td>47 (52.2)</td>
<td>6 (85.7)</td>
<td>41 (49.4)</td>
<td>3.41</td>
<td>0.07</td>
</tr>
<tr>
<td>Mortality 1 month</td>
<td>2 (2.2)</td>
<td>2 (28.6)</td>
<td>0.0 (0.0)</td>
<td>24.25</td>
<td>0.00*</td>
</tr>
<tr>
<td>Mortality 6 month</td>
<td>3 (3.3)</td>
<td>3 (42.9)</td>
<td>0.0 (0.0)</td>
<td>36.79</td>
<td>0.00*</td>
</tr>
</tbody>
</table>

IQR: Interquartile Range, POD: Post-operative delirium, TIA: Transient Ischemic attack  
^ All-cause morbidity includes vascular complications, acute kidney injury, major bleeding, systemic inflammation and any neuropsychiatric symptoms post TAVI.  
*p significance: p<0.0.5

3.3 Analyses to test Hypotheses

3.3.1 Primary Hypothesis: Cognitive impairment on the Mini-Cog test will predict increased risk of POD in TAVI.

Results from multivariate analysis predicting POD with the Mini-Cog adjusted for age, history of stroke, atrial fibrillation, diabetes and the type of anesthesia protocol used during TAVI found that patients screening positive on the Mini-Cog were trending to predict a higher risk of
POD (OR: 6.62, p=0.09) (Table 3). The model was statistically significant, \( \chi^2 (6) = 18.4, p=0.01 \) and explained 44.0% (Nagelkerke \( R^2 \)) of the variance in predicting the risk of POD. The model correctly classified 92.2% of cases of delirium post TAVI with a sensitivity of 14.3% and specificity of 98.8%. The Hosmer & Lemeshow test of the goodness of fit suggested the model is a good fit to the data (p=0.67).

### Table 3: Multivariate logistic regression model with Mini-Cog predicting risk of POD

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p*</th>
<th>Odds ratio</th>
<th>95% CI for Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Cog(^1)</td>
<td>1.89</td>
<td>1.11</td>
<td>2.93</td>
<td>1.00</td>
<td>0.09</td>
<td>6.62</td>
<td>0.76-57.68</td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>0.11</td>
<td>0.87</td>
<td>1.00</td>
<td>0.35</td>
<td>1.11</td>
<td>0.89-1.39</td>
</tr>
<tr>
<td>Hx of stroke</td>
<td>1.71</td>
<td>1.19</td>
<td>2.07</td>
<td>1.00</td>
<td>0.15</td>
<td>5.52</td>
<td>0.54-56.41</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.50</td>
<td>1.03</td>
<td>0.23</td>
<td>1.00</td>
<td>0.63</td>
<td>1.65</td>
<td>0.22-12.35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.89</td>
<td>1.34</td>
<td>4.65</td>
<td>1.00</td>
<td>0.03*</td>
<td>17.90</td>
<td>1.30-246.61</td>
</tr>
<tr>
<td>General Anesthesia(^#)</td>
<td>3.42</td>
<td>1.33</td>
<td>6.57</td>
<td>1.00</td>
<td>0.01*</td>
<td>30.42</td>
<td>2.24-413.80</td>
</tr>
<tr>
<td>Constant</td>
<td>-15.46</td>
<td>10.07</td>
<td>2.36</td>
<td>1.00</td>
<td>0.13</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Patients screening positive on the Mini-Cog  
\(^#\)compared to local anesthesia under conscious sedation  
CI: Confidence interval, Hx: History  
*p significance, p<0.05

### 3.3.2 Secondary Hypothesis: Higher anticholinergic burden measured using the ACB scale will predict increased risk of POD in TAVI.

Results from multivariate analysis with the ACB scale adjusted for age, history of stroke, atrial fibrillation, diabetes and the type of anesthesia protocol used during TAVI found that the ACB scale was not an independent predictor of POD in this model (OR: 1.62, p=0.17) (Table 4). The model was statistically significant, \( \chi^2 (6) = 16.9, p=0.01 \) and explained 40.7% (Nagelkerke \( R^2 \)) of the variance in predicting risk of POD. The model correctly classified 92.2% of cases of
delirium post TAVI with a sensitivity of 14.3% and specificity of 98.8%. The Hosmer & Lemeshow test of the goodness of fit suggested the model is a good fit to the data (p=0.58).

Table 4: Multivariate logistic regression model with ACB scale predicting risk of POD

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p*</th>
<th>Odds ratio</th>
<th>95% CI for Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACB scale</td>
<td>0.48</td>
<td>0.35</td>
<td>1.84</td>
<td>1.00</td>
<td>0.17</td>
<td>1.62</td>
<td>0.81-3.24</td>
</tr>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.10</td>
<td>0.69</td>
<td>1.00</td>
<td>0.41</td>
<td>1.09</td>
<td>0.89-1.34</td>
</tr>
<tr>
<td>Hx of stroke</td>
<td>1.10</td>
<td>1.29</td>
<td>0.73</td>
<td>1.00</td>
<td>0.39</td>
<td>3.00</td>
<td>0.24-37.39</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.03</td>
<td>1.26</td>
<td>0.00</td>
<td>1.00</td>
<td>0.98</td>
<td>1.03</td>
<td>0.09-12.08</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.22</td>
<td>1.21</td>
<td>3.38</td>
<td>1.00</td>
<td>0.07</td>
<td>9.21</td>
<td>0.86-98.33</td>
</tr>
<tr>
<td>General Anesthesia*</td>
<td>2.87</td>
<td>1.17</td>
<td>6.01</td>
<td>1.00</td>
<td>0.01*</td>
<td>17.55</td>
<td>1.78-173.48</td>
</tr>
<tr>
<td>Constant</td>
<td>-12.91</td>
<td>9.06</td>
<td>2.03</td>
<td>1.00</td>
<td>0.15</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

*compared to local anesthesia under conscious sedation
ACB: Anticholinergic Cognitive burden, CI: Confidence interval, Hx: History
*p significance, p<0.05

3.3.3 Exploratory Hypothesis: Cognitive impairment on the Mini-Cog test in conjunction with a higher anticholinergic burden measured using the ACB scale will predict increased risk of POD in TAVI.

Results from multivariate analysis with the interaction between the Mini-Cog and ACB scale adjusted for all other covariates selected a-priori: age, history of stroke, atrial fibrillation, diabetes and the type of anesthesia protocol used during TAVI found that the interaction term was a significant predictor of POD in this model (OR:6.94, p=0.01). Table 5 summarizes these results with their respective odds ratios and 95% confidence intervals in this model. The model was statistically significant, $\chi^2 (6) =29.1$, p<0.001 and explained 65.6% (Nagelkerke $R^2$) of the variance in the incidence of POD. The model correctly classified 94.4% of cases of POD in
TAVI with a sensitivity of 57.1% and specificity of 97.6%. The Hosmer & Lemeshow test of the goodness of fit suggested the model is a good fit to the data (p=0.61).

Table 5: Multivariate logistic regression model with the interaction between Mini-Cog and the ACB scale predicting risk of POD

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p*</th>
<th>Odds ratio</th>
<th>95% CI for Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Cogǂ*ACB scale</td>
<td>1.94</td>
<td>0.71</td>
<td>7.36</td>
<td>1.00</td>
<td>0.01*</td>
<td>6.94</td>
<td>1.71-28.15</td>
</tr>
<tr>
<td>Age</td>
<td>0.16</td>
<td>0.14</td>
<td>1.25</td>
<td>1.00</td>
<td>0.26</td>
<td>1.17</td>
<td>0.89-1.56</td>
</tr>
<tr>
<td>Hx of stroke</td>
<td>3.28</td>
<td>1.91</td>
<td>2.93</td>
<td>1.00</td>
<td>0.09</td>
<td>26.55</td>
<td>0.62-1132.48</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>-1.77</td>
<td>1.72</td>
<td>1.06</td>
<td>1.00</td>
<td>0.30</td>
<td>0.17</td>
<td>0.01-4.92</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.85</td>
<td>2.36</td>
<td>6.16</td>
<td>1.00</td>
<td>0.01*</td>
<td>345.88</td>
<td>3.42-34963.96</td>
</tr>
<tr>
<td>General Anesthesiaǂ</td>
<td>5.91</td>
<td>2.31</td>
<td>6.52</td>
<td>1.00</td>
<td>0.01*</td>
<td>367.62</td>
<td>3.95-34244.47</td>
</tr>
<tr>
<td>Constant</td>
<td>-23.16</td>
<td>13.67</td>
<td>2.87</td>
<td>1.00</td>
<td>0.09</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

ǂPatients screening positive on the Mini-Cog
ǂǂcompared to local anesthesia under conscious sedation
ACB: Anticholinergic Cognitive burden, CI: Confidence interval, Hx: History
*p significance, p<0.05

3.4 Post-hoc Analyses

Bivariate associations between the incidence of POD and baseline characteristics found that POD was significantly associated with a previous history of stroke, the ACB scale, anxiolytic and antipsychotic medication use pre TAVI and the use of general anesthesia during TAVI (Table 1).

Post hoc analyses were conducted for variables that were significantly different between patients with and without POD and had not been previously analysed. However, only one patient in the POD group was on an antipsychotic drug, therefore antipsychotic use was not
added to the logistic regression model in post hoc analysis. Only anxiolytic use were adjusted for in the regression models in post hoc analyses.

### 3.4.1 Anxiolytic Use

The Mini-Cog was trending as a predictor of risk of POD when anxiolytic use was added to the primary regression model (OR: 7.38, p=0.08) (Table 6). The model was statistically significant, \( \chi^2 (7) =18.7, p=0.009 \) and explained 44.5% (Nagelkerke \( R^2 \)) of the variance in the incidence of POD. The model correctly classified 91.1% of cases of POD in TAVI with a sensitivity of 14.3% and specificity of 97.6%. The Hosmer & Lemeshow test of the goodness of fit suggested the model is a good fit to the data (p=0.99).

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Df</th>
<th>p*</th>
<th>Odds ratio</th>
<th>95% CI for odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mini-Cog</strong></td>
<td>2.00</td>
<td>1.13</td>
<td>3.11</td>
<td>1.00</td>
<td>0.08</td>
<td>7.38</td>
<td>0.80-67.91</td>
</tr>
<tr>
<td><strong>Anxiolytic use</strong></td>
<td>0.69</td>
<td>1.36</td>
<td>0.26</td>
<td>1.00</td>
<td>0.61</td>
<td>1.99</td>
<td>0.14-28.36</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.10</td>
<td>0.11</td>
<td>0.86</td>
<td>1.00</td>
<td>0.35</td>
<td>1.11</td>
<td>0.89-1.38</td>
</tr>
<tr>
<td><strong>Hx of stroke</strong></td>
<td>1.68</td>
<td>1.21</td>
<td>1.93</td>
<td>1.00</td>
<td>0.16</td>
<td>5.36</td>
<td>0.50-57.09</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>0.38</td>
<td>1.06</td>
<td>0.13</td>
<td>1.00</td>
<td>0.72</td>
<td>1.46</td>
<td>0.18-11.75</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>2.95</td>
<td>1.38</td>
<td>4.55</td>
<td>1.00</td>
<td>0.03*</td>
<td>19.09</td>
<td>1.27-286.89</td>
</tr>
<tr>
<td><strong>General Anesthesia</strong></td>
<td>3.36</td>
<td>1.36</td>
<td>6.07</td>
<td>1.00</td>
<td>0.01*</td>
<td>28.68</td>
<td>1.99-413.89</td>
</tr>
<tr>
<td><strong>Constant</strong></td>
<td>-15.29</td>
<td>9.87</td>
<td>2.40</td>
<td>1.00</td>
<td>0.12</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

1Patients screening positive on the Mini-Cog

*compared to local anesthesia under conscious sedation*

CI: Confidence interval, Hx: History

*p significance, p<0.05*
The ACB scale was not a significant predictor of the risk of POD when anxiolytic use was added to the model testing the secondary hypothesis (Table 7). The model was statistically significant, $\chi^2 (7) = 17.0$, $p=0.02$ and explained 40.8% (Nagelkerke $R^2$) of the variance in predicting risk of POD. The model correctly classified 92.2% of cases of POD in TAVI with a sensitivity of 14.3% and specificity of 98.8%. The Hosmer & Lemeshow test of the goodness of fit suggested the model is a good fit to the data ($p=0.99$).

**Table 7: Multivariate logistic regression model with ACB predicting risk of POD adjusted for the use of anxiolytics**

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p*</th>
<th>Odds ratio</th>
<th>95% CI for Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACB scale</td>
<td>0.48</td>
<td>0.36</td>
<td>1.86</td>
<td>1.00</td>
<td>0.17</td>
<td>1.62</td>
<td>0.81-3.26</td>
</tr>
<tr>
<td>Anxiolytic use</td>
<td>0.23</td>
<td>1.27</td>
<td>0.03</td>
<td>1.00</td>
<td>0.85</td>
<td>1.26</td>
<td>0.10-15.27</td>
</tr>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.10</td>
<td>0.69</td>
<td>1.00</td>
<td>0.41</td>
<td>1.09</td>
<td>0.89-1.33</td>
</tr>
<tr>
<td>Hx of stroke</td>
<td>1.07</td>
<td>1.30</td>
<td>0.68</td>
<td>1.00</td>
<td>0.41</td>
<td>2.91</td>
<td>0.23-36.92</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.02</td>
<td>1.25</td>
<td>0.00</td>
<td>1.00</td>
<td>0.99</td>
<td>1.02</td>
<td>0.09-11.86</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.24</td>
<td>1.22</td>
<td>3.36</td>
<td>1.00</td>
<td>0.07</td>
<td>9.38</td>
<td>0.85-102.91</td>
</tr>
<tr>
<td>General Anesthesia*#</td>
<td>2.83</td>
<td>1.19</td>
<td>5.71</td>
<td>1.00</td>
<td>0.02*</td>
<td>16.99</td>
<td>1.66-173.38</td>
</tr>
<tr>
<td>Constant</td>
<td>-12.88</td>
<td>9.00</td>
<td>2.05</td>
<td>1.00</td>
<td>0.15</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

* compared to local anesthesia under conscious sedation
ACB: Anticholinergic Cognitive burden, CI: Confidence interval, Hx: History
*p significance, $p<0.05$

The interaction term between the Mini-Cog and ACB scale (OR: 16.13, $p=0.02$) was a significant predictor of the risk of POD when anxiolytic use was added to the model testing the exploratory hypothesis (Table 8). The model was statistically significant, $\chi^2 (7) = 32.0$, $p<0.001$ and explained 71.0% (Nagelkerke $R^2$) of the variance in predicting risk of POD. The model correctly classified 95.6% of cases of POD in TAVI with a sensitivity of 57.1% and specificity
of 98.8%. The Hosmer & Lemeshow test of the goodness of fit suggested the model is a good fit to the data (p=0.99).

Table 8: Multivariate logistic regression model with the interaction between Mini-Cog and the ACB scale predicting risk of POD adjusted for use of anxiolytics

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p*</th>
<th>Odds ratio</th>
<th>95% CI for Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Cog*ACB scale</td>
<td>2.78</td>
<td>1.14</td>
<td>5.94</td>
<td>1.00</td>
<td>0.02*</td>
<td>16.13</td>
<td>1.73-150.90</td>
</tr>
<tr>
<td>Anxiolytic use</td>
<td>3.41</td>
<td>2.11</td>
<td>2.61</td>
<td>1.00</td>
<td>0.11</td>
<td>30.31</td>
<td>0.48-1899.28</td>
</tr>
<tr>
<td>Age</td>
<td>0.18</td>
<td>0.15</td>
<td>1.47</td>
<td>1.00</td>
<td>0.23</td>
<td>1.19</td>
<td>0.90-1.59</td>
</tr>
<tr>
<td>Hx of stroke</td>
<td>4.54</td>
<td>2.51</td>
<td>3.29</td>
<td>1.00</td>
<td>0.07</td>
<td>93.99</td>
<td>0.69-12752.35</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>-3.08</td>
<td>2.07</td>
<td>2.21</td>
<td>1.00</td>
<td>0.14</td>
<td>0.05</td>
<td>0.00-2.66</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.18</td>
<td>3.54</td>
<td>5.34</td>
<td>1.00</td>
<td>0.02*</td>
<td>3580.73</td>
<td>3.46-3705222.08</td>
</tr>
<tr>
<td>General Anesthesia#</td>
<td>7.66</td>
<td>3.29</td>
<td>5.43</td>
<td>1.00</td>
<td>0.02*</td>
<td>2121.50</td>
<td>3.37-1335376.04</td>
</tr>
<tr>
<td>Constant</td>
<td>-27.91</td>
<td>15.28</td>
<td>3.33</td>
<td>1.00</td>
<td>0.07</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

*Patients screening positive on the Mini-Cog
# compared to local anesthesia under conscious sedation
ACB: Anticholinergic Cognitive burden, CI: Confidence interval, Hx: History
*p significance, p<0.05

3.4.2 Post-hoc power analysis

A post hoc power analysis of the primary hypothesis with the Mini-Cog predicting risk of POD with the given α (0.09), odds ratio (6.62) and sample size (n=90) indicated that the study was underpowered (73.3%). Given the reported prevalence of cognitive impairment and incidence of delirium post TAVI in this study population, in order to obtain statistically significant results (α <0.05) with an analytical power of 80%, the sample size required would be 132 participants.
4. Chapter 4

4.1 Summary of findings

Pre-existing cognitive impairment, an important consideration prior to cardiac intervention (Rosengart et al., 2005; Silbert et al., 2007) is a risk factor for poor peri-procedural outcomes in cardiac surgery. Cognitive impairment and deficits in executive function based on pre-determined criteria have been reported as independent predictors of delirium after cardiac surgery (Kazmierski et al., 2010; Kazmierski et al., 2006; Rudolph et al., 2006). However, despite the literary evidence on the importance of cognitive impairment in predicting outcomes following a cardiac intervention, surgical risk assessments like the STS-PROM and EuroScore used in current clinical practices do not screen for and subsequently manage geriatric specific risk factors like cognitive impairment (Nashef et al., 2012; Shahian et al., 2009). This is particularly important while assessing a geriatric, multi-morbid TAVI population who may present with subtle cognitive deficits.

As already mentioned, the Mini-Cog is a brief, easy to administer test to detect cognitive impairment in older adults and include a 3 word memory recall and clock drawing task (Neville, 2015). To our knowledge, this is the first study looking at the predictive value of cognitive impairment assessed using the Mini-Cog test in identifying risk of delirium in the elderly TAVI population. Elderly TAVI patients with high co-morbidity burden are also at risk of polypharmacy and high anticholinergic burden driven by the cumulative effects of less potent anticholinergic medicines including oral anticoagulants, diuretics and opioids (Magin et al., 2016; Mintzer & Burns, 2000). Deleterious effects on cholinergic and dopaminergic pathways due to concomitant medication use with anticholinergic properties make them susceptible to increased risk of delirium following TAVI (Brown, 2000; L. Tune et al., 1992; L.
This study investigated the role of pre-operative cognitive deficits using the Mini-Cog test and the role of medication use with anticholinergic properties using the ACB scale in predicting risk of POD in TAVI. It was hypothesized that patients screening positive on the Mini-Cog and those with a higher anticholinergic burden will predict increased risk of POD. In this sample, neither the Mini-Cog nor the ACB scale were significant predictors of POD in regression models when assessed individually after adjusting for covariates selected a-priori. However, patients who screened positive on the Mini-Cog and had a high score on the ACB scale, assessed as an interaction term between the Mini-Cog and the ACB scale in the regression model, significantly predicted higher risk of POD after adjusting for covariates. Other predictors that were selected a-prior based on literary evidence and had significant findings in this study in predicting risk of POD include pre-existing diabetes and the use of general anesthesia during the TAVI procedure.

4.2 Interpretation of results

Cognitive impairment may be critical in the incidence of delirium in an aging population. Several cognitive tools have been used to screen for cognitive deficits in a cardiac population. The MMSE is a widely used tool to assess patients with cognitive deficits and a cut off score of <25 has been previously reported to identify patients that are predisposed to risks of delirium (Kazmierski et al., 2010; Kazmierski et al., 2006). In a prospective study assessing 113 patients prior to cardiac surgery, individuals with MCI, diagnosed based upon the criteria of the National Institute on Aging and Alzheimer's Association using the MoCA and Trails Making Test A, were at a significantly higher risk of post-operative delirium (Kazmierski et al., 2010). Another retrospective cohort study analysing data from 679 patient charts also documented that cognitive impairment was independently associated with delirium along with age and other pre-
existing neurologic conditions in TAVI and other cardiac surgery patients (Tse, Schwarz, et al., 2015). A recent review of screening measures in heart failure patients suggested that standard, brief, sensitive screening instruments should be adopted to detect subtle cognitive impairment in the areas of attention, memory, executive function and psychomotor speed (Davis & Allen, 2013).

However, an extensive cognitive battery may not always be viable to incorporate in routine cardiac assessments to screen patients’ subtle deficits in cognition. On the contrary, the Mini-Cog test is validated and has been successfully used in the past to identify preoperative baseline cognitive deficits in elderly patients and those having an elective non-cardiac surgery (Alagiakrishnan et al., 2007; Heng et al., 2016; Robinson, Wu, Pointer, Dunn, & Moss, 2012). Findings from these studies have shown that elderly patients positive for cognitive impairment on the Mini-Cog test were more likely to have adverse postoperative outcomes including delirium (Alagiakrishnan et al., 2007; Heng et al., 2016; Robinson et al., 2012). Cognitive impairment based on abnormal Mini-Cog test results also predicted poorer outcomes in elderly patients with cancer (Korc-Grodzicki et al., 2015) and with heart failure (Agarwal et al., 2016). In a one-year prospective cohort quality improvement program, Agarawal and colleagues found that cognitive impairment, which is frequently undocumented in heart failure patients indicate greater risk of readmission compared to those without (Agarwal et al., 2016). Therefore, the Mini-Cog may be the ideal, brief cognitive screen to use in the elderly TAVI population that is acceptable to both patients and cardiac staff. In addition, the clock-drawing test, which is a part of the Mini-Cog has been shown to be a moderately sensitive and specific adjunct for detecting executive cognitive dysfunction with good reliability and predictive validity for screening cognitive deficits in a multidisciplinary geriatric assessment clinic and in an older population.

In this study, more than one third of the included patients screened positive for cognitive impairment on the Mini-Cog test, a rate that is comparable to the prevalence of cognitive impairment in other TAVI populations (Auffret et al., 2016; Ghanem et al., 2013; Schoenenberger et al., 2016; Tse, Bowering, et al., 2015). Patients screening positive on the Mini-Cog had a trending association with higher odds of predicting POD when controlled for other risk factors like age, history of stroke, atrial fibrillation, diabetes and use of general anesthesia. However, a higher anticholinergic burden did not significantly predict higher risk of POD in the multiple regression model adjusted for age, history of stroke, atrial fibrillation, diabetes and use of general anesthesia. This may be because the effect of ACB was overridden by other strong predictors of POD like general anesthesia in this small sample of patients with POD. The ACB scale may also not be sensitive enough to independently detect risk of POD in this population. However, in a model where both cognitive deficits and anticholinergic burden were assessed together as an interaction term between the Mini-Cog and the ACB scale, the interaction term independently predicted risk of POD. This suggests a synergistic deleterious effect of cognitive deficits and anticholinergic burden on the risk of POD supporting the hypothesis that both factors may be exercising their relationship on delirium using the cholinergic system and thereby mediating each other’s relationship with POD.

According to the cholinergic hypothesis of geriatric cognitive dysfunction, disease related changes in the cholinergic system in the elderly lead to a decline in release and synthesis of acetylcholine. Reduced cholinergic activity in the brain, in turn lead to the incidence of delirium (Dumas & Newhouse, 2011; Hshieh et al., 2008; van der Mast, 1998). In addition, an
imbalance of the cholinergic system due to the cumulative effect of anticholinergic medications that can cross the blood brain barrier augment the risk of delirium in patients with cognitive impairment (Hshieh et al., 2008; Leentjens & van der Mast, 2005). The results from this study complement clinical findings from studies that support the association between anticholinergic deficits and delirium (Flacker et al., 1998; Trzepacz, 1996; L. E. Tune, 2000, 2001; L. E. Tune et al., 1981). These results suggesting that patients identified with cognitive impairment using the Mini-Cog are at higher risk of delirium post TAVI also complement findings from studies assessing cognitive screening and retrospective chart review of outcomes in the past (Agarwal et al., 2016; Alagiakrishnan et al., 2007; Heng et al., 2016; Kazmierski et al., 2010; Kazmierski et al., 2006; Robinson et al., 2012; Tse, Schwarz, et al., 2015).

Among other variables that were included and controlled for in the logistic regression models, use of general anesthesia (GA) during TAVI was one of the stronger predictor of the risk of POD in this population. General anesthetics affect neuronal function at multiple levels including neurotransmitters pathways, cerebral blood flow and metabolism. The aged brain is more susceptible to anesthetic effects due to changes in neuronal function of neurotransmitter systems including the central muscarinic cholinergic system that interact with drugs of anesthesia (Pratico et al., 2005). General anesthetics affects several neuronal processes involving the intra-neuronal signal transduction and the second messenger system and may interact with the central cholinergic system, all of which have been implicated in the incidence of delirium (Pratico et al., 2005; Trzepacz, 1996). In a study assessing 114 elderly patients over the age of 65 who underwent hip fracture repair, the use of light propofol sedation decreased the prevalence of POD by 50% compared to deep sedation (Sieber et al., 2010). Recent systematic reviews have shown that lighter sedation may decrease the incidence of POD in both cardiac and non-cardiac patients (Khan et al., 2015; Lin et al., 2012). Another review of ten
studies, including 5919 TAVI patients found that while the choice for a specific anesthesia technique did not affect 30-day mortality rate or other safety endpoints, locoregional anesthesia was associated with a significantly shorter procedure time and a reduction in hospital length of stay when compared to general anesthesia (Maas et al., 2016; Toppen et al., 2017). This makes conscious sedation a more cost effective choice of anesthesia and is reason why more and more TAVI procedures are done without general anesthesia (Toppen et al., 2017). Findings from this study are consistent with the anesthesia literature that TAVI patients will have higher risk of POD with general anesthesia compared to local anesthesia and conscious sedation. A recent meta-analysis comparing the use of dexmedetomidine and propofol in patients after cardiac surgery found that dexmedetomidine sedation reduce postoperative delirium and was associated with shorter length of intubation compared to propofol (Liu et al., 2017). In addition, inhalation anesthetics used in GA may produce a number of changes affecting the central nervous system such as headaches and emergence increasing the risk of POD (Ancelin et al., 2000; Pratico et al., 2005). Therefore, it is not surprising that our findings were similar to that in the literature favoring use of conscious sedation over general anesthesia to reduce the risk of peri-procedural delirium in TAVI.

Other prominent pre-disposing factors of delirium following cardiac surgery include advanced age, cognitive impairment, atrial fibrillation, and prior history of stroke (Koster et al., 2011; Lin et al., 2012; Thorsteinsdottir et al., 2015). Increasing age (Raats et al.) has been commonly associated with an increased risk of POD in the past although age was not a significant predictor of delirium in our model. Pre-existing neurological condition has also been implicated with a higher risk of delirium in TAVI (Tse, Schwarz, et al., 2015) and other cardiac surgical procedures (Kumar et al., 2017). Prior history of stroke and atrial fibrillation, both common risk factors of POD in TAVI were not significant predictors of POD in this model. Interestingly,
pre-existing diabetes was a strong predictor of POD in this cohort of TAVI patients. As already mentioned, diabetes has been identified as an independent predictor for POD in many studies (Bucerius et al., 2004; Nikolic et al., 2012; Sockalingam et al., 2005; M. C. Tan et al., 2008). Diabetic patients may experience post-operative hypoglycemic episodes or diabetic ketoacidosis, the most severe of case which lead to an increased risk of POD (Boland et al., 2001; Kitabchi et al., 2001; Lewis, 1999). Direct brain insults including general and regional energy deprivation as a result of hypoglycaemia and other metabolic abnormalities following an intervention can also lead to POD (Maclullich et al., 2008). Moreover, it has been suggested that patients suffering from co-morbid psychiatric disorders are more prone to risk of hypoglycemic delirium (Balhara, 2011). Pre-existing cognitive deficits along with cholinergic deficiency due to high anticholinergic burden may have predisposed diabetic patients in this study to very high odds of predicting POD.

Anxiolytic use was associated with POD in bivariate associations. Post hoc analysis with the use of anxiolytics did not affect the result of the Mini-Cog, ACB scale or the interaction between Mini-Cog and ACB scale predicting risk of POD. The interaction term between the Mini-Cog and the ACB scale remained an independent predictor of the risk of POD in the post hoc model adjusted for use of anxiolytics.

This sample had a very small number of patients experiencing delirium post TAVI, yet POD was significantly associated with higher rates of stroke and mortality at 1 and 6 months respectively. However, given the small number of patients with POD and the small cohort of patients that did not survive 6 months post TAVI, it is difficult to draw a conclusion regarding the association between POD and mortality from this cohort. Moreover, the dataset contains valid data for POD only for the period of hospital stay until discharge. Therefore conclusions
about the duration and reversibility of POD, which are important parameters of quality of life and resource consumption as well as midterm consequences, could not be estimated.

4.3 Limitations and future implications

This study must be interpreted in the context of several limitations that merit discussion. The incidence of POD in the included cohort was only 8% which is lower than the documented prevalence of delirium between 28 to 44% in TAVI (Eide et al., 2016; Tse, Bowering, et al., 2015; Tse, Schwarz, et al., 2015). However, rate of delirium is lower in transfemoral TAVI compared to the transapical approach and ranges between 12 to 18% (Maniar et al., 2016; Tse, Bowering, et al., 2015; Tse, Schwarz, et al., 2015). Since this analysis only included patients undergoing TAVI with the transfemoral approach, our rates are comparable to that reported in the literature. The lower rate could also be attributed to a number of other reasons. In this study, only patients who had been screened using the Mini-Cog during TAVI pre-assessment have been included. Therefore, patients who refused to or were unable to complete the screen due to a physical (too frail to draw clock, blind, difficulty hearing) or language barrier (non-English speaking) were not included in the study. Physical frailty (Assmann et al., 2016; Eide et al., 2015) and visual and hearing impairments (Raats et al., 2016) have been associated with increased risk of delirium, therefore excluding these patients may have accounted for a lower incidence of delirium in our population. The low incidence of POD may also lead to the problem of under fitting the risk prediction model in our multivariate analysis with chances of unjustly excluding important risk factors.

Delirium was screened by an attending physician or nurse practitioner in the Intensive Care Unit (ICU) at Sunnybrook hospital using the ICDSC tool. However, this analysis was limited to
treating the incidence of POD as a categorical variable only due to missing data on the ICSDS score and delirium severity. Most of the models presented in this study correctly classified 91-96% of the cases of POD with high specificity ranging between 97.6-98.8%. However the sensitivity of the prediction models ranged between 14.3-57.1% meaning a substantial number of patients were wrongly regarded as high-risk due to this model’s poor positive predictive value. Nevertheless, given the poor prognosis of delirium with an increased risk of death, institutionalization, and dementia and the simplicity of administering the Mini-Cog to identify cognitive deficits, this was deemed an appropriate trade-off. Another potential limitation for using the Mini-Cog test is that it does not provide enough information for a definitive diagnosis. However, the purpose of this study was not to diagnose, but rather to provide sufficient information that can be used to stratify at-risk patient that will require further evaluation. Moreover, the Mini-Cog was used as a categorical variable in this analysis due to missing data on the actual test score. The actual test score could be used to find the optimal cut-off score to detect cognitive impairment in the TAVI population in future analysis. Although anticholinergic activity has been previously associated with delirium (Plaschke et al., 2016), the ACB scale may also not be sensitive enough to detect anticholinergic burden in this population. Measuring serum anticholinergic activity in future studies may provide useful and more accurate information regarding the effect of anticholinergic burden on POD.

Finally, the study was underpowered and limited from its relatively small sample size in relation to the surplus of variables that could potentially be associated with cognitive impairment and POD and could not be adjusted for in our model. There were very high odds ratios and wide confidence intervals for some of the significant predictors of POD presented in the models including the Mini-Cog, diabetes and general anesthesia. One of the reasons for such high odds ratio could be overfitting the model when the incidence of POD was so low.
4.4 Conclusions and recommendations

While cognitive impairment, defined using the Mini-Cog test was not an independent risk factor for POD, this study supports the conventional conception that POD is a multifactorial disease. The results suggest that concomitant medication use contributing to anticholinergic burden in TAVI prior to the procedure may be a factor precipitating delirium in patients with underlying cognitive deficits. Postoperative outcomes were significantly worse in delirious patients making it a serious complication after TAVI. Therefore, identifying patients at risk of POD may be important in post-TAVI patient management. Preoperative identification of patients susceptible to poorer outcomes using simple screening tools has the potential to improve patient management by providing a means for risk stratification and focused implementation of neuroprotective strategies to improve survival and quality of life in the TAVI population.

In addition to cognitive impairment and the effect of anticholinergic burden increasing risk of POD in TAVI, multiple factors have been identified including pre-disposing factors like diabetes and potentially remediable precipitating factors like the use of general anesthesia in TAVI that can provide opportunities for future research in delirium prevention and management. This study can also pave the way to design a large delirium screening trial to elucidate the benefits of delirium screening coupled with a multicomponent intervention versus usual care trial.

The Mini-Cog has been previously validated to identify preoperative baseline cognitive deficits in elderly patients and those having an elective non-cardiac surgery (Alagiakrishnan et al., 2007; Heng et al., 2016; Robinson et al., 2012) although it had a poor positive predictive value in this study. This could be a result of a less stringent cut off score used for the Mini-Cog in this
study. Therefore, it is recommended that the findings from this study are replicated in a larger trial screening for cognitive deficits predicting risk of POD in TAVI before adopting it as part of a multidisciplinary risk assessment tool catered to the needs of elderly TAVI patients. The Mini-Cog test can be used to inform decision-making for patient selection and peri-procedural management such as assistance with sedation for patients at risk for POD in TAVI, and also more widely, in the assessment of other multi-morbid patient populations with similar risk profiles.

Geriatric patients are over-represented in hospitalizations, surgeries, and perioperative complications because of the prevalence of comorbid diseases, functional impairments, and other deficits. Therefore, it is recommended that a comprehensive preoperative risk evaluation strategy is conducted to identify and address issues that delay recovery and subsequently increase healthcare costs. The ability to identify patients at higher risk of delirium, while performing systematic, multi domain assessments paired with risk reduction efforts will allow for early intervention as well as optimization of resource utilization for post-operative care. For example, screening for and identification of cognitive deficits prior to TAVI may lead to further assessments and subsequent referral to a psychiatrist for a diagnoses of MCI, followed by a review of prescription medications to optimize prevention and management of delirium by reducing anticholinergic load of concomitant medications. In addition, at risk patients identified using the Mini-Cog test may inform health care professionals to prevent and optimize POD treatment and management according to the American Geriatrics Society Expert Panel best practice guidelines e.g. consider not using antipsychotic medications prophylactically prior to TAVI, consider using regional anesthetic during TAVI, and improve pain management postoperatively using non-opioid pain medication to prevent delirium in older adults (American Geriatrics Society Expert Panel on Postoperative Delirium in Older, 2015).
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LIST OF PUBLICATIONS AND ABSTRACTS

PUBLICATIONS

ABSTRACTS
5. Lanctôt KL, Swardfager WL, Herrmann N, Andreazza AC, Swartz RH, Khan MM, Black SE. Post-stroke neuropsychiatric symptoms; relationships with IL-17 and oxidative stress [abstract]. Stroke 2014 45: e259-e298; co-author

POSTER PRESENTATIONS
Outcomes following Transcatheter Aortic Valve Implantation (TAVI). *Presented at Canadian Psychiatric Association Annual Conference (Toronto ON) Sep 2016.*


**AWARDS AND HONORS**

Glaxo Welcome Sunnybrook Drug Safety Clinic Graduate Student Fellowship (OSOTF) (CAD26491.69) Sep 2016-Aug 2017

University of Toronto Fellowship (CAD2000.00), Dept. of Pharmacology (declined) Sep 2016

School of Graduate Studies Conference Grant (CAD790.00) Winter/Spring 2016

University of Toronto Fellowship (CAD6000.00), Dept. of Pharmacology Sep 2015

Merit Entrance Scholarship (CAD2000.00), Faculty of Medicine Sep 2015
APPENDIX: REB APPROVAL
To: Dr. Nathan Herrmann  
Psychiatry  
Room FG19

From: Dr. Brian J. Murray

Date: April 22, 2016

Subject: Screening for And Managing Risk Factors in TAVI: An Interdisciplinary Endeavor (SMARTIE)

Project Identification Number: 128-2015

The Research Ethics Board is in receipt of your amendment submission form dated April 7, 2016 pertaining to the above referenced study. A delegated review has been conducted and the following documents have been approved.

- Summary of Changes letter dated April 6, 2016  
- Amended Protocol Version 1.3 dated March 2016  
- Smartie Chart Review form dated August 2014  
- Smartie Prospective Chart Review form dated August 2014

This study may continue at Sunnybrook Health Sciences Centre.

During the course of the research, any significant deviations from the approved protocol and/ or any unanticipated developments must be brought to the attention of the Research Ethics Board.

Thank you for keeping the Board informed.

[Signature]

Brian J. Murray, MD FRCP(C) D,ABSM  
Chair, Research Ethics Board

OR

Philip C. Hébert, MD PhD FCFPC  
Vice-Chair, Research Ethics Board

The Research Ethics Board of Sunnybrook Health Sciences Centre Operates in Compliance with the Tri-Council Policy Statement 2nd edition, ICH GCP Guidelines, Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, and Part 3 of the Medical Devices Regulations. All Health Canada regulated trials at Sunnybrook are conducted by a Qualified Investigator.

Fully affiliated with the University of Toronto