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A RISK OF POST-OPERATIVE DELIRIUM IN TRANSCATHETER AORTIC VALVE IMPLANTATION: A REVIEW OF DIAGNOSIS AND TREATMENT STRATEGIES

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Abstract:
This study proposed to use the Mini-Cog as a screening tool to identify patients with cognitive impairment or dementia before transcatheter Aortic Valve Implantation with the hypothesis that patients screening positive on the Mini-Cog will be at higher risk of Post-operative delirium. We also hypothesized that patients with a higher anticholinergic burden will be at higher risk of Post-operative delirium. Therefore, we suggest that while identification of predisposing factors like cognitive impairment may be used for risk evaluation in Transcatheter Aortic Valve Implantation, careful consideration of precipitating factors like concomitant medication use contributing to anticholinergic burden prior to procedure may also help to reduce risk of Post-operative delirium and improve survival and quality of life post Transcatheter Aortic Valve Implantation.
Keywords: *Higher anticholinergic burden, Anticholinergic Cognitive Burden scale, Transcatheter Aortic Valve Implantation*

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INTRODUCTION:

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). transcatheter Aortic Valve Implantation 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, transcatheter Aortic Valve Implantation 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). transcatheter Aortic Valve Implantation 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, transcatheter Aortic Valve Implantation 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).

Post-operative delirium

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). Post-operative delirium 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).

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Risk Factors of Post-operative delirium

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 transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation (Abawi et al., 2016; Tse, Schwarz, et al., 2015). Age is a key predictor of Post-operative delirium in elective cardiac and general surgery as well as transcatheter Aortic Valve Implantation (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 transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation (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 Post-operative delirium. Cardiac arrhythmia and atrial fibrillation are also common and major risks for Post-operative delirium (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 transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation (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 Post-operative delirium (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., 2014). The prevalence of Post-operative delirium 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 Post-operative delirium. 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 Post-operative delirium (Pratico et al., 2005). Muscarinic acetylcholine receptors in the central nervous system play a role in the pathogenesis of Post-operative delirium 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 Post-operative delirium 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 (Freye & Levy, 2004; Pratico et al., 2005).

Pathophysiology of Post-operative delirium

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, Post-operative delirium 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 (Hshieh 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).

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.

Cholinergic deficiency in Post-operative delirium

As already mentioned, one of the leading hypothesis for the neurobiology and molecular mechanism of Post-operative delirium 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 Post-operative delirium, due to age-related cerebral changes in stress-regulating neurotransmitter and intracellular signal transduction systems (van der Mast, 1998).

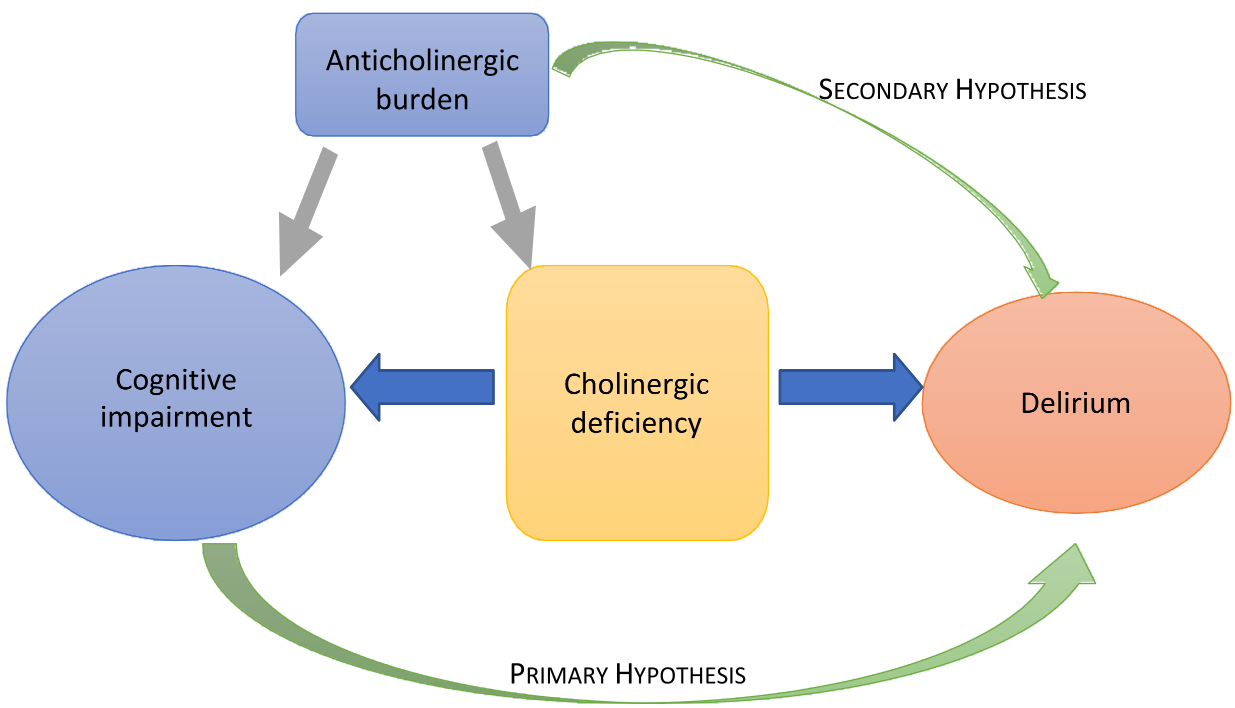

Figure 1*:* A schematic representation of the '*the central cholinergic deficiency*' hypothesis that may be a possible

mechanism underlying the pathophysiology of delirium.

Pharmacotherapy for Post-operative delirium

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 Post-operative delirium 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 Post-operative delirium in the elderly, there is still no pharmacological intervention approved for the prevention and treatment of Post-operative delirium (Khan et al., 2015). A systematic review on the pharmacotherapy of Post-operative delirium 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 Post-operative delirium in elderly patients found a 50% reduction in the relative risk of Post-operative delirium 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 Post-operative delirium in the elderly using pharmacological agents found that the incidence of Post-operative delirium 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).

Prevention of Post-operative delirium

Over time, only limited success has been availed by studies targeting treatment development for Post-operative delirium. 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 Post-operative delirium can improve patient outcomes by offering avenues for targeted prevention and treatment efforts (McCoy, Hart, & Perlis, 2017). Transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation patients (Stortecky et al., 2012).

Hypothesis: Higher anticholinergic burden measured using the Anticholinergic Cognitive Burden (ACB) scale will predict increased risk of Post-operative delirium in Transcatheter Aortic Valve Implantation.

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 Post-operative delirium in elderly transcatheter Aortic Valve Implantation 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 Post-operative delirium in Transcatheter Aortic Valve Implantation.

Hypothesis: Cognitive impairment on the Mini-Cog test in conjunction with a higher anticholinergic burden measured using the Anticholinergic Cognitive Burden scale will predict increased risk of Post-operative delirium in Transcatheter Aortic Valve Implantation.

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 Post-operative delirium in the elderly transcatheter Aortic Valve Implantation population but have not been previously studied. Therefore, in this study we hypothesized that elderly transcatheter Aortic Valve Implantation 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 Post-operative delirium.

METHODS:

Study Design

A prospective observational study design was used to assess outcomes of transcatheter Aortic Valve Implantation in severe aortic stenosis patients referred to the Sunnybrook Structural Heart Clinic for Transcatheter Aortic Valve Implantation. Consecutive patients referred for transcatheter Aortic Valve Implantation were screened for cognitive impairment using the Mini-Cog test as part of their clinical assessment prior to TAVI. Clinic charts for transcatheter Aortic Valve Implantation 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).

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 transcatheter Aortic Valve Implantation between August 2017 and January 2018 were included in this study.

Mini-Cog test

Patients were screened for cognitive deficits prior to transcatheter Aortic Valve Implantation using the Mini-Cog test as part of transcatheter Aortic Valve Implantation 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 transcatheter Aortic Valve Implantation clinic at Sunnybrook.

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 transcatheter Aortic Valve Implantation 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.

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.

Sample Size Calculation

Sample size of this study was calculated based on a previous cohort study looking at the incidence of Post-operative delirium in TAVI, that reported delirium in 12% of TF- transcatheter Aortic Valve Implantation 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 Post-operative delirium with an ∝ of 0.05 for the power of 0.8 in a logistic regression model. The transcatheter Aortic Valve Implantation population presents with a number of comorbidities and concomitant medication use that may be associated with cognitive impairment and Post-operative delirium. 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.

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.

RESULTS:

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 Post-operative delirium in Transcatheter Aortic Valve Implantation. 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 transcatheter Aortic Valve Implantation found that the interaction term was a significant predictor of Post-operative delirium in this model (OR:6.94, p=0.01). Table 1 summarizes these results with their respective odds ratios and 95% confidence intervals in this model. The model was statistically significant, $\chi2$ (6) =29.1, p<0.001 and explained 65.6% (Nagelkerke R^2) of the variance in the incidence of Post-operative delirium. The model correctly classified 94.4% of cases of Post-operative delirium in transcatheter Aortic Valve Implantation 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 1: Multivariate logistic regression model with the interaction between Mini-Cog and the ACB scale predicting risk of Post-operative delirium

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

‡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**

Post-hoc Analyses

Bivariate associations between the incidence of Post-operative delirium and baseline characteristics found that Post-operative delirium was significantly associated with a previous history of stroke, the ACB scale, anxiolytic and antipsychotic medication use pre transcatheter Aortic Valve Implantation and the use of general anesthesia during transcatheter Aortic Valve Implantation (Table 1).

Post hoc analyses were conducted for variables that were significantly different between patients with and without Post-operative delirium and had not been previously analysed. However, only one patient in the Post-operative delirium 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.

Anxiolytic Use

The Mini-Cog was trending as a predictor of risk of Post-operative delirium when anxiolytic use was added to the primary regression model (OR: 7.38, p=0.08) (Table 2). The model was statistically significant, $\chi2$ (7) =18.7, p=0.009 and explained 44.5% (Nagelkerke R^2) of the variance in the incidence of Post-operative delirium. The model correctly classified 91.1% of cases of Post-operative delirium in transcatheter Aortic Valve Implantation 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 2: Multivariate logistic regression model with Mini-Cog predicting risk of Post-operative delirium adjusted for the use of anxiolytics

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

‡Patients 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 Post-operative delirium when anxiolytic use was added to the model testing the secondary hypothesis (Table 3). 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 Post-operative delirium. The model correctly classified 92.2% of cases of Post-operative delirium in transcatheter Aortic Valve Implantation 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 3: Multivariate logistic regression model with ACB predicting risk of Post-operative delirium **adjusted for the use of anxiolytics**

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

‡‡ ***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 Post-operative delirium when anxiolytic use was added to the model testing the exploratory hypothesis. The model was statistically significant, $\chi2$ (7) =32.0, p<0.001 and explained 71.0% (Nagelkerke R^2) of the variance in predicting risk of Post-operative delirium. The model correctly classified 95.6% of cases of Post-operative delirium in transcatheter Aortic Valve Implantation 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 4: Multivariate logistic regression model with the interaction between Mini-Cog and the ACB scale predicting risk of Post-operative delirium **adjusted for use of anxiolytics**

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

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

Finding of the study

Pre-exiting 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 transcatheter Aortic Valve Implantation population who may present with subtle cognitive deficits.

Interpretation of results

Impairment on the Mini-Cog test, a rate that is comparable to the prevalence of cognitive impairment in other transcatheter Aortic Valve Implantation 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 Post-operative delirium 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 Post-operative delirium 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 Post-operative delirium like general anesthesia in this small sample of patients with Post-operative delirium. The ACB scale may also not be sensitive enough to independently detect risk of Post-operative delirium 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 Post-operative delirium. This suggests a synergistic deleterious effect of cognitive deficits and anticholinergic burden on the risk of Post-operative delirium 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 Post-operative delirium.

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 transcatheter Aortic Valve Implantation 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).

Limitations and future implications

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 Post-operative delirium 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 Post-operative delirium 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 transcatheter Aortic Valve Implantation 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 Post-operative delirium Post-operative delirium.

CONCLUSIONS AND RECOMMENDATIONS:

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 Post-operative delirium in transcatheter Aortic Valve Implantation before adopting it as part of a multidisciplinary risk assessment tool catered to the needs of elderly transcatheter Aortic Valve Implantation 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 Post-operative delirium in TAVI, and also more widely, in the assessment of other multi-morbid patient populations with similar risk profiles.

Cognitive deficits are critical in a geriatric population and are reductive 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 transcatheter Aortic Valve Implantation patients but is under-recognized. Post-operative delirium 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 Post-operative delirium (Clegg & Young, 2011; Naja et al., 2016; Young & Inouye, 2007).

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