CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1476607

Available online at: http://www.iajps.com Research Article

PREOPERATIVE MEDICATION USE AND POSTOPERATIVE DELIRIUM: A PREDICTORS OF POST-OPERATIVE DELIRIUM

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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.

Keywords: *Transcatheter Aortic Valve Implantation, Post-operative delirium*

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Please cite this article in press Nudrat Hussain et al., ***Preoperative Medication Use and Postoperative Delirium: A Predictors of Post-Operative Delirium .,*** *Indo Am. J. P. Sci, 2018; 05(11).*

INTRODUCTION:

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.

Purpose of the Study

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-exiting 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 effects 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.

Statement of Research Hypotheses and Rationale for Hypotheses

1.1.1 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.

METHODS:

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).

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 2017 and December 2017 were included in this study.

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.

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.

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.

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.

RESULTS:

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

	patients (n=90)	POD (n=7)	No POD (n=83)	Chi square or t-score	p*
Age	83±6	84.3±6.0	83.2±6.0	-0.47	0.64
Gender (Male)	55 (61.1)	6 (85.7)	49 (59.0)	1.93	0.16
Mini-Cog (+ve screen)	31 (34.4)	4 (57.1)	27 (32.5)	1.73	0.19
Comorbidities					
Atrial fibrillation	31 (34.4)	4 (57.1)	27 (32.5)	1.73	0.19
CAD	59 (65.6)	5 (71.4)	54 (65.1)	0.12	0.73
CHF	25 (27.8)	4 (57.1)	21 (25.3)	3.26	0.07
PVD	9 (10.0)	0 (0.0)	9 (10.8)	0.84	0.36
History of stroke	14 (15.6)	3 (42.9)	11 (13.3)	4.31	0.04*
Diabetes	19 (21.1)	3 (42.9)	16 (19.3)	2.16	0.14
Hypertension	77 (85.6)	5 (71.4)	72 (86.7)	1.23	0.27
Hyperlipidemia	60 (66.7)	4 (57.1)	64 (77.1)	1.39	0.24
Depression	7 (7.8)	0 (0.0)	7 (8.4)	0.64	0.42
Renal disease	26 (28.9)	1 (14.3)	25 (30.1)	0.79	0.38
Liver disease	6 (6.7)	0 (0.0)	5 (6.0)	0.45	0.50
Lung disorder	9 (10.0)	0 (0.0)	9 (10.8)	0.84	0.36
Frailty	9 (10.0)	2 (28.6)	7 (8.4)	2.91	0.09
History of surgery (non- cardiac)	27 (30.0)	3 (42.9)	24 (28.9)	0.60	0.44
Cancer	17 (18.9)	0 (0.0)	17 (20.5)	1.77	0.18
Concomitant medication use (pre-TAVI)					
Anti-arrhythmic	8 (8.9)	1 (14.3)	7 (8.4)	0.27	0.60
Beta blocker	50 (55.6)	5 (71.4)	45 (54.2)	0.78	0.38
Ca channel blocker	32 (35.6)	2 (28.6)	30 (36.1)	0.16	0.69

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<0.0.5

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

	patients (n=90)	POD (n=7)	o POD (n=83)	r U test score	p*
Stroke/TIA	7 (7.8)	4 (57.1)	3.6	25.80	0.00*
Permanent pacemaker	15 (16.7)	3 (42.9)	14.5	3.75	0.05
Hospital length of stay Median(IQR)	3.0 (2.0-6.8)	7.0 (2.0-12.0)	3.0 (2.0-6.0)	231.00	0.41
Number of readmissions Median(IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.3)	238.50	0.33
All cause morbidity^	47 (52.2)	6 (85.7)	41 (49.4)	3.41	0.07
Mortality 1 month	2 (2.2)	2 (28.6)	0.0 (0.0)	24.25	0.00*
Mortality 6 month	3 (3.3)	3 (42.9)	0.0 (0.0)	36.79	0.00*

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**

Analyses to test Hypotheses

1.1.2 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

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

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

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

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.

Summary of findings

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. E. Tune, 2001). 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-exiting diabetes and the use of general anesthesia during the TAVI procedure.

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).

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.

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 that 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.

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.

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.

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.

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