Delirium After Transcatheter Aortic Valve Implantation: A Retrospective Chart Review of Associated Risk Factors and Outcomes

by

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Abstract

A retrospective chart review was performed to determine the incidence and risk factors of delirium after transfemoral and transapical transcatheter aortic valve implantation (TAVI), and open-heart aortic valve replacement (AVR) (n = 45 per group). A number of secondary outcomes were also compared between the surgeries, including 24-hour, 30-day, 1-year and 2-year mortality; time spent in intensive care; total length of hospitalization; need for emergency cardiopulmonary bypass during operation (for TAVI procedures only); and frequencies of postoperative complications.

Delirium occurred significantly less frequently in transfemoral TAVI (16%) than in transapical TAVI (51%) or open-heart AVR (38%) ($p < 0.01$ for transfemoral vs. transapical; $p < 0.05$ for transfemoral vs. open-heart). There were no significant differences in the use of emergency cardiopulmonary bypass between the two TAVI procedures. Transapical TAVI patients required longer periods of intensive care compared to transfemoral or open-heart patients (84 ± 118.4 hours for transapical compared to 36 ± 36.9 hours for transfemoral and 41 ± 32.1 hours for open-heart; $p = 0.014$ for transapical vs. transfemoral; $p = 0.025$ for transapical vs. open-heart), and transfemoral patients had significantly shorter lengths of hospitalization (8 ± 6.0 days for transfemoral compared to 14 ± 9.5 days for transapical and 11 ± 7.2 days for open-heart; $p = 0.001$ for transfemoral vs. transapical; $p = 0.047$ for transfemoral vs. open-heart). The 2-year cumulative mortality rate was significantly lower for open-heart patients than for

TAVI patients (2% of open-heart patients, compared to 20% of transapical patients and 18% of transfemoral patients; $p = 0.007$ for transapical vs. open-heart; $p = 0.014$ for transfemoral vs. open-heart). Transapical and open-heart patients suffered from more postoperative complications than transfemoral patients. A large number of risk factors for delirium were also identified within each surgical group.

This study demonstrated that benefits are incurred with transfemoral TAVI compared to transapical TAVI and compared to open-heart AVR. The contribution of medications taken in the perioperative period on the outcome of postoperative delirium is discussed, and clinical considerations with regards to using TAVI for mitigating the incidence of delirium are mentioned.

Preface

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1 Introduction

1.1 The General Scope and Specific Aims of This Research

Postoperative delirium is a medical condition that is frightening for patients to experience, and is associated with serious consequences like cognitive decline and early mortality. In a conversation with S. Schwarz, M.D., and J. Bowering, M.D., (January 2011), it was unanimously agreed that postoperative delirium may be considered the most frequent and serious complication after heart surgery today. One area of cardiac surgery for which the incidence of postoperative delirium has never been reported is with the novel aortic valve implantation technique called transcatheter aortic valve implantation (TAVI).

Prior to the advent of TAVI, people with severe aortic stenosis deemed to be 'non-surgical' by cardiac surgeons and cardiologists due to advanced age or significant co-morbidities were unable to receive aortic valve replacement (AVR) as treatment because of the high risks involved. However, over the last decade these patients have been able to receive surgical therapy for their condition via a minimally invasive technique that involves the insertion of a stented heart valve through a small incision in the body. While there have been a number of studies published on the mortality and morbidity outcomes of TAVI procedures (e.g., Webb, 2008; Ye *et al*., 2009; Leon *et a*l., 2010), there is currently no report of the incidence of postoperative delirium after these novel valve replacement techniques, nor has there ever been an in-depth look at the risk factors for postoperative delirium in this particular population. Since patients that currently

receive TAVI procedures are non-surgical, data on delirium must be produced in order to improve the well-being of these individuals who are already in a state of compromised health.

The drugs that patients take perioperatively, including drugs taken as outpatients, during anesthesia, and in the postoperative period, can be important influences on postoperative delirium in cardiac patients. Given that patients undergoing TAVI procedures are on average older and sicker than surgical candidates, and given that they are likely on a large number of medications to manage these co-morbidities, the contribution of drugs to the outcome of delirium stands to be major in these populations.

Therefore, the aim of this thesis was to determine the incidence of postoperative delirium after transfemoral TAVI, transapical TAVI, and open-heart AVR, and to identify medications and other risk factors that are associated with the diagnosis of postoperative delirium within each of these procedure.

1.2 Delirium: A Condition with Many Faces and Many Expressions

Delirium is an acute and fluctuating state of 'brain failure' that results from physiological disturbance, usually in the form of a medical condition (Fricchione *et al.*, 2008). Ancient physicians and medical philosophers have given some of history's best prose descriptions of delirium, but it is a medical condition that has not been systematically studied since the past 10 years (Culley, 2010). Neuropsychiatric abnormalities develop during delirium, such as confusion and

disorientation, and it is often affected by changes in attention, cognition, consciousness, sleep patterns, or perception. Symptoms develop abruptly, and they usually last for no more than several days. Delirium is frequently associated with illness, such as terminal cancer, or it may appear following a surgical procedure, like hip fracture replacement, jaw surgery, and particularly after cardiac surgery. Upon recovery, some patients recall being confused and report feeling scared, anxious, and helpless, but most patients do not remember the experience (Koster *et al*., 2009).

A delirious episode may be denominated as a hyperactive, hypoactive, or mixed psychomotor subtype depending on the amount of physical activity and the behavioural tendencies exhibited by the patient. A person with hyperactive delirium, for instance, may be violent or agitated, or he or she may be experiencing vivid hallucinations, while a person with hypoactive delirium may be catatonic, withdrawn and unresponsive. States of intermediate physical and behavioural arousal may also exist in between these two extremes. Thus, delirium is not a dichotomous condition; rather, it exists along a continuum.

Worthy of special consideration is a particularly complex and distressing form of delirium known as postoperative delirium. Postoperative delirium may occur after surgeries of varying degrees of trauma, but it poses a special problem in patients undergoing cardiac surgery because of the large number of drugs that these patients require perioperatively (many of which are known to be deliriogenic), and because of the advanced age and frailty of many cardiac

patients. The baseline risk for patients who are receiving cardiac surgery may be twice as high as the baseline risk for patients undergoing non-cardiac surgeries (Redelmeier *et al.*, 2008). Moreover, postoperative delirium consistently affects one-third of North American cardiac surgery patients, despite a number of efforts to reduce incidence through pre-operative screening techniques and off-label use of pharmaceutical prophylaxes. Systematic reviews on the effectiveness of these prevention strategies in the cardiac population are limited in number, and those that have been published claim that with such a small number of interventional studies and the heterogeneity that exists between them, conclusions are difficult to draw (Cole *et al.*, 1996). Disappointingly, conclusions that are drawn report that existing intervention strategies produce only modest reductions in the rates of postoperative delirium (Holroyd-Leduc *et al.*, 2010).

Another consequence of the lack of synthesis of studies on postoperative delirium is that postoperative delirium has proven to be challenging to predict, prevent, and control. Studies vary greatly in terms of their methodologies, and in terms of the types and definitions of variables investigated. For instance, inconsistencies in the diagnostic strategies have made it especially difficult to synthesize incidence rates: some studies assess for delirium only once in the postoperative period, but the fluctuating nature of delirium means that it is necessary for multiple assessments to be performed in order for it to be properly diagnosed, and care must be taken to seek for the symptoms of the hypoactive subtype since they are easily missed. And because of these difficulties, clinicians

and investigators have suggested that the real incidence of delirium after cardiac surgery may actually be greater than the typical 30% that is commonly reported for this surgical population.

Despite the growing number of studies published on postoperative delirium, there are certain perioperative factors that have historically been left out of analysis, some, because of their novelty, and others, because of authors' personal motivations, or lack thereof. For instance, while many risk factor studies have looked at 'outpatient medications' as variables in their databases, there have been no studies that have been published where this is the primary focus. But given the large number of drugs that cardiac patients are on prior to, during, and following surgery, it would seem to be very important to reveal any significant associations between commonly used pharmacological agents in cardiac patients and postoperative delirium. There have also been no studies that have looked at the incidence of delirium after percutaneous cardiac surgeries like transcatheter aortic valve implantation, mostly because these types of surgeries are relatively new and less frequently performed. However, the trend in cardiovascular surgery is moving towards these less invasive techniques with the goal of reducing mortality, morbidity, and postoperative complications, and for this reason the data for the incidence of delirium associated with these surgeries must also be generated in order to determine the true benefits afforded by these modern advances.

Throughout the rest of this thesis, the terms ‘delirium’, ‘postoperative delirium’, and ‘delirium after cardiac surgery’ will be used interchangeably.

1.3 Incidence

The estimated incidence of postoperative delirium is a sizeable range. A more conservative quote estimates that between 15-60% of medical and surgical inpatients experience delirium (Fricchione *et al*., 2008), but these incidences of delirium largely depend on the surgical procedure that is being studied. Interestingly, probably the highest rates of delirium are seen after hip fracture repair, and it is not uncommon for such an estimate to reach 50% (Marcantonio *et al*., 2001). Studies that report incidences of delirium vary according to their methodology: some studies are retrospective, while others are prospective or interventional; some studies use standardized diagnostic tools to determine delirium, while others only consider clinical diagnoses made by physicians based on the criteria outlined in the *Diagnostic and Statistical Manual* (DSM); and some studies include multiple assessments in the postoperative period for delirium, while others only include one. For cardiac surgeries on cardiopulmonary bypass, however, delirium rates consistently hover around 30% (e.g., Smith and Dimsdale, 1989; Santos *et al*., 2004; Prakanrattana and Prapaitrakool, 2007; Rudolph *et al*., 2008; Gamberini *et al*., 2009; Hudetz *et al*., 2009; Afonso *et al*., 2010; Burkhart *et al*., 2010). Importantly, this incidence of 30% remains consistent regardless of the geographical location of surgical facility or diagnostic

instrument that is used. This suggests that there may be something inherent about cardiac procedures on cardiopulmonary bypass or the patient population that makes one-third of these individuals susceptible to developing postoperative delirium. One thing to keep in mind is that the average age of the patient samples from all of these studies does fall within the range of 60-74 years old, so it is possible that although geography and method of diagnosis may not matter, the incidence rate of 30% after cardiac surgery may only be applicable to individuals within this age range.

1.4 Diagnosis

Having said that delirium seems to consistently affect one-third of the cardiac surgery population, it is also true that postoperative delirium is commonly under-diagnosed in more than two-thirds of clinical cases (Truman and Ely, 2003). Part of the difficulty of diagnosing delirium is recognizing the condition, especially the hypoactive subtype, but for most clinicians, a more relevant reason is because there is currently no biomarker for confirming the neuropathological state of delirium. Currently, delirium remains a purely psychiatric condition and diagnosis relies solely on the recognition of clinical symptoms.

Along its continuum of mental and behavioural states, it is easy to confuse postoperative delirium with a few differential diagnoses. Postoperative cognitive impairment, depression, dementia, and psychosis are distinct from postoperative delirium, and patients with these other conditions require different medical

attention. What clearly distinguishes delirium is that the symptoms of delirium develop abruptly and may disappear and re-appear in a cyclical manner over a short period of time. In contrast, the symptoms of these other conditions never really cease like they would in delirium, even though they may show changes in severity over time. Thus, one of the most crucial elements for specific diagnosis of delirium is to perform multiple, frequent assessments within the postoperative period to observe for fluctuations in behaviour. Delirium may be cured with or without pharmacological agents (with the exception of 'prolonged' delirium), but its appearance after cardiac surgery should not be considered lightly because it may be a harbinger of degenerating health and functional decline (Deiner and Silverstein, 2009; Rudolph *et al*., 2010).

Psychiatrists diagnose delirium with the criteria that are described in the *Diagnostic and Statistical Manual, Fourth, Text-Revised* edition (DSM-IV-TR, item #293.0). These diagnostic criteria are shown in **Table 1**. The DSM classifies delirium into four types – substance intoxication delirium, substance withdrawal delirium, delirium due to multiple etiologies, and delirium not otherwise specified – according to its suspected etiology (American Psychiatric Association, 2000). Postoperative delirium is most often classified as 'delirium due to multiple etiologies'. The DSM does not define the psychomotor subtypes of delirium since they were not described at the time of the latest DSM revision, which was back in 2000. However, since these psychomotor subtypes were first described by Meagher *et al*. (2008), they have been clinically validated by eletronic motion

analysis that shows concurrence between clinically observed motor behaviours and electronically measured activity levels (Godfrey *et al*., 2010).

Table 1. DSM-IV-TR diagnostic criteria for delirium

A. Disturbance of consciousness *(i.e., reduced clarity of awareness of the environment) with reduced ability to* focus*,* sustain*, or* shift attention

B. A change in cognition *(such as memory deficit, disorientation, language disturbance) or the development of a* perceptual disturbance *that is not better accounted for by a pre-existing, established, or evolving dementia*

C. The disturbance develops over a short period *of time (usually hours to days) and tends to* fluctuate during *the course of the day.*

Adapted from the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision (DSM-IV-TR). 2000.

Since diagnoses rely solely on recognition of clinical symptoms, standardized diagnostic tools have been constructed from these DSM criteria in an effort to create objective measures for delirium. Popular validated evaluation tools include, but are not limited to: the Confusion Assessment Method (CAM), the CAM for the Intensive Care Unit (CAM-ICU), the Delirium Symptom Interview (DSI), the Delirium Rating Scale (DRS), the Memorial Delirium Assessment Scale (MDAS), the Mini-Mental State Examination (MMSE), and the recently validated, Neelon and Champagne (NEECHAM) Confusion Scale.

The test of choice may depend on the amount of time available for the assessment, as well as the personal preference of the clinician (Wong *et al*.,

2010), but certain tests are more appropriate to achieve certain goals. For instance, the MMSE, and other tests including the clock-drawing test and the Glasgow Coma Scale, are meant to be used as screening tools (Fricchione *et al*., 2008), whereas the DSI and the CAM were designed and validated specifically for faciliatating diagnoses (Fricchione *et al*., 2008). However, in research the MMSE is routinely used for facilitating diagnoses as well (e.g., Gamberini *et al*., Tan *et al*., 2008; Rudolph *et al*., 2008). The DRS and MDAS are special tools in that are able to assess delirium severity, while the NEECHAM Confusion Scale and the CAM-ICU were designed and validated specifically for patients in intensive care, where communication with patients may be limited because of intubation (Ely *et al*., 2001).

The original intention of these evaluation tools was meant to provide standardized assessments of patients, but currently they are by no means superior with regards to sensitivity and specificity to formal diagnoses made by psychiatrists (Laurila *et al*., 2002). This is especially true of the CAM. Part of the appeal of the CAM is that it was originally designed to aid non-psychiatric clinicians to diagnose delirium (Inouye *et al*., 1990). However, it is not an instrument that can stand on its own, since formal cognitive assessments including the MMSE must be performed prior to the CAM in order for its validation to have relevance (Perneger and Klag, 1991). Preliminary validation studies reported that the CAM has exceptionally high specificity (93%) and sensitivity (97%) compared to clinical diagnoses (Inouye *et al*., 1990), but Laurila *et al*.

(2002) demonstrated these sensitivity and specificity rates might be overestimated. While a large number of studies that look at delirium after cardiac surgery use the standardized tools like the CAM as their diagnostic instrument of preference (e.g., Burkhart *et al*., 2010; Gamberini *et al*., 2009; Tan *et al*., 2008; Rudolph *et al*., 2008), it is unclear how frequently the these assessments are used in clinical practice.

1.5 Delirium Pathophysiology

Hippocampal neurons are affected during the early stages of delirium, while subcortical, brainstem, and cerebellar neurons and gray matter are affected in the later stages of delirium (Brown, 2000). States of cerebral pathophysiology that are most commonly described for delirium include neurotransmitter imbalance, neuronal metabolic dysfunction, physiological stress, inflammation, and melatonin dysregulation. Whether all these suggested mechanisms contribute to one pathophysiological state, or whether they each produce a unique outcome that together creates delirium, is unknown. Because of this reason, there are a number of different, albeit related, theories regarding the etiology of postoperative delirium that are probably more complementary than they are competing hypotheses (Maldonado, 2008).

A. The Neurotransmitter Hypothesis

The most popular explanation for how delirium develops is the neurotransmitter hypothesis of delirium etiology. It came from the suggestion that decreased neuronal metabolism from oxygen deprivation during cardiac surgery alters neurotransmitter function and causes generalized dysfunction in the brain (van der Mast, 1998; Maldonado, 2008). The most popularly implicated neurotransmitter system in this theory is the ubiquitous cholinergic system, which is believed to be deficient in the delirious patient (Inouye, 2006; Hshieh, *et al.*, 2008).

Acetylcholine is a common neurotransmitter that is found in synapses all over the brain, and is one of the principle neurotransmitters for generating attention and consciousness (Hshieh *et al.*, 2008). Thus, reducing levels of acetylcholine, or blocking its effects with the use of anticholinergic agents, would produce alterations in attention and consciousness similar to what is seen for delirium. Early investigators noticed that many medications used in cardiac surgery patients had anticholinergic effects, so it was hypothesized that perhaps this was what was causing delirium in patients after receiving cardiac surgery (Tune *et al.*, 1981). One study attempted to evaluated this concept by measuring anticholinergic drug use on the days prior to the appearance of delirium before and after surgery, and they found that exposure to anticholinergic drugs on the day before delirium onset was independently associated with increased delirium

severity (Han *et al.*, 2001). Further discussion on the influence of anticholinergic medications on delirium is presented below (see Section 1.5B: Anticholinergics).

Studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) have found some correlation between the areas of the brain affected by delirium and cholinergic pathways (Hshieh *et al.*, 2008); but since cholinergic pathways are so widespread in the brain, the value of these neuroimaging studies in determining the role of cholinergic contribution to delirium is questionable. Importantly, neither the studies that looked at anticholinergic medication use, nor the neuroimaging studies, show a casual relationship between cholinergic deficiency and delirium – merely that anticholinergic activity is associated with delirium onset.

Although the primary evidence for the causal effect of acetylcholine on the development of postoperative delirium has not been strong, the true significance of the cholinergic deficiency hypothesis lies in the fact that the cholinergic neurotransmitter system functions like a modulator of many other neurotransmitter systems, namely, for dopamine, serotonin, glutamate, norepinephrine, melatonin and gamma-aminobutyric acid (GABA) (Hshieh *et al.*, 2008). These monoamine neurotransmitters are important for producing arousal and are also frequently found in synapses in the brain (Hshieh *et al.*, 2008). Excesses of dopamine, norepinephrine, and glutamate are thought to produce the cognitive and motor abnormalities of delirium, while serotonin and GABA levels may be increased or decreased in the delirious state (van der Mast, 1998;

Hshieh *et al.*, 2008). Furthermore, the abnormal melatonin secretion patterns that have been observed in delirious patients (Shigeta *et al.*, 2001) may explain the irregular sleep-wake cycles associated with delirium. Interestingly, treatment of severe postoperative delirium has been successful with melatonin adminstration (Hanania and Kitain, 2002), but it is not known if or how irregular sleep-wake patterns contribute to the delirious state.

Related to the neurotransmitter hypothesis, there has been some evidence for the role of amino acids in the etiology of postoperative delirium. Since amino acids form the structural basis of the monoamine neurotransmitters mentioned above, it is plausible that fluctuations in amino acid availability within the brain tissue may lead to alterations in mental status after surgery (Morandi *et al.*, 2009). Amino acid precursors of monoamine neurotransmitters, such as tryptophan and phenylalanine, being relatively large molecules, require a protein transporter called the large amino acid transporter-1 (LAT-1) to gain entry into the brain across the blood-brain-barrier (Morandi *et al.*, 2009). Like all protein transporters, however, there may be competition between different amino acids to bind to the transporter, and this may result in a disproportionate amount of one neurotransmitter being made over the others (Morandi *et al.*, 2009). As mentioned above, this excess of certain neurotransmitters like dopamine, norepinephrine or glutamate could give rise to the symptoms of delirium.

B. The Neuronal Aging Hypothesis

Certainly related to the concept of neurotransmitter imbalance is the idea that neuronal aging predisposes individuals to postoperative delirium. Along with pathology and drug use, aging can change neurotransmitter metabolism, function, and response (Maldonado, 2008). There may also be age-related changes to brain anatomy or and other aspects of physiology that could increase the likelihood that an elderly person undergoing cardiac surgery will develop postoperative delirium, like deterioration of the blood-brain barrier, altered neuroplasticity, lowered resilience to chemical or physical stressors, variations in epigenetic regulation of gene expression, and changes in intracellular signal transduction (Shalev *et al.*, 2009; Maldonado, 2008, Lockett *et al.*, 2010).

C. Response to Systemic Inflammation Hypothesis

A systemic inflammatory response normally occurs after an invasive procedure like cardiac surgery. The magnitude of this inflammatory response after cardiac surgery is associated with a greater risk of developing delirium (Rudolph *et al.*, 2008). Normally, the brain is protected from systemic inflammation because the cytokines that are released in the periphery do not readily cross the BBB into the brain tissue (Rudolph *et al.*, 2008). Cytokine receptors are expressed within the BBB, but the mechanism by which they transport cytokines is complex and apparently very selective (Banks, 2005); nonetheless, since it has been suggested that general anesthesia during cardiac surgery may actually compromise the integrity of the BBB during the

postoperative period (Rudolph *et al*., 2008), it is possible for peripherally released cytokines to affect the brain. Similarly, the majority of cells within the brain (including glial cells and neurons) are also able to produce cytokines in response to surgical insults. Cytokines are problematic for the brain because they have been shown to alter neurotransmission and may even cause neuronal cell death (Broadhurst and Wilson, 2001; George and Mukaetova-Ladinksa, 2007). For these reasons, postoperative delirium has been hypothesized to be a state of 'brain inflammation'. Older adults have up to four times the amount of circulating cytokine levels (Katznelson *et al*., 2009), so they may be especially susceptible to delirium according to the inflammation hypothesis. Some evidence for the inflammation hypothesis of delirium comes from an oncology study where 30%-50% of patients who received infusions of interleukin-2 (IL-2) for the treatment of cancer were more likely to develop delirium (Rosenberg *et al*., 1989). In matched patients receiving cardiac surgery on cardiopulmonary bypass, a correlational study showed that patients who developed delirium had higher circulating levels of chemokines when they were measured in intensive care, but not when they were measured four days after (Rudolph *et al*., 2008). The same study also showed that delirious patients did not differ from non-delirious patients in their levels of inflammatory, T-helper 1 or T-helper 2 cytokines at either time points (Rudolph *et al*., 2008). From these studies, it appears that serum cytokine levels may not be the strongest measure of central nervous system inflammation. However, the level of C-reactive protein (CRP) in the postoperative period has

been shown to be an independent risk factor for delirium (Burkhart *et al.*, 2010). CRP probably increases the risk for delirium by disrupting the brain's defense by activating the endothelial cells of the BBB (Uchikado *et al.*, 2004) from side that faces the periphery, and promoting the infiltration of circulating cytokines to the brain.

D. The Physiologic Stress Hypothesis: Emphasis on Cortisol

Essentially, the stress hypothesis of delirium suggests that there can be adverse side-effects of a system that normally has adaptive effects when this system is activated in excess (MacLullich *et al.*, 2008). The stress hypothesis of delirium centers on the neuroimmunological relationship between stress and the immune system, and traditionally the emphasis was on the effect of stress on thyroid hormone concentrations (Maldonado, 2008), but recently, there has been some interest in the influence of increased cortisol levels on postoperative delirium (MacLullich *et al.*, 2008; Plaschke, *et al.*, 2010; Mu *et al.*, 2010; Kazmierski and Kloszewska, 2011). Cortisol is a hormone that is important for maintaining the homeostasis in glucose metabolism and electrolyte balance, and it also affects the functions of most major organ systems including the cardiovascular and central nervous systems (Schleimer, 2008). This means that cortisol could have important implications in the pathophysiology of postoperative delirium.

Cortisol is released by the adrenal glands after prolonged periods of exposure to psychologically or physically stressful stimuli. In the case of surgery,

it is likely that an individual will experience both types of stressors. Pre-surgical psychological stress has been shown to influence short-term recovery after cardiac surgery (Snyder, 1985), and the high stress environment of the cardiac surgery intensive care unit could also increase the activation of the sympathetic nervous system and concomitantly increase the levels of cortisol (Gunther *et al.*, 2008; Reich *et al.*, 2010). Delirium has also been described as a manifestation of a psychosomatic defense mechanism against 'death anxiety', which is an abnormal fear of death or dying (Reich *et al.*, 2010), but an optimistic attitude has shown to reduce the likelihood of delirium after cardiac surgery (Hudetz *et al.*, 2010), most likely by reducing this psychological state of anxiety and decreasing the physiological stress response.

The sharpest rise in cortisol is seen after sternal incision (Frater *et al.*, 1981). And following cardiopulmonary bypass, a distinct pattern of cortisol release is observed, and these elevated cortisol levels persist well into the postoperative period (Frater *et al.*, 1981). In the postoperative period, there is a great chance that the surgical patient may experience infection-induced stress (Schleimer, 2008). Once cortisol is released into the bloodstream, it readily cross the blood-brain barrier and may affect neuronal metabolism by altering glucose uptake rate (Kern, 2008), neurotransmitter function (Stokes, 1995), and calcium uptake into synaptosomes (Sze and Iqbal, 1994). Cortisol has also been shown to increase the rate of neuronal death under conditions of transient global ischemia in the brain, such as that which occurs in cardiac arrest (Antonawich *et*

al., 1999). These cortisol-mediated changes could potentially occur on a global scale in the brain and could contribute to the alteration of mental status after cardiac surgery. It is also well known that cortisol secretion is synchronized according to the body's circadian rhythm; this might help to explain the disturbed sleep-wake cycle in delirious patients. Thus, the evidence suggests that cortisol could have detrimental and conceivably deliriogenic effects in frail or vulnerable patients who undergo cardiac surgery. What makes the cortisol hypothesis so intriguing is that it is able to elegantly encompass the numerous etiological theories that came before it, namely, the concepts of surgical and psychological stress, inflammation, dysregulation of the sleep-wake cycle, neuronal cell death, and generalized cerebral metabolic abnormalities.

1.6 Clinical Pharmacological Risk Factors

Cardiac outpatients and inpatients are generally on a large number of drugs to manage hemodynamics, lipid levels, glucose levels, heartbeat, and pain, and the influence of all these drugs on postoperative delirium after cardiac surgery should be a major concern. The classes of drugs that are most regularly associated with delirium include anticholinergics, sedatives, and opioids (Goldman, 2000), all of which are standard for cardiac surgical procedures. Compounding this problem is the issue that cardiac surgery patients are typically older individuals who have different anatomical and physiological features that are the result of advanced age and underlying disease, both of which alter the

pharmacokinetics and pharmacodynamics of most drugs. In fact, medications are one of the most common causes of delirium in elderly individuals (Grob *et al*., 2000). But while there is ample data on the different types of risk factors for postoperative delirium after cardiac surgery, cardiac medications have never been considered in studies to be the primary contributors of the risk endowed. Here, special emphasis will be placed on the drugs used in cardiac surgery that have been identified in the literature since the year 2000 to have deliriogenic effects (see **Table 2** for a summary of the studies that are reviewed). Strategies for the pharmacologic prevention of postoperative delirium will also be discussed.

A. Characteristics of Drugs with Potential CNS Side-Effects

In order to evaluate the deliriogenic potential of cardiac and non-cardiac prescription medications and anesthetic drugs, it is necessary to have a discussion about some of the qualities that might make a drug more likely to cause postoperative delirium in cardiac surgery patients. The key to understanding how a drug might affect the central nervous system (CNS) lies in understanding how the brain regulates the uptake and efflux of endogenous and exogenous chemical substances.

The main regulatory mechanism for these processes is the blood-brain barrier (BBB), which is a structure that evolutionarily protected the brain from deathly infections (Misra *et al*., 2003). It is made up of capillaries that are lined with specialized endothelial cells that are joined together at tight junctions called *zona occludens* that prohibit the passage of small solutes from the blood to the

brain tissues. Because of these tight junctions and lack of fenestrations in the endothelium, all passive diffusion of drug molecules into and out of the brain is achieved via direct, nonspecific passage across the plasma membrane of endothelial cells. In pharmacology, the BBB has been referred to as the 'bottleneck' in brain drug development (Pardridge, 2005), and this terminology serves to illustrate how effective the BBB is in keeping most drug compounds out of the brain parenchyma. However, in cardiac surgery patients who have hypertension, hypercapnia, hypoxia, or ischemia, their BBBs may be weakened from pathology (Misra *et al.*, 2003) and/or age, and the tight restrictions on molecular exchange may be compromised. In younger, healthier individuals, however, the fatty barriers in the brain make it so that small, lipid-soluble compounds have a higher likelihood of influencing cognitive and perceptual processes than larger lipophilic and/or hydrophilic compounds. And because compounds may diffuse across the BBB via nonspecific processes, this means that any small lipid-soluble drug with a medium to long half-life that is consumed by a patient has the potential to produce CNS side-effects. Lipophilicity, however, is not entirely predictive of a drug's ability to produce psychiatric lability. One particular factor that could affect a lipophilic drug's actions in the brain is the presence of active efflux mechanisms (Misra *et al.*, 2003). Efflux protein transporters are expressed in the plasma membrane of endothelial cells of the BBB to maintain tight regulation of the intracranial environment and to influence the concentration of free drug in the brain (Misra *et al.*, 2003). Therefore, a

lipophilic drug may not have the expected pharmacological properties as predicted by its physicochemical properties if efflux transporters for the drug are expressed in the brain, since levels of the drug may be increased or decreased by modulating the amount of efflux.

Hydrophilic drugs do still enter the brain, albeit at a slower rate, and at negligible amounts compared to lipophilic drugs (Prichard, 1987). For the most part, this is because active transport mechanisms are also present to regulate the passage of both lipophilic and hydrophilic substances (Misra *et al.*, 2003). These include protein carrier-mediated uptake and efflux of peptides, and a mechanism called adsorptive-mediated transcytosis, which involves nonspecific, ionic binding of molecules to the surface of the endothelial membrane and vesicular transport of the molecules across the cytoplasm to another surface of the cell where the contents are exocytosed (Misra *et al.*, 2003; Hervé *et al.*, 2008). Notably, both passive and active transport mechanisms may have special implications at the region of the choroid plexus, since the BBB is 'leaky' in this area of the brain. Such permissive exchange in this region would affect the quality of the cerebrospinal fluid that is produced, and this has the potential to influence the global functioning of the brain as the fluid bathes the entire CNS and renders an interface of communication between neuronal extracellular fluid and the peripheral circulation (Misra *et al.*, 2003).

If a drug is able to bind to a wide repertoire of receptors within its range of therapeutic doses, then this could also suggest its ability to contribute to the

outcome of postoperative delirium and other CNS side-effects (a “dirty drug”). The explanation of this concept is simply an issue of chance – if, for example, an antihypertensive agent predominately works to lower blood pressure through its actions as a calcium channel blocker, but it also antagonizes cholinergic receptors, then there may be a chance that it will bind to one of the multiple receptors that are implicated in the etiology of postoperative delirium if it is able to cross the BBB. Another reason why drugs with diverse receptor affinities would be more likely to cause delirium is derived from the suggestion that delirium is a disorder characterized by global cerebral metabolic dysfunction. This implies that many different neuronal receptors are affected in delirium, which in turn explains why so many different pharmacological agents have been shown to be associated with delirium. Interestingly, most psychoactive drugs that treat psychiatric disorders do so by acting as ‘multifunctional’ drugs; in other words, they are drugs that impart symptomatic relief via two or more pharmacological targets within a therapeutic dose range (Stahl, 2009). Whether this is because relief from psychiatric symptoms may only be procured through diverse stimulation/inhibition of receptors, or whether this suggests that the pathophysiology of most psychiatric conditions involve global connections in the brain makes this a fascinating observation that leaves much to be considered.

To summarize, a drug will have implications for potentially contributing to the expression of postoperative delirium if it:

i) Is able to diffuse across the BBB due to its small size and lipophilicity, or if there is a specific protein transporter present in the plasma membrane of capillary endothelial cells of the BBB for active transport of a large lipophilic or hydrophilic molecule,

ii) Is effectively retained within the cerebrum and is not extruded by protein transporters,

iii) And has a significantly large repertoire of pharmacological action within its therapeutic dose range

Specific classes of drugs that are considered typical for Canadian cardiac patients will be discussed below.

B. Anticholinergics

A rather dated expression that has been used to describe the general effects of all anticholinergic agents is, “red as a beet, dry as a bone, mad as a hatter, and blind as a bat”, which refers to the peripheral vasodilation, dry mucous membranes, delirium, and visual impairment that is frequently associated with the use of these drugs (Grob *et al.*, 2000). Since cholinergic deficiency is implicated in delirium etiology, it should not be surprising that the use of drugs with anticholinergic effects is a major cause for concern with respect to postoperative delirium. One of the first studies to come across the relationship examined the correlation between delirium and serum levels of anticholinergic drugs (Tune *et al.*, 1981). Lower scores on the MMSE were correlated with high serum anticholinergic levels (Tune *et al.*, 1981). Later work by this group

assigned ‘atropine equivalents’ to the twenty-five most prescribed drugs in the elderly in the United States, and fourteen of those drugs were found to have detectable anticholinergic effects as measured by radioreceptor assay (Tune *et al.*, 1992).

With this evidence from preliminary correlation studies, there has been some effort in producing an animal model of delirium by administering an anticholinergic agent. A competitive antagonist for the muscarinic receptor, atropine, was used in Wistar rats to produce a ‘delirious’ state in these animals (Trzepacz *et al.*, 1992). Delirium was confirmed in the rats by measuring cortical electroencephalographic (EEG) changes, performance in a maze, and behavioural changes (Trzepacz *et al.*, 1992), but it is questionable how well these measures really indicate the presence of delirium since the validity of this animal model was not completely addressed in this study. For instance, a dose-response curve was not produced for demonstrating if the differences in behaviour, EEG waves, or learning of the maze was correlated to the doses of atropine administered, nor was there any mention of whether the differences in doses were able to produce the different motor subtypes of delirium that are seen clinically. Additionally, the validity of the model would have been strengthened by the use of a rescue agent or a therapeutic drug, such as haloperidol, which did not occur.

The limitations of this animal model and the paucity of follow-up studies unfortunately do not provide strong evidence for the cholinergic deficiency

hypothesis of postoperative delirium, but more rigorous study designs have also failed to show associations between anticholinergic drug use and delirium; in fact, there have been no convincing studies published over the past decade in the context of cardiac surgery that have shown support for the cholinergic deficiency hypothesis, despite its popularity. In a randomized, double-blind, prospective interventional study, the cholinesterase inhibitor, rivastigmine (which has an on-label use for treating dementia), was given to cardiac surgery patients the evening before their procedures, and was continued for every 6-hours following surgery for six days; disappointingly, this prophylactic regimen failed to lower the incidence of delirium, and the incidence for rivastigmine-treated patients remained at 32% compared to 30% for placebo-treated patients (Gamberini *et al.*, 2009). Tan *et al*. (2008) were also unable to show a statiscally significant association between patients' history of use of 'other' anticholinergic medications (a term that was undefined in the paper) to the presentation of delirium after cardiopulmonary bypass procedures. However, this may have been due to a lack of power or lack of attention to detail in data extraction since the proportion of delirious patients who reported a history of taking 'other' anticholinergic medications was much greater than non-delirious patients (58.3% of delirious compared to 31.7% of non-delirious) (Tan *et al.*, 2008).

Using a pharmacology perspective to determine how anticholinergic compounds increase the risk of patients to develop postoperative delirium is challenging. To begin, there is quite a large variation in the pharmacokinetic

qualities of anticholinergic drugs due to the metabolic capacity, genetic predisposition, and physiological state of individuals (Tune *et al.*, 1981); for instance, a ten-fold variation in serum anticholinergic levels of benztropine in patients taking the same dose was found in one study (Tune *et al.*, 1981). In addition, there are some drugs that have clear, direct antagonistic action on cholinoceptors, such as atropine or pancuronium, but there are also many drugs that have 'probable' direct anticholinergic activity, like warfarin, furosemide, hydrochlorothiazide, and ranitidine, which are all used in cardiac surgery patients (Cancelli *et al.*, 2009). Not to mention, it is also possible for metabolites from unrelated drugs to have antagonistic activity on cholinoceptors; for instance, disopyramide, which is a proarrhythmic, negatively inotropic drug used to treat ventricular arrhythmias, is metabolized to mono-N-dealkyldisopyramide, which has two-to-four times the anticholinergic activity of disopyramide (Baines *et al.*, 1976). Another challenge in studying the effect of anticholinergic drugs in delirium is that it is also possible for compounds to have an indirect anticholinergic effect by inhibiting vagal afferents. One example is quinidine, which is a prototypical class IA antiarrhythmic that produces a change in heart rate by means of a vagolytic mechanism (Wallace *et al.*, 1966).

Nonetheless, drugs that are most suspect in causing delirium will likely bind to and antagonize the G-protein coupled muscarinic acetylcholine receptor, since it is found in greater proportions in the brain compared to nicotinic acetylcholine receptors (Mulsant *et al.*, 2003). With respect to structure, direct

receptor antagonists drugs should contain the essential pharmacophore which is a non-cyclic, acetylcholine-like moiety made up of an ester of acetic acid and a positively charged choline. Also, most quaternary ammonium compounds have anticholinergic properties (Webb *et al*., 2000). The acetylcholine binding-site in muscarinic receptors is thought to have complementary negative charges in the form of ionized carboxylic acid groups (Ehlert *et al*., 2000) that participate in long-range electrostatic interactions with ligands (Stauffer and Karlin, 1994).

Due to the ionization of the choline moiety, agonists and competitive antagonists of cholinoceptors are usually lipid-insoluble and hydrophilic, and less than 10% of the total amount of choline taken up by the brain is from passive diffusion (Allen and Smith, 2001). However, a protein transporter in the BBB is able to bind to choline and its derivatives, so it may be possible for anticholinergic drugs to be transported from the plasma to the brain (Allen and Lockman, 2003). In fact, this BBB choline transporter has been demonstrated to be able to bind to a number of pharmacological agents, including derivatives of isoarecolone, lobeline, lithium, procainamide, quinine, and serotonin, but only one assay has demonstrated the ability of the transporter to actually transport a compound, a nicotine derivative, across the BBB (Lockman and Allen, 2002). Data on how age affects the function of this transporter is limited and contentious; human clinical studies have suggested that the choline transporter in the BBB has decreased functional capacity but increased choline affinity (Lockman and Allen,

2002), while *in situ* perfusion assays in rats have found no significant differences in function with age (Allen and Smith, 2001).

However, the aging process has been shown to affect the distribution of muscarinic receptors in the rat brain (Gurwitz *et al.*, 1987), and this suggests that similarly, older humans may have different responses to acetylcholine antagonists than younger human beings. In aged male and female rat brains, the density of muscarinic receptor distribution is decreased in the cerebral cortex, hippocampus, striatum, and the olfactory bulb, and is increased in male brain stems (Gurwitz *et al.*, 1987), so there may be sex differences in the way anticholinergic agents act in males and females to influence the outcome of delirium.

There are few anticholinergics prescribed in cardiology that have direct muscarinic blockade; the prototypical example is atropine, which is used for controlling vagally-stimulated bradycardia or heart block and increasing heart rate (Pappano and Katzung, 2004). However, atropine is not prescribed very commonly in Canada for hypertension[*]. Drugs that antagonize the nicotinic acetylcholine receptors are more commonly used in cardiology, especially during

[*]This is most likely because prescription recommendations by the Canadian Hypertension Education Program (CHEP Recommendations, 2010) suggest that 'first-line' drugs for treating hypertension should include peripherally-acting drugs like thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and long-acting calcium channel blockers (CCB); and if the individual is under the age of 60 years old, β-blockers. Centrally acting drugs such as atropine are only considered if blood pressure is still not controlled after double, triple, or quadruple therapy with peripheral agents like the ones mentioned above.

cardiac anesthesia where they are used as neuromuscular blocking agents; these include the drugs rocuronium, pancuronium, atracurium, and succinylcholine. Aside from atropine and the muscle relaxants, other drugs with some degree of anticholinergic activity that are commonly used in cardiac patients for treating target organ damage or co-morbidities include drugs that treat alimentary tract conditions, such as dimenhydrinate, prochlorperazine, and ranitidine; anticoagulants like warfarin; antiarrhythmic agents like digoxin, disopyramide and quinidine; diuretics like furosemide; calcium-channel blockers such as nifedipine; antidepressants including amitriptyline, desipramine, duloxetine, imipramine, nortriptyline, paroxetine and trimipramine; benzodiazepines like diazepam and oxazepam; and respiratory drugs like ipratropium (Cancelli *et al.*, 2009). However, there have been no studies published over the past 10 years that have found an association between any of these drugs (with the exception of diazepam) and delirium after cardiac surgery.

C. Antiadrenergics

Apart from a few case studies published in the past ten years reporting several substantial but rare CNS side-effects from metoprolol (see Fisher *et al.*, 2002; Ahmed *et al.*, 2010), there is unfortunately a very limited amount of recent evidence accrued from randomized controlled trials, prospective studies, interventional studies, or even retrospective studies for the influence of antiadrenergics on delirium after cardiac surgery. Most antiadrenergics prescribed in the cardiac surgery population act as direct α- and β-adrenoceptor

antagonists and are used for the treatment of hypertension, in large part, by decreasing peripheral vascular resistance and decreasing chronotopy, inotropy and conduction velocity of the heart (Hoffman, 2004); these include the beta-blockers metoprolol and bisoprolol, and the α_1-blocker terazosin. Metoprolol and bisoprolol are both very commonly used antihypertensives in Canadian cardiac patients, but metoprolol has been suggested to affect delirium after cardiac surgery in a number of case studies (Fisher *et al.*, 2002; Ahmed *et al.*, 2010), while bisoprolol has not. Both are predominately cardioselective β_1-adrenoceptor antagonists with no intrinsic sympathomimetic activity, although metoprolol does have low affinity for the β_2-adrenoceptor that is approximately 50-100 fold less potent than that of propranolol (Benowitz, 2004).

To compare the lipophilicity of metoprolol and bisoprolol, the pH-dependent distribution coefficients (logD) for both compounds were computed in one study under physiological conditions, at pH 7.4, and 37°C, by using quantitative structure-property relationship (QSPR) algorithms with physicochemical data obtained from a number of other studies (Yamazaki and Kanaoka, 2004). The water/n-octanol ratio for bisoprolol was 0.37, and 0.01 for metoprolol (Yamazaki and Kanaoka, 2004). This suggests that bisoprolol is approximately 2.3-times more hydrophilic than metoprolol, and is thus slightly less lipid soluble. This may explain why metoprolol has been implicated in delirium whereas bisoprolol has not. Differences in lipophilicity may be explained by looking at the chemical structures of metopolol and bisoprolol. Structurally,

both metoprolol and bisoprolol are para-substituted phenyls. The substituent on the 1-carbon in the benzene ring in metoprolol is an alcohol functional group that also contains an ether group and an amine while the subsituent on the 4-carbon is an ether functional group. Bisoprolol, on the other hand, is a bulkier, more nucleophilic compound: it contains a total of one alcohol, one amine, and three ethers; this would explain its greater polarity than metoprolol. In addition to being more lipophilic, metoprolol is also known to have mild anticholinergic effects (Han *et al*., 2001). In one rating system of the anticholinergic effect of drugs, metoprolol was given a rating of 1 on a 3-point scale, with a score of 3 indicating the highest degree of cholinergic antagonism (Han *et al*., 2001). Although this scale was based on clinicians' prior experiences with the drugs, and not based on measurable binding assays, this observation additionally increases suspiciousness around the ability of metoprolol to precipitate delirium after cardiac surgery.

D. Statins

Preoperative use of statins has paradoxically been shown to be both protective (Katznelson *et al*., 2009) and predictive (Redelmeier *et al*., 2008) of delirium after cardiac surgery. In the study that demonstrated that the preoperative use of statins may be predictive of postoperative delirium, Redelmeier *et al*. (2008) retrospectively looked at preoperative statin use in two types of surgeries– cardiac surgeries, and non-cardiac surgeries – and found that while statin use was significantly associated with delirium in both types of

surgeries, only patients who were receiving non-cardiac surgeries and who were taking preoperative statins had increased odds of developing delirium. Statin use was not found to increase the odds of developing delirium after cardiac surgeries, nor did any other cardiac medications that were studied (Redelmeier *et al.*, 2008). On the other hand, Katznelson *et al.* (2009) prospectively found that patients who were taking preoperative statins (mostly atorvastatin) had half the odds of developing delirium after cardiac surgery as individuals who were not taking statins, but interestingly, this relationship between statin use and delirium was only true for patients aged 60 years and older. Other studies that looked at rate of delirium after cardiac surgery have failed to find a significant association of postoperative delirium with preoperative statin use in either direction (e.g., Hudetz *et al.*, 2009; Burkhart *et al.*, 2010), but this may have been due to the much smaller sample sizes and lower frequency counts of patients who were taking statins in these studies. One confounding factor that was not controlled for in the Katznelson *et al.* (2009) study, but was considered in the Redelmeier *et al.* (2008) study, was the incidence of atherosclerosis in their samples. This is important is because atherosclerosis has been shown to be an independent risk factor for delirium after cardiac surgery (Marcantonio, 2008; Rudolph *et al.*, 2005).

It seems that statins do not require direct entry into the brain in order to exert a CNS effect. One explanation for how statins may influence the risk for delirium relates to the inflammation hypothesis of delirium etiology. Statins

impart antiinflammatory properties by upregulating the expression of endothelial nitric oxide synthase (eNOS) (Marcantonio, 2008). Nitric oxide produced by eNOS inhibits inflammation in blood vessels by blocking the secretion of cytokines from endothelial cells (Vaughan and Delanty, 1999). In light of the inflammation hypothesis, this means that the chances of developing delirium are reduced with statin administration. Futhermore, the upregulated eNOS can mediate vasodilation. While Redelmeier *et al*. (2008) suggest that the vasodilation caused by statins could shunt blood away from neurons in the postoperative period to increase the odds of delirium, it is also possible to say the opposite – that blood flow may be increased in the cerebral vasculature – if there is no evidence to show that vasodilation occurs to a greater extent in the periphery than within the CNS after statin administration. In fact, statins have been described to be 'neuroprotective' by some investigators because of its vasodilatory effect (Vaughan and Delanty, 1999), but increased cerebral blood flow from vasodilation may not be a completely beneficial outcome either. Increased blood flow could promote hypermetabolism and inflammation, and both of these mechanisms have been implicated in postoperative delirium (Fricchione *et al*., 2008). Statins are also associated with decreased levels of nuclear factor-κB and tumor necrosis factor in the body, which are both important for maintaining synaptic function (Drummond *et al*., 2010). Some research has shown that synaptic function may also be disrupted when statins interfere with the ability of membrane lipid rafts (comprised mostly of cholesterol) to enhance

intracellular signaling in neurons, which could lead to eventual neurotoxicity (Drummond *et al*., 2010). By decreasing the levels of certain immunological proteins that are important for proper synaptic communication, and by interacting with the cholesterol in membrane lipid rafts, statins may disrupt proper synaptic communication and increase the likelihood of postoperative delirium.

E. Antihypertensives

Antihypertensives have been linked to postoperative delirium in other settings, such as after vascular surgery (Katznelson *et al*., 2009), but no antihypertensives have been shown to be significantly associated with delirium after cardiac surgery. Studies that looked at preoperative medication use have recorded differences in the use of nitrates, beta-blockers, diuretics, calcium channel blockers, and ACE inhibitors, but failed to reveal any significant correlations (Afonoso *et al*., 2010; Hudetz *et al*., 2009; Maldonado *et al*., 2009; Rudolph *et al*., 2008; Tan *et al*., 2008; Santos *et al*., 2004). Rudolph *et al*. (2008) did find that non-delirious patients were more likely to have hypertension than delirious patients, but there were no significant differences in use of preoperative beta-blockers, ACE inhibitors, angiotensin-receptor blockers, calcium channel blockers, nitrates, or diuretics between the two groups. All of these studies grouped antihypertensive medications into a single category, and none of them reported differences between specific drugs or even stated that they recorded such data. Grouping of the drugs into one category could have been an *a posteriori* decision that came about in these studies because there were low

frequency counts for specific drugs, but this problem could be mitigated with more detailed data abstraction or larger sample sizes. Thus, it is possible that information may be missing about significant associations between a specific antihypertensive medication (most likely one with some degree of anticholinergic activity) and delirium after cardiac surgery.

F. Anesthetic Drugs

In order to properly address the role of anesthetic drugs in delirium, it is necessary to discuss another form of delirium that occurs in patients just as they emerge from a sedated, anesthetized state. This form of delirium, known as 'emergence delirium', is different from postoperative delirium in the timing of its onset. Emergence delirium occurs concurrent to or immediately following awakening from sedation, while postoperative delirium by definition develops after a lucid period, within 30 days after surgery (Sharma *et al*., 2005). These two forms of delirium may or may not be etiologically different. Emergence delirium is generally attributed to the effects of anesthetic agents, and usually resolves within minutes to hours without residual long-term consequences (Jithoo, 2008). Postoperative delirium, on the other hand, is attributed to multiple causes (perhaps including anesthesia), takes hours or days to resolve, and may predict long-term consequences like permanent cognitive dysfunction, other morbidities, and even early mortality. If the anesthetic agents traditionally used in cardiac surgery do contribute to the development of postoperative delirium, then it should become a priority to reassess conventional cardiac anesthesia for the

reasons listed above. In prospective studies published over the past 10 years that looked at the risk factors for delirium after open-heart surgery on cardiopulmonary bypass, only the use of the anesthetic drugs fentanyl (Burkhart *et al.*, 2010) and diazepam (Santos *et al.*, 2004) have been found to be independently predictive of postoperative delirium, while ketamine (Hudetz *et al.*, 2009) has been shown to be associated with a decrease in the incidence of delirium after cardiac surgery.

Patients receiving higher total doses of fentanyl per kilogram of body weight during cardiac surgery with cardiopulmonary bypass were considerably more likely to become delirious than those who were on lower doses (Burkhart *et al.*, 2010). Even after correcting for an important confounding variable, operation time, multivariate logistic regression predicted that for every 10-μg/kg increase in dose, an individual would be 3.4 times more likely to become delirious (Burkhart *et al.*, 2010). The risk that fentanyl imparts is likely not due to its central anticholinergic effects, which has been described to be minimal (Han *et al.*, 2001), because recent work has been unable to replicate earlier findings demonstrating that fentanyl affects serum anticholinergic levels (Chew *et al.*, 2008; Burkhart *et al.*, 2010). Apart from fentanyl, no other opioids (including sufentanil) have been reported in the cardiac surgery literature to show a significant positive or negative association with postoperative delirium. It is unclear whether this association between fentanyl use and increased incidence of postoperative delirium is due to the pharmacologic action of fentanyl acting

directly on opioid receptors, or if the onset of delirium is somehow affected by sedation depth. One double-blind, randomized controlled trial that looked at 114 elderly patients receiving hip fracture repairs under spinal anesthesia with propofol sedation reported that light sedation decreased the incidence of delirium by 50% compared to deep sedation, and that those that did develop delirium in the light sedation group spent considerably less time in the delirious state than those in the deep sedation group (Sieber *et al.*, 2010). Despite the fact that this study was conducted in a different surgical setting using different anesthetic techniques compared to cardiac surgery, it still suggests that the sedative effect of fentanyl could impart an influence on the development of postoperative delirium.

Benzodiazepines and their derivatives are another class of anesthetic drug that are implicated in the development of delirium after cardiac surgery. The use of 5-10 mg oral diazepam as a pre-anesthetic was associated with an increased incidence of delirium after coronary artery bypass graft surgery, but this relationship did not persist after multivariate analysis when all preoperative and surgical risk factors investigated were considered (Santos *et al.*, 2004).

Ketamine has paradoxically been shown to decrease the incidence of postoperative delirium after cardiac surgery (Hudetz *et al.*, 2009). Patients who randomly received a 0.5-mg/kg dose of intravenous ketamine during anesthetic induction, along with fentanyl and etomidate, had an incidence of delirium that was about ten times lower than in patients who received placebo (Hudetz *et al.*,

2009). There was also an association between ketamine usage and the levels of C-reactive protein in patients, whereby patients who were using ketamine had lower c-reactive protein levels (Hudetz *et al*., 2009). This led the authors to postulate that, similar to what Katznelson *et al*. (2009) thought about the anti-inflammatory and anti-thrombotic effects of statins, perhaps ketamine was conferring a protective effect by acting as an anti-inflammatory agent in the postoperative period to prevent cytokines from disrupting brain metabolism (Hudetz *et al*., 2009). Another reason why ketamine may be associated with a decreased rate of postoperative delirium may be because using ketamine reduces postoperative opioid consumption during the first 48-hours after cardiac surgery since it is able to serve as an adequate adjunct to analgesic management for pain from sternotomies (Lahtinen *et al*., 2004). One thing to note about the Hudetz *et al*. (2009) study is that along with ketamine, fentanyl was also given during anesthesia, in doses varying between 3-10-μg/kg for induction and between 650-2,050-μg for maintenance, but the total amount of fentanyl received during surgery did not statistically differ between the placebo group and the ketamine group (Hudetz *et al*., 2009). Taking into consideration the results from the study by Burkhart *et al.* (2010), it may have been crucial for investigators in this study to calculate the total doses of fentanyl according to kilograms of body weight, since Burkhart *et al.* (2010) were able to find a significant association between fentanyl-use and postoperative delirium only when they normalized their doses in accordance to body weight.

G. Pharmacological Prevention of Delirium

The first step in pharmacological prevention of delirium is to prevent pharmacological withdrawal from drugs that patients were taking prior to surgery, including alcohol, opioids or benzodiazepines. Benzodiazepine withdrawal should be considered different from postoperative delirium (Higgins and Yared, 2001) because they are wrought from different etiology, but the two are often not easy to differentiate (Fricchione *et al*., 2008) and one may be quite easily misdiagnosed as the other. Therefore, it is important in the preoperative screening process to identify the regular or abusive use of alcohol, benzodiazepines, and opioids to improve the sensitivity of the diagnosis in the postoperative period.

When it comes to using a pharmacological agent to prevent delirium, two sedative-analgesics, ketamine and dexmedetomidine, have been shown to attenuate delirium after cardiac surgery and they both have been demonstrated to have neuroprotective effects (Ma *et al*., 2004; Hudetz *et al*., 2009). A description of the protective effects of ketamine demonstrated in the study by Hudetz *et al*. (2009) is reviewed above. Of particular interest to primary caregivers is the highly selective α-2 agonist dexmedetomidine, which has proven to be an especially promising preventative drug for postoperative delirium after cardiac surgery. Dexmedetomidine provides central anxiolysis and sedation without producing significant respiratory depression (Panzer *et al*., 2009) like the sedatives propofol and midazolam. This quality of dexmedetomidine makes it a

desirable drug for sedating cardiac surgery patients. Studies that have shown dexmedetomidine to be beneficial for postoperative delirium suggest that these effects may not only be due to its opioid-sparing properties, but could also be due to the fact that it produces minimal respiratory depression (Shehabi *et al*., 2009). Patients may be extubated while remaining sedated under dexmedetomidine and may be maintained under sedation for as long as necessary (Maldonado *et al*., 2009) so that homeostasis may be recovered and pain and anxiety may be kept under control (Campos *et al*., 2001). A study by Shehabi *et al*., (2009) compared the incidence of delirium after cardiac surgery in one group of patients who received postoperative sedation with dexmedetomidine to another group of patients who received morphine after surgery. While the incidence of delirium was not significantly different between the two groups, dexmedetomidine-treated patients did experience shorter durations of delirium and were extubated sooner than morphine-treated patients (Shehabi *et al*., 2009). But compared to the use of propofol or midazolam for postoperative sedation, however, the rate of delirium is decreased in dexmedetomidine-treated patients (Maldonado *et al*., 2009). One large difference between these two studies is the method by which they made their diagnoses of delirium; Shehabi *et al*. (2009) used a standardized diagnostic algorithm, the CAM-ICU, while Maldonado *et al*. (2009) used formal clinical diagnoses based on DSM-IV-TR criteria. This difference in diagnoses is also reflected in the incidences of delirium that were obtained for dexmedetomidine-treated patients from each study: 8.6% of dexmedetomidine patients from

Shehabi *et al*. (2009) had delirium, while only 3% of dexmiditomidine patients from Maldonado *et al*. (2009) had delirium. Shehabi *et al*. (2009) also reported that 15% of the patients who were treated with morphine developed delirium, while Maldonado *et al*. (2009) reported rates of 50% for both their propofol- and midazolam-treated groups. Since the CAM-ICU has lower sensitivity and specificity compared to formal diagnoses of delirium by clinicians (van Eijk *et al*., 2009), the incidences reported by Shehabi *et al*. (2009) may be overestimated compared to Maldonado *et al*. (2009). But even so, this suggests that regardless if dexmedetomidine is used for postoperative sedation, patients postoperatively sedated with morphine may potentially be at less risk for developing delirium than patients postoperatively sedated with propofol or midazolam.

The atypical antipsychotic risperidone, which is thought to antagonize dopamine D_2 and serotonin 5-HT_2 receptors, has been used for prevention of postoperative delirium. Risperidone is used in a number of facilities to treat delirium once it has been diagnosed, but because of its relatively long half-life, which can reach up to 20-hours in poor metabolizers due to the similar pharmacology of its active metabolite (Huang *et al*., 1993), it has been tested as a prophylaxis. When it is administered at a single dose of 1-mg o.d. immediately following awakening from sedation in the intensive care unit after cardiac surgery, it lowers the incidence of delirium to one-third the incidence that is seen in placebo-treated patients (Prakanrattana and Prapaitrakool, 2007). It is possible that 1-mg risperidone may be mediating this effect by producing sedation without

respiratory depression in these elderly patients, similar to the use of dexmedetomidine for postoperative sedation, although it is not known whether sedation was an effect that was seen with this dosing or not. In spite of these findings, the future of risperidone prophylaxis in cardiac surgery patients for preventing delirium is questionable since, adverse effects of risperidone, such as hypotension, symptomatic orthostasis, and cardiac arrest, have been reported to be associated with cardiovascular disease and its treatment (Zarate *et al.*, 1997). Compared to intravenous administration of ketamine and dexmedetomidine during anesthesia, another challenge to using risperidone for prophylaxis immediately upon awakening is maintaining adequate absorption of the drug in its oral form. The majority of patients experience nausea and emesis after surgery, and this would interfere with effective absorption of oral prophylactic treatments.

Table 2. Summary of recent studies that looked at drugs in relation to delirium after cardiac surgery

Authors	Year	Title	Journal	Design	Country	Sample	Average age	Surgeries	Diagnostic instruments	Number of assessments	Average duration of delirium	Incidence	Results
Santos *et al.*	2004	Risk factors for delirium in the elderly after coronary aftery bypass graft surgery	International Psychogeriatrics	Prospective	Brazil	N=220	69.74 (no delirium); 72.62 (delirium)	Nonemerg-ency CABG	DSM-IV	Daily up until POD#5, but also read nurses and physicians notes to make retrospective diagnoses as well; only considered assessments from POD #2 onward because they wanted to rule out the residual effects of emergence confusion/ agitation	Not reported	33.6%	No significant association between any preoperative diuretics, CCBs, beta-blockers, ACEi, nitrates, PPI and delirium (beta-blockers, p=0.179; closest drug class to significance was ACEi at p=0.088). Diazepam was associated with higher incidence of delirium (midazolam trending toward opposite effect, but no significance).
Prakanrat-tana and Prapaitra-kool	2007	Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery	Anesthesia and Intensive Care	Double-blind RCT	Thailand	N=126	61.3 (risperidone); 60.7 (placebo)	CABG, valve, others	CAM-ICU	Twice daily in ICU, and once daily in evening on ward	Not reported	11.1% (risperidone); 31.7% (placebo)	Risperidone decreased the incidence of delirium.
Rudolph *et al.*	2008	Chemokines are associated with delirium after cardiac surgery	Journal of Gerontology	Prospective	USA	N=42	74.7 (delirious); 73.9 (non-delirious)	CABG, valve, CABG+ valve	CAM, MMSE, Delirium Symptom Interview (DSI), MDAS, digit span test	Once preoperatively, daily postoperative beginning on POD #2	Not reported	29%	Recorded proportion taking preoperative ASA, NSAIDs, steroids, beta-blockers, ACEi/ARB, CCB, nitrates, and diuretics, but no significant differences between delirious and non-delirious patients.
Tan *et al.*	2008	Incidence and predictors of post-cardiotomy delirium	American Journal of Geriatric Psychiatry	Prospective	USA	N=53	66.8 (delirious); 61.5 (non-delirious)	Valve, CABG, valve+ CABG	CAM, Memorial Delirium Assessment Scale (MDAS), MMSE, recitation of months and days of week backward	Daily assessment from POD #1-7	Not reported	23%	No association between preoperative 'chemical dependency', preoperative 'other' anticholinergics, postoperative morphine equivalents and delirium. 'Chemical dependency' and 'other' anticholinergics were not defined.
Gamberini *et al.*	2009	Rivastigmine for the prevention of postoperative delirium in eldery patients undergoing elective cardiac surgery - A randomized controlled trial	Neurologic Critical Care	Double-blind RCT	Switzerland	N=57 (placebo); N=56 (rivastigmine)	74.4 (placebo); 74.1 (rivastigmine)	CABG, valve (both with or without bypass)	CAM, MMSE, CDT	Everyday until POD #6	3 (median, placebo); 2.5 (median, rivastigmine)	30% (placebo); 32% (rivastigmine)	No significant difference between incidence of delirium in placebo and rivastigmine groups (administered preoperatively with the intention of preventing delirium)

Table 2. Summary of recent studies that looked at drugs in relation to delirium after cardiac surgery

Authors	Year	Title	Journal	Design	Country	Sample	Average age	Surgeries	Diagnostic instruments	Number of assessments	Average duration of delirium	Incidence	Results
Shehabi *et al.*	2009	Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery	Anesthesiology	Double-blind RCT	Australia	N=306 (total); N=152 (dex-medetomidine); N=147 (morphine)	71.5 (dexmedetom-idine) 71 (morphine)	CABG, valve, CABG+valve	CAM-ICU	Once daily up to POD #5	2 (median, dexmede-tomidine); 5 (median, morphine)	8.6 % (dexmede-tomidine); 15% (morphine)	Postoperative dexmedetomidine and morphine were comparable for maintaining adequate sedation; incidence of delirium was comparable, but dexmedetomidine reduced duration of delirium, decreased intubation time, reduced the need for norepinephrine, and reduced the incidence of systolic hypotension. Incidence was lower in subgroup of patients receiving IABP and treated with dexmedetomidine. Dexmedetomidine patients had more bradycardia.
Hudetz *et al.*	2009	Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass	Journal of Cardiothoracic and Vascular Anesthesia	Prospective	USA	N=29 (placebo); N=29 (ketamine)	60 (placebo); 68 (ketamine)	CABG, valve replacement/ repair	Intensive Care Delirium Screening Checklist (based on DSM-IV)	Monitored and reassessed until POD #5	Not reported	3% (ketamine); 31% (placebo)	Incidence was significnatly lower in ketamine group; postoperative C-reactive protein was lower in ketamine group. Placebo patients were 13-times more likely to become delirious; ketamine likely works via an anti-inflammatory effect to reduce incidence of delirium.
Maldonado *et al.*	2009	Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery	Psychosomatics	Open-label, randomized	USA	N=30 per study arm (dexmedetomid ine, propofol, midazolam)	55 (dexmedeto-midine); 58 (propofol); 60 (midazo-lam)	Valve	DSM-IV-TR	Twice daily until POD #3	2 (mean, dexmedeto-midine); 3 (mean, propofol); 5.4 (mean, midazolam)	3% (dexmedeto-midine); 50% (propofol); 50% (midazolam)	Incidence was significantly reduced in postoperative dexmedetomidine group compared to propofol or midazolam; delirious patients had much longer durations of intensive care and total length of stay. No difference in preoperative medications.

Table 2. Summary of recent studies that looked at drugs in relation to delirium after cardiac surgery

Authors	Year	Title	Journal	Design	Country	Sample	Average age	Surgeries	Diagnostic instruments	Number of assessments	Average duration of delirium	Incidence	Results
Katznelson *et al.*	2009	Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery	Anesthesiology	Prospective	Canada	N=1059	Not reported	Cardiac surgeries on CPB, excluding congenital and redo surgeries	CAM-ICU	Once every 12 hours while in CSICU	Not reported	11.5%	Preoperative statin use in those aged ≥ 60 years was associated with reduced postoperative delirium; preoperative use of statins had a protective effect, reducing the odds of delirium by 46% (incidence with statins - 13%; incidence without statins - 20%)
Burkhart *et al.*	2010	Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass	Journal of Cardiothoracic and Vascular Anesthesia	Post-hoc analysis of a previously published prospective study	Switzerland	N=113	74.3	CABG, valve replacement	CAM	Daily starting on day before surgery until POD #6	Not reported (may be found in Gamberini et al., 2009)	30%	Postoperative CRP, intraoperative dose of fentanyl kg^{-1} body weight, duration of mechanical ventilation were independent risk factors. Fentanyl remained an independent risk factor even when the dose was corrected for surgery time; recent work not able to show an increase in serum anticholinergic activity with fentanyl administration, so this relationship may not be due to cholinergic deficiency
Afonso *et al.*	2010	Predictive model for postoperative delirium in cardiac surgical patients	Seminars in cardiovascular and vascular anesthesia	Prospective	USA	N=112	66	CABG, CABG+valve, valve, LVAD, aortic aneurysm repair, transplant, other	Richmond Agitation-Sedation Scale (RASS); CAM-ICU	Every 12 hours for the duration of ICU stay	Not reported	34%	No association between pre-op ACE-inhibitors and delirium. No association between preoperative medications (nitrates, benzodiazepines, SSRIs, ACEi, but only analyzed ACEi data since none of the other drug classes exceeded a frequency of 1)

RCT *randomized controlled trial*; CABG *coronary artery bypass graft*; CAM *confusion assessment method*; CAM-ICU *confusion assessment method for the intensive care unit*; MMSE *mini-mental state examination*; CDT *clock drawing test*; MDAS *memorial delirium assessment scale*; POD *postoperative day*; DSM-IV-TR *diagnostic and statistical manual, fourth, text-revised edition*; CRP *C-reactive protein*; IABP *intra-aortic balloon pump*; LVAD *left ventricular assist device*; CPB *cardiopulmonary bypass;* CCBs *calcium channel blockers*; ACEi *angiotensin converting enzyme inhibitor*; PPI *proton-pump inhibitor*; SSRI *selective serotonin reuptake inhibitor*; NSAID *non-steroidal anti-inflammatory drug*; ARB *angiotensin receptor blocker*; ASA *acetylsalicylic acid*

1.7 Other Risk Factors

Research into the risk factors for delirium is a popular area of investigation. It is commonly studied through retrospective chart reviews, prospective observational studies, and less commonly, through interventional experimental designs. In fact, the pilot study for this thesis was a retrospective chart-review that looked at risk factors for delirium in patients who had open-heart cardiac surgery during a 2-week period in 2007 at St. Paul's Hospital (Burns *et al*., 2009). This was the first study to report that alcohol consumption within the 7-days prior to surgery was identified to be the most significant risk factor in this population (Burns *et al*., 2009). Retrospective diagnoses of delirium were made according to the nurses' CAM ratings, the presence of DSM-IV-TR criteria in the medical progress notes, or if any of the attending physicians had recorded a diagnosis of delirium in the patients' charts (Burns *et al*., 2009), so sensitivity and specificity for delirium *per se* were crude. Thus, it is possible that the group was picking up on *delirium tremens*, which is delirium induced by alcohol withdrawal, rather than postoperative delirium induced by surgery and its associated elements (Burns *et al*., 2009). Besides this study, there have been a small number of clinical prediction algorithms published for postoperative delirium after cardiac surgery (e.g., Koster *et al.* 2008; Rudolph *et al*., 2009), and a few meta-analyses on the strongest independent risk factors (Smith and Dimsdale, 1989; van der Mast and Roest, 1996). Preoperative psychiatric intervention was identified in the earlier meta-analysis by Smith and Dimsdale (1989) as having

the strongest correlation with delirium in the negative direction, while things that are normally thought of as being prominent risk factors for delirium, such as older age, history of psychiatric illness, and time on bypass did not produce significant differences. Van der Mast and Roest (1996) challenged these findings in a follow-up meta-analysis of the same 44-studies that were reviewed by Smith and Dimsdale (1989) and concluded that in fact, no strong risk factors have yet been identified. In the fifteen years since this last meta-analysis, numerous studies have been published and over two hundred risk factors for delirium have been identified in the recent literature. With such a large number of potential risk factors, it is helpful to classify them as either 'modifiable' (e.g., incident factors) or 'non-modifiable' (e.g., predisposing factors) categories rather than consider them as individual factors (Culley, 2010, Burkhart *et al.*, 2010, Afonso *et al.*, 2010; Inouye and Charpentier, 1996).

Non-modifiable and modifiable types of risk factors are usually both evident in a patient who becomes delirious after cardiac surgery. Non-modifiable risk factors may be thought of as predisposing factors that increase the underlying vulnerability of an individual to develop postoperative delirium after cardiac surgery. Such characteristics include genetic risk factors, demographic risk factors, and risk factors pertaining to a patient's medical history. When predisposing factors are aggravated by incident factors that appear within the perioperative period of cardiac surgery, such as fluctuations in blood oxygen saturation, disturbances in the sleep-wake cycle, utilization of a large number of

drugs, and the experience of inflammation and pain, then the likelihood of a vulnerable patient to develop postoperative delirium becomes increased (Culley, 2010; Caraceni and Simonetti, 2009). Ideally, if the number of incident risk factors encountered in the perioperative period can be reduced (for instance, aggravating medications, as discussed above), then a vulnerable patient who undergoes cardiac surgery could likely be saved from experiencing severe postoperative delirium. However, non-modifiable risk factors are more difficult to manage, and several important ones will be mentioned below.

A. Genetics

Previous authors have identified many predisposing factors that influence a patient's underlying vulnerability to postoperative delirium, but there are some factors that remain contentious, while others tend to reappear as significant predictors of delirium time and time again. The existence of a genetic component for postoperative delirium is one controversial issue that has yet to be resolved, mostly because of a lack of control over confounding variables in these studies, although for a multi-causal condition like delirium to be strongly influenced by genetics is not unlikely (Wijeysundera and Katznelson, 2010). One important gene that has been shown to be associated with postoperative delirium is the apolipoprotein E-ε4 allele (APO-E4), which produces a lipoprotein that is important for acetylcholine synthesis. Patients who are have one copy of the APO-E4 allele have been demonstrated to be more likely to develop postoperative delirium within the 48-hour period after non-cardiac surgery (Leung

et al., 2007). However, a recent study on patients receiving vascular surgery showed that the development of delirium did not statistically correlate with the presence of the APO-E4 allele (Bryson *et al.*, 2011). A moderate odds ratio was calculated from these data (OR = 1.63, n = 88), so it could be that this study may have just been underpowered for producing a statistically significant effect (Wijeysundera and Katznelson, 2010). It is also possible that this association might simply be stronger in patients who receive non-vascular surgeries (Wijeysundera and Katznelson, 2010). Genetic predisposition to developing postoperative delirium may indeed have clinical significance, despite a lack of statistical significance (Wijeysundera and Katznelson, 2010). Other genes that could potentially affect a person's predisposition to postoperative delirium include genes that code for regulators of neurotransmitter metabolism or neurotransmission, such as cathechol-o-methyl transferase (COMT), an enzyme necessary for the synthesis and breakdown of dopamine, and monoamine oxidase A (MAO-A), an enzyme necessary for the deamination of the monoamine neurotransmitters (Morandi *et al.*, 2009).

B. Age

Advanced age is generally considered by clinicians to be an independent risk factor for developing delirium after cardiac surgery. Possible age-related neurobiological and physiological changes that could compromise the functional integrity of neurons after cardiac surgery include decreased neuroplasticity, cerebral atrophy, diminished blood flow, altered neurotransmitter release,

different membrane receptor profiles, and destabilization of the blood-brain barrier (Parikh and Chung, 1995). In a clinical setting, these maturation processes have important implications for the anesthetic and analgesic regimen that is used during surgery, since these changes affect the pharmacokinetics and metabolism of the drugs that are given to these patients. It is difficult to say what aspects of the neurobiology of old age causes postoperative delirium, or if the increased risk imparted by old age is due to some confounding variable. Most studies that treat age as a categorical variable report significantly increased odds of developing postoperative delirium in people over 60 years of age; such studies commonly show that older individuals are more than twice as likely to become delirious after surgery than younger individuals (e.g., Katznelson *et al.*, 2009 (OR = 2.47); Kazmierski *et al.*, 2006 (OR = 4); Norkiene *et al.*, 2007 (OR = 3.82)). When treated as a continuous variable, however, there appears to be greater inconsistency amongst studies in describing the relationship between age and delirium (for instance, Burns *et al.*, 2009, Detroyer *et al.*, 2008, Rudolph *et al.* 2006 were all unable to identify age as an independent predictor of delirium after using logistic regression). In a conversation with A.M. Barr, PhD., (personal communication, October 2010), it was suggested that the reason age may not demonstrate an association with delirium when it is analyzed continuously is because this relationship between age and delirium could follow a sigmoidal function rather than a linear one. If this truly were the case, then patients with ages that fall above or below the linear portion of this relationship between age

and delirium would show no such association. In practice, clinicians have determined that age does have a significant clinical significance for putting older patients at much greater risk for postoperative delirium after cardiac surgery than younger patients because this is often a question in preoperative assessment tools.

C. Preoperative Cognitive Impairment

Independent of old age, pre-existing cognitive impairment has been shown to be a specific risk factor for delirium after open-heart surgery. Impairments in higher order cognition, such as executive function and memory, are especially important factors that can lead to a state of transient confusion following cardiac surgery (Rudolph *et al.*, 2006).

1.8 Associated Outcomes and Long-Term Complications

Delirium after cardiac surgery is associated with highly detrimental outcomes and economic costs. Delirium predicts mortality up to 10 years following surgery (Gottesman *et al.*, 2010), and it predicts premature death within a year after surgery (Leslie *et al.*, 2005). Having delirium increases the length of time spent in intensive care, as well as the total length of hospitalization (Prakanrattana and Prapaitrakool, 2007).

Since delirium usually appears within the first three postoperative days and frequently precedes the onset of other postoperative complications, it may be

thought of as a complication that increases the risk of other complications, rather than a symptomatic consequence of other complications (Brouquet *et al.*, 2010). For instance, in a study of 14,301 patients who received coronary artery bypass graft surgery, delirium was demonstrated to be an independent predictor of postoperative sepsis (Martin *et al.*, 2010).

There is little doubt that the occurrence of incidental delirium is associated with changes in long-term cognition (Jackson *et al.*, 2004; MacLullich *et al.*, 2009). In these patients, the surgical trauma that is experienced may simultaneously trigger the onset of acute delirium and chronic cognitive impairment, or delirium may be acting as a marker of chronic progressive pathology, or delirium may be the direct cause of permanent cognitive dysfunction (MacLullich *et al.*, 2009). Related to cognitive abnormalities, postoperative delirium also predicts greater risk of functional decline 1 month after surgery; patients who develop longer periods of postoperative delirium are less likely to be independent after their surgeries (Rudolph *et al.*, 2010).

In circumstances where symptoms of delirium persist, then the condition itself becomes a relatively long-term complication and is known as prolonged delirium. In the context of hip fracture surgery, prolonged delirium lasting well into the post-discharge period may occur in as many as 20% of delirious patients (Lee *et al.*, 2011). Prolonged delirium may occur more frequently in patients with pre-existing dementia, a large number of co-morbidities, or hypoxic illness, and

may develop from deliria characterized by higher proportions of hypoactive symptoms (Dasgupta and Hillier, 2010).

1.9 Percutaneous Transcatheter Aortic Valve Implantation

Patients with severe aortic stenosis who require aortic valve replacement, but whom are deemed non-surgical were once quite limited with regards to their treatment options, and available pharmacological therapies provided only symptomatic relief but never treated the underlying causes. Nowadays, however, in a small number of facilities in North America and many others around the world, a percutaneous alternative to open-heart surgery is offered to patients with severe aortic stenosis who are deemed to be high risk for open-heart surgery, and this procedure is called transcatheter aortic valve implantation (TAVI). TAVI procedures are minimally invasive techniques that are methodologically based on the same techniques as balloon angioplasty insertion for treating atherosclerosis. The valve devices that are implanted consist of a stainless steel stent that holds the valve in place within the patient's native, diseased aortic valve, and creates the framework for holding open the valve leaflets, which are taken from bovine sources. Initially, the valve is inserted in a crimped fashion and is mounted onto the end of a catheter, and is expanded once it reaches the intended position within the patient's own aortic valve. The insertion of this valve does not require a sternotomy and may be done within a catheterization laboratory. All transcatheter valve insertion techniques are performed under general anesthesia

with fluoroscopy for imaging purposes, but compared to open-heart surgery, patients undergoing TAVIs avoid prolonged, deep anesthesia, and CPB. The length of fluoroscopy does not usually exceed 20 minutes, which is the normal duration that occurs for angiogram procedures. Mortality and re-hospitalization rates are lower than traditional aortic valve replacement, and patients experience a greater reduction in the severity of cardiac symptoms compared to patients who undergo conventional valve replacement surgery (Leon *et al.,* 2010). Many different vascular routes have been described for inserting the specialized stented bioprosthetic valves into the proper location within the native valve of the heart. The very first percutaneous valve insertion was performed using a balloon-expandable, bovine-extracted jugular valve mounted on a stented frame, and it was inserted in an antegrade direction via the femoral vein to replace the native pulmonary valve in a child with an aortopulmonary shunt (Bonhoeffer *et al.*, 2000). Two years later, the first report was published for replacement of the aortic valve in a patient with peripheral vascular disease and severe aortic stenosis via a transseptal route (Cribier *et al.*, 2002). However, many of these techniques and devices were not without problems. Other surgeons have attempted to investigate the potential benefits of other valve models and vascular routes for valve insertion, including the use of self-expandable rather than balloon-expandable valves inserted via the iliac artery (Grube *et al.*, 2005), and the use of valves that could be repositioned once expanded (Buellesfeld *et al.*, 2008). There are two transcatheter valve insertion techniques that were first

performed and are now preferred by surgeons and cardiologists at St. Paul's Hospital in Vancouver, British Columbia, and they include a retrograde approach via the femoral artery (i.e., the 'transfemoral' approach; first described by Webb *et al.,* 2006), and an anterograde approach via a mini-thoracotomy and an apical puncture of the left ventricle (i.e., the 'transapical' approach; first described by Lichtenstein *et al.*, 2006). At St. Paul's, both procedures are offered to non-surgical patients only, since the valves that are implanted (Edwards SAPIEN™ Transcatheter Heart Valve Model 9000TFX) with these techniques are first generation devices that have not yet been approved by the FDA, so the safety and effectiveness of this currently experimental valve has not yet been approved for commercial use.

One remarkable possibility that TAVI presents to patients is that it is feasible to perform a valve-in-valve procedure, should the first implanted bioprosthesis fail. However, this technique, which one author describes with the analogy of the "Russian doll concept" (Piazza *et al.*, 2009), has never been compared against traditional re-do operations of open-heart aortic valve replacement in terms of complication rates and risks of mortality and morbidity, although the first study to describe the long-term outcomes this procedure reported normal ECG activity, normal transvalvular gradient, and no bioprosthesis migration or deterioration in a 3-year period following implantation (Ruiz *et al.*, 2008).

While there seems to be a consensus in the literature with regards to the health outcomes of TAVI over conventional surgery, there has yet to be any regard for the incidence of delirium in this particular population. Considering the fact that TAVI procedures do not require CPB, which is a factor of coronary artery bypass graft surgery that has been shown to be associated with delirium (Bucerius *et al*., 2004), it is possible that the the incidence of delirium might be lower compared to open-heart AVR. However, it may also be the case that because these patients are older and sicker, they may be at greater risk for developing delirium compared to surgical patients (e.g., Sockalingham *et al*., 2005). Knowing the implications of the issue of delirium in the surgical population, investigating its occurence in non-surgical TAVI patients should become a focus of high priority.

1.10 Research Question and Hypothesis

The purpose of this thesis was to retrospectively study the incidence and risk factors for delirium after cardiac surgery. A large database with more than 1200 variables was produced in order to address this topic, but because of the broadness of this scope, the work presented in this thesis was done exclusively on a specialized subset of cardiac patients in order to determine the incidence of and risk factors for delirium in patients who received transfemoral TAVI and transapical TAVI, compared to open-heart AVR as control.

It was hypothesized that the rates of delirium would be comparable across all three groups. This is because the greater surgical trauma and the need for cardiopulmonary bypass in open-heart AVR would make patients receiving this surgery more likely to have delirium, but the fact that only sicker, older patients undergo transcatheter TAVI procedures would mitigate the reduction of risk conveyed by the minimal invasiveness of TAVI. In other words, while the modifiable risk factors probably play a greater role in open-heart AVR, the non-modifiable risk factors probably play a greater role in TAVI patients to equalize the rate of delirium. Chi-square analysis will determine if the incidences of delirium between valve replacement procedures significantly differ.

2 Methods

2.1 Study Design and Patient Selection

A retrospective cohort study was performed at St. Paul's Hospital in order to investigate the incidence and risk factors for delirium after transfemoral TAVI, transapcial TAVI, and open-heart AVR surgery. Ethical approval was granted from the University of British Columbia Providence Health Care Research Ethics Board.

The first 45 patients to receive transfemoral and transapical TAVI, and a random selection of 45 open-heart AVR patients who underwent surgery between January 2008 and December 2009 were selected from lists of patients generated by Health Records Services at St. Paul's (total n=135 patients). The reason sample sizes were limited to 45 patients in each group is because only 45 transfemoral TAVI procedures were performed between 2008 and 2009. TAVI patient list was generated with the search filter: "inpatient transfemoral and transapical heart valve insertions for Jan 01/08 to Dec 31/09 discharges". Open-heart AVR patients were included for comparison purposes against TAVI patients, and they were selected from a list of open-heart cardiac surgery patients from 2008 only that included coronary artery bypass graft patients, heart transplant patients, and patients who received other types of valve replacements. When all aortic valve replacement patients had been extracted from this list, there were a total of 152 patients. From this number, 45 AVR patients were randomly chosen using random number assignment and selection. Baseline

characteristics were not matched between groups to allow for all potential risk factors to be identified and compared. No exclusion criteria were applied so that the largest sample sizes could be obtained, and also so that all potential risk factors may be identified.

At St. Paul's, patients are selected for TAVI if they meet the cardiac surgeon's personal evaluation to be deemed 'non-surgical'. Evaluations usually include calculating a patient's Society of Thoracic Surgeons (STS) score or the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which determine the risk for mortality and morbidity following the procedure. In the case of transfemoral TAVI, a surgeon will perform a CT scan as a part of the evaluation in order to determine if the inner circumference of the femoral artery, from the puncture site to the iliac artery, is at least 6 mm wide to allow for the passage of the catheter. If patients meet, or for some tests, fail to meet these criteria, then he or she is deemed non-surgical and may be offered the transfemoral TAVI procedure. If a non-surgical patient has advanced peripheral vascular disease or tortuosity of the vasculature, then he or she may be considered for transapical TAVI instead of transfemoral TAVI.

Two abstractors completed all the reviews. An estimate of inter-rater reliability was calculated by establishing the percent agreement between the two abstractors, and this was found to be 96%. The same medical documents were used to extract data for each variable, so all efforts were taken to ensure that data collection remained consistent and objective.

2.2 Determining Potential Risk Factors and the Data Extraction Process

The potential risk factors for postoperative delirium were accrued through an in-depth literature search of studies that were specifically interested in delirium after cardiac surgeries. Out of the 22 studies published from the past 10 years, over 200 potential preoperative, intraoperative, and postoperative risk factors were identified, and over 1000 more were added to the database, and these were based on the interests of the investigators. In total, 1245 variables were extracted for each patient chart that was reviewed (see **Table 3** for a complete list of these variables). This information included details on patient demographics, past medical history, laboratory values, pharmacological treatments, surgical details, and postoperative management. An annotated version of this database was used to collect information on the transcatheter patients, since some of the surgical and bypass variables did not apply to them. For most categorical variables, patients were considered to have the condition if an obvious note was seen in the medical records; in some cases, specifically for conditions like respiratory acidosis or hypoxia, which were conditions that had to be determined by studying the laboratory values (see **Table 4** for definitions of these variables). Patient medical charts were accessed through an electronic health records system (Sunrise Clinical Manager, Eclipsys Corp., Boca Raton, Fla). All the data were kept in an Excel (Microsoft Corp., Redmond, WA) spreadsheet, and a separate patient coding list was saved as another Excel file

to ensure that identifiable information was not kept in the same spreadsheet as the medical data.

Table 3. Complete list of variables obtained from medical charts

Preoperative Variables			Intraoperative Variables	Postoperative Variables		
Age	BMI	Pantoprazole	Surgeon	Time in ICU	Prochlorperazine (POD #0, 1, 2, 3)	Allopurinol (POD #0, 1, 2, 3)
Sex	Obesity	Lansoprazole	Anesthetist	Readmission to ICU within 1 week	Dimenhydrinate (POD #0, 1, 2, 3)	Methyldopa (POD #0, 1, 2, 3)
Race	Pulmonary hypertension	Ranitidine	Surgery time	Time in CCU	Metoclopramide (POD #0, 1, 2, 3)	Tamsulosin (POD #0, 1, 2, 3)
Marital status	Hypertension	Furosemide	Anesthesia time	Length of hospitalization	Loperamide (POD #0, 1, 2, 3)	Candesartan (POD #0, 1, 2, 3)
Living situation	Dyslipidemia	Metolazone	Urgency	Restraints used	Insulin (POD #0, 1, 2, 3)	Losartan (POD #0, 1, 2, 3)
Postal code	Hypercholesterolemia	HCTZ	Elective surgery	Discharged to clinic	Metformin (POD #0, 1, 2, 3)	Amlodipine (POD #0, 1, 2, 3)
Preoperative diagnosis (aortic stenosis: congenital-bicuspid; aortic stenosis: degenerative; aortic stenosis: prosthetic valve dysfunction; aortic stenosis: rheumatic; aortic stenosis: native valve endocarditis; aortic regurgitation: prosthetic valve dysfunction; aortic regurgitation: iatrogenic; aortic regurgitation: degenerative; aortic regurgitation: native valve endocarditis; mitral regurgitation: native valve endocarditis; mitral stenosis: degenerative; mitral stenosis: prosthetic valve dysfunction; mitral regurgitation: myxomatous; mitral regurgitation: degenerative: mitral regurgitation: ischemic; tricuspid regurgitation: degenerative; tricuspid regurgitation: unknown; pulmonary valve disease; triple vessel disease; double vessel disease; single vessel disease; ventricular septal defect: ischemic; congenital heart disease: ventricular septal defect; congenital heart disease: atrial septal defect; congenital heart disease: patent foramen ovale; Wolff-Parkinson-White Syndrome; left ventricular aneurysm; cardiomyopathy: ischemic; cardiomyopathy: dilated; ventricular tachycardia; supraventricular tachycardia; ascending aorta: atherosclerotic; ascending aorta: collagen; saphenous vein graft aneurysm; complete heart block; peripheral vascular accurate dissection; aortic root aneursym; endocarditis: bacterial)	Aortic stenosis	Spironolactone	CABG	Code white	Glyburide (POD #0, 1, 2, 3)	Diltiazem (POD #0, 1, 2, 3)
	Carotid stenosis	Indapamide	Number of vessels grafted	Violence	Gliclazide (POD #0, 1, 2, 3)	Felodipine (POD #0, 1, 2, 3)
	Mitral stenosis	Ipratropium	Valve replacement (xenographic; prosthetic)	Readmission to the hospital after discharge for cardiac problems	Pioglitazone (POD #0, 1, 2, 3)	Nifedipine (POD #0, 1, 2, 3)
	Pulmonary stenosis	Tiotropium	Transcatheter valve replacement (transfemoral; transapical)	Re-exploration for bleeding	Dextrose (POD #0, 1, 2, 3)	Verapamil (POD #0, 1, 2, 3)
	Atherosclerosis	Oxybutynin	Total fluoro time	Pleural effusion	Heparin (POD #0, 1, 2, 3)	Phenylephrine (POD #0, 1, 2, 3)
	Atrial fibrillation	Atropine	Amount of fluoro	IABP	Enoxaparin (POD #0, 1, 2, 3)	Beclomethasone (POD #0, 1, 2, 3)
	Aortic insufficiency	Butylscopolamine	Combination CABG + valve (xenographic; prosthetic)	Mortality within 24-hours	Warfarin (POD #0, 1, 2, 3)	Hydrocortisone (POD #0, 1, 2, 3)
	Mitral insufficiency	Metoprolol	Heart transplant	Mortality at the time chart was reviewed	Integrilin (POD #0, 1, 2, 3)	Prednisone (POD #0, 1, 2, 3)
	Tricuspid insufficiency	Bisoprolol	Additional procedures	Psychiatry consult	Clopidogrel (POD #0, 1, 2, 3)	Meythlprednisone (POD #0, 1, 2, 3)
	Pulmonary insufficiency	Atenolol	Cardiac index	Myocardial infarction	Amiodarone (POD #0, 1, 2, 3)	Tacrolimus (POD #0, 1, 2, 3)
	CAD	Sotalol	Total intubation time	Hypotension on POD #0	ASA (POD #0, 1, 2, 3)	Triamcinolone (POD #0, 1, 2, 3)
	LVH	Carvedilol	Reintubation	Creatinine (POD #0, 1, 2)	Dobutamine (POD #0, 1, 2, 3)	Docusate (POD #0, 1, 2, 3)
	Left ventricular dysfunction	Betaxolol	Intraoperative fluid	Peak creatinine	Salbutamol (POD #0, 1, 2, 3)	Digoxin (POD #0, 1, 2, 3)
	Ventricular arrhythmia	Acebutalol	Cell saver (volume lost; volume processed)	Urea (POD #0, 1, 2)	Metoprolol (POD #0, 1, 2, 3)	Methylene blue (POD #0, 1, 2, 3)
	Cardiac arrhythmia	Propranolol	Hemofiltration volume	Renal insufficiency	Bisoprolol (POD #0, 1, 2, 3)	Protamine (POD #0, 1, 2, 3)
	Brunch blockade	Salbutamol	Intraoperative complications	Renal failure	Atenolol (POD #0, 1, 2, 3)	Simvastatin (POD #0, 1, 2, 3)
	Depolarization alteration	Salmeterol	Need for pacemaker stimulation (ventricular; atrial)	Lowest GFR	Labetolol (POD #0, 1, 2, 3)	Pravastatin (POD #0, 1, 2, 3)
	Most recent NYHA	Budesnoide-formoterol	IABP	Glucose (POD #0, 1, 2)	Sotalol (POD #0, 1, 2, 3)	Atorvastatin (POD #0, 1, 2, 3)
	Worst NYHA	Nadolol	Vascular conduits	Urine output (POD #0, 1, 2)	Timolol (POD #0, 1, 2, 3)	Rosuvastatin (POD #0, 1, 2, 3)
	Unstable angina	Levobunolol	Cardioplegia	Fluid balance (POD #0, 1, 2)	Nadolol (POD #0, 1, 2, 3)	Fenofibrate (POD #0, 1, 2, 3)
	Most recent CCS	Terazosin	Temperature on cardioplegia	Total bilirubin (POD #0, 1, 2)	Acebutolol (POD #0, 1, 2, 3)	Ezetimibe (POD #0, 1, 2, 3)
	Worst CCS	Clonidine	Longest interval off cardioplegia	Hypoxia	Salmeterol (POD #0, 1, 2, 3)	Sennosides (POD #0, 1, 2, 3)
	STS score	Methyldopa	Total duration off cardioplegia	PCO2 (POD #0, 1, 2)	Carvedilol (POD #0, 1, 2, 3)	Zopiclone (POD #0, 1, 2, 3)
	IABP before surgery	Loratidine	Pump number	Arterial oxygen saturation (POD #0, 1, 2)	Fluticasone-salmeterol (POD #0, 1, 2, 3)	Loxapine (POD #0, 1, 2, 3)
	Stroke/TIA	Tamsulosin	CPB	PO2 (POD #0, 1, 2)	Esmolol	Seroquel (POD #0, 1, 2, 3)
	Cerebrovascular disease	Doxazosin	Beating-heart surgery	Average fractional inspired O2 (POD #0, 1, 2)	Budesonide-formoterol (POD #0, 1, 2, 3)	Raloxifene (POD #0, 1, 2, 3)
	Peripheral vascular disease	Hydralazine	CPB time	Poor nutritional status	Quinine sulfate (POD #0, 1, 2, 3)	Haloperidol (POD #0, 1, 2, 3)
	Type II diabetes	Aliskiren	Prolonged CPB	Infection	Theophylline (POD #0, 1, 2, 3)	Risperidone (POD #0, 1, 2, 3)
	Type I diabetes	Allopurinol	Average pump flow	Blood transfusion (packed red blood cells, plasma, platelets)	Furosemide (POD #0, 1, 2, 3)	Methotrimeprazine (POD #0, 1, 2, 3)
	Mulitple organ dysfunction syndrome	Amiodarone	Cross-clamp time	Hemoglobin (POD #0, 1, 2)	HCTZ (POD #0, 1, 2, 3)	Hydroxychloroquine(POD #0, 1, 2, 3)
	Infection	Propafenone	Initial pulse	White blood cell count (POD #0, 1, 2)	Ramipril (POD #0, 1, 2, 3)	Dexamethasone (POD #0, 1, 2, 3)
	Cancer	Triamcinolone	Initial blood pressure	Hematocrit (POD #0, 1, 2)	Captopril (POD #0, 1, 2, 3)	Mycophenolate (POD #0, 1, 2, 3)
	COPD	Fluorometholone	Lowest systolic blood pressure	Platelets (POD #0, 1, 2)	Lisonopril (POD #0, 1, 2, 3)	Cyclosporine (POD #0, 1, 2, 3)
	Asthma	Fluticasone-salmeterol	Highest systolic blood pressure	Hypoalbuminemia	Enalapril (POD #0, 1, 2, 3)	Voluven (POD #0, 1, 2, 3)
	Dyspnea	Quinine sulfate	Highest pulse	Hypernatremia	Trandolapril (POD #0, 1, 2, 3)	Phenytoin (POD #0, 1, 2, 3)
	Renal disease	Hydroxyquinoline	Lowest central venous pressure	Hyponatremia	Donepezil (POD #0, 1, 2, 3)	Bupropion (POD #0, 1, 2, 3)
	Dialysis	Pentoxifylline	Lowest pulmonary artery diastolic pressure	Sodium (POD #0, 1, 2)	Perindopril (POD #0, 1, 2, 3)	Pentastarch (POD #0, 1, 2, 3)
	Neurological dysfunction	Cephalexin	Highest pH	Potassium (POD #0, 1, 2)	Ranitidine (POD #0, 1, 2, 3)	Levodopa-Carbidopa (POD #0, 1, 2, 3)
	Anxiety disorder	Ciprofloxacin	Lowest pH	Metabolic acidosis	Rabeprzole (POD #0, 1, 2, 3)	Citalopram (POD #0, 1, 2, 3)
	Depression	Amoxicilin	Highest PCO2	Respiratory acidosis	Pantoprazole (POD	Escitalopram (POD #0, 1, 2, 3)
	Other psychiatric impairment	Rifampicin	Lowest PCO2	pH (POD #0, 1, 2)		Tramadol (POD #0, 1, 2, 3)
	Schizophrenia	Mupirocin	Fluid balance	Alkaline phosphatase (POD #0, 1, 2)		Amitriptyline (POD #0, 1, 2, 3)
	Psychiatric impairment in anamnesis	Metronidazole	Urine output	Alanine transaminase (POD #0, 1, 2)		
	Dementia	Clarithromycin	Lowest venous temperature	Aspartate aminotransferase (POD #0, 1, 2)		
	Physical impairment	Chlorhexidine	Anoxic cerebral damage	Gamma GT (POD #0, 1, 2)		
	Cognitive impairment	Acetaminophen	Lowest hematocrit	Lactate dehydrogenase (POD #0, 1, 2)		
	Vision impairment	Vancomycin	Lowest hemoglobin	Base excess		
	Hearing impairment	Cefazolin	Blood tranfusion (packed red blood cells, plasma, platelets)	Pneumonia		
	Pain rating	Cefuroxime	Estimated blood loss	Fever		
	Disturbed sleep	Diltiazem	Hyperkalemia	Low body temperature		
	Hemoglobin	Diazepam	Hypokalemia	Pain		
	Hematocrit	Nifedipine	Hyponatremia	Mobility issues		
	INR	Felodipine	Metabolic acidosis	Sensory disturbance		
	PTT	Amlodipine	Metabolic alkalosis	Stroke		
	White blood cell count	Verapamil	Respiratory acidosis	Ejection fraction		
	Sodium	Cyclosporine	Respiratory alkalosis	Low cardiac output syndrome		
	Potassium	Mycophenolate	Highest glucose	Atrial fibrillation		
	Glucose	Insulin	Lowest glucose	Cardiogenic shock		
	Urea	Metformin	ASA score	Heart block		
	Creatinine	Glyburide	Isoflurane	Postoperative complications		
	GFR	Pioglitazone	Sevoflurane	Morphine (POD #0, 1, 2, 3)		
	Peak troponin	Gliclazide	Desflurane	Hydromorphone (POD #0, 1, 2, 3)		
	Cardiac output	Heparin	Thiopental	Fentanyl (POD #0, 1, 2,		
	Alkaline phosphatase	Warfarin	Succinylcholine			
	Alanine transaminase	Clopidogrel	Cis-atracurium			
	AST	Integrilin	Atracurium			
	Gamma GT	Levophed	Midazolam			
	Lactate dehyrogenase	Milrinone	Fentanyl			
	Total bilirubin	Olanzapine	Sufentanil			
	Zopiclone	Quetiapine	Remifentanil			
	Loxapine	Tetrabenazine	Naloxone			
	Oxazepam	Prochlorperazine	Propofol			
	Paroxetine	Amitriptyline	Epinephrine			
	Fluoxamine	Bupropion	Norepinephrine			
	Venlafaxine	Sertraline	Neostigmine			
	Domperidone	Citalopram	Glycopyrrolate			
	Pregabalin	Escitalopram	Nitroglycerin			
	Levodopa-Carbidopa	Trazodone				
	Lorazepam	Mirtazapine				
	Prednisone	Fluvoxamine				
	Morphine	Cyclobenzaprine				
		Clonazepam				
		Oxycodone				
		Lidocaine				
		Truvada				
		Kaletra				
		Nortriptyline				
		Lamotragine				

Table 3. Complete list of variables obtained from medical charts

Preoperative Variables			Intraoperative Variables	Postoperative Variables		
surgeries Prior percutaneous cardiac intervention (angioplasties/ stents; ICD; pacemaker, pathway ablation; cardioversion; impella insertion; defibrillator insertion; left ventricular assist device; valve replacement) Myocardial infarction Congestive heart failure Cardiogenic shock Brain injury History of delirium History of syncope History of embolism Other diseases/surgeries (nutritional deficiency; genetic abnormality; bone/joint disorder; skin and subcutaneous disorder; immune/ inflammatory disorder; endocrine disorder; pain disorder; metabolic disorder; lung disorder; gastrointestinal disorder; urogenital disorder; musculoskeletal/ connective tissue disorder; liver disorder; blood disorder; vascular conditions; nervous tissue disorder; other cardiac disorder)	Dextropropoxyphene Simvastatin Atorvastatin Rosuvastatin Lovastatin Ezetimibe Pravastatin Digoxin Gentamicin Gabapentin Ramipril Captopril Enalapril Lisonopril Cilazapril Perindopril Trandolapril Donepezil Restoril Benzapril Quinapril Monopril ASA Diclofenac Ketorolac Indomethacin Naproxen Hydroxyquinine Hydroxyzine Nitroglycerin Valsartan Candesartan Losartan Telmisartan Irbesartan Eprosartan Rabeprazole Esomprazole Omeprazole	Betahistine Trimipramine Metoclopramide Duloxetine	Hydromorphone Milrinone Dopamine Vasopressin Desmopressin Lidocaine Ketamine Morphine Tranexamic acid Rocuronium Protamine Heparin Ephdrine Phenylephrine Cefazolin Vancomycin Ciprofloxacin Calcium chloride Magnesium sulphate Amiodarone Beta-blockers Corticosteroids Diuretics Ondansetron Insulin	3) Meperidine (POD #0, 1, 2, 3) Oxycodone (POD #0, 1, 2, 3) Acetaminophen (POD #0, 1, 2, 3) Lorazepam (POD #0, 1, 2, 3) Midazolam (POD #0, 1, 2, 3) Oxazepam (POD #0, 1, 2, 3) Diltiazem (POD #0, 1, 2, 3) Clonazepam Propranolol (POD #0, 1, 2, 3) Propofol (POD #0, 1, 2, 3) Levophed (POD #0, 1, 2, 3) Vasopressin (POD #0, 1, 2, 3) Desmopressin (POD #0, 1, 2, 3) Epinephrine (POD #0, 1, 2, 3) Milrinone (POD #0, 1, 2, 3) Dopamine (POD #0, 1, 2, 3) Inotropes > 24-hours Ipratropium (POD #0, 1, 2, 3) Tiotropium (POD #0, 1, 2, 3) Rocuronium (POD #0, 1, 2, 3) Oxybutynin (POD #0, 1, 2, 3) Venlafaxine (POD #0, 1, 2, 3) Atropine (POD #0, 1, 2, 3) Cyclobenzaprine (POD #0, 1, 2, 3) Ondansetron (POD #0, 1, 2, 3)	#0, 1, 2, 3) Lansoprazole (POD #0, 1, 2, 3) Esoneprazole (POD #0, 1, 2, 3) Omeprazole (POD #0, 1, 2, 3) Nitroglycerin (POD #0, 1, 2, 3) Nitroprusside (POD #0, 1, 2, 3) Diclofenac (POD #0, 1, 2, 3) Cefazolin (POD #0, 1, 2, 3) Vancomycin (POD #0, 1, 2, 3) Ciprofloxacin (POD #0, 1, 2, 3) Moxifloxacin (POD #0, 1, 2, 3) Cephalexin (POD #0, 1, 2, 3) Cloxacilin (POD #0, 1, 2, 3) Amoxicilin (POD #0, 1, 2, 3) Rifampicin (POD #0, 1, 2, 3) Ceftriaxone (POD #0, 1, 2, 3) Pip-taz (POD #0, 1, 2, 3) Chlorhexidine (POD #0, 1, 2, 3) Basilixmab (POD #0, 1, 2, 3) Cotimoxazole (POD #0, 1, 2, 3) Azithromycin (POD #0, 1, 2, 3) Clindamycin (POD #0, 1, 2, 3) Clonidine (POD #0, 1, 2, 3) Hydralazine (POD #0, 1, 2, 3) Terazosin (POD #0, 1, 2, 3) Amiloride (POD #0, 1, 2, 3)	Oxycodone (POD #0, 1, 2, 3) Sertraline (POD #0, 1, 2, 3) Mirtazipine (POD #0, 1, 2, 3) Fluoxetine (POD #0, 1, 2, 3) Naloxone (POD #0, 1, 2, 3) Venlafaxine (POD #0, 1, 2, 3) Neostigmine (POD #0, 1, 2, 3) Fluvoxamine (POD #0, 1, 2, 3) Gabapentin (POD #0, 1, 2, 3) Paroxetine (POD #0, 1, 2, 3) Propafenone (POD #0, 1, 2, 3) Bupivacaine (POD #0, 1, 2, 3) Truvada (POD #0, 1, 2, 3) Kaletra (POD #0, 1, 2, 3) Doxazosin (POD #0, 1, 2, 3) Lamotrigine (POD #0, 1, 2, 3) Trazodone (POD #0, 1, 2, 3) Diphenhydramine (POD #0, 1, 2, 3) Sildenafil (POD #0, 1, 2, 3) Olanzapine (POD #0, 1, 2, 3) Baclofen (POD #0, 1, 2, 3) Pregabalin (POD #0, 1, 2, 3) Delirium (physician diagnosis; medications for treatment; flexible diagnosis; non-delirious)

CABG *coronary artery bypass graft*;; ICD *implantable cardioverter-defibrillator*; BMI *body mass index*; CAD *coronary artery disease*; LVH *left ventricular hypertrophy*; NYHA *New York heart association*; CCS *Canadian cardiovascular society angina classification*; STS *society of thoracic surgeons*; IABP *intra-aortic balloon pump*; TIA *transient ischemic attack*; COPD *chronic obstructive pulmonary disease*; INR *international normalized ratio*; PTT *partial thromboplastin time*; GFR *glomerular filtration rate*; AST a*spartate aminotransferase*; ASA *acetylsalicylic acid*; HCTZ *hydrochlorothiazide*; CPB *cardiopulmonary bypass*; ASA *American society of anesthesiologists score*; ICU *intensive care unit*; CCU *cardiac care unit*; POD *postoperative day (POD #0 is the period immediately after surgery)*;

Table 4. Definitions of specialized categorical variables

Inpatient status	-Patient had been at the hospital for more than 1-day prior to surgery, or had been transferred from another hospital
Recent alcohol use	-Alcohol consumption in the 7-days prior to surgery
Obesity	-Body mass index > 30 kg/m^2
Prolonged cardiopulmonary bypass	-Length of cardiopulmonary bypass > 80-minutes
Hyperkalemia	-Potassium levels > 4.7 mmol/L
Hypokalemia	-Potassium levels < 3.6 mmol/L
Hyponatremia	-Sodium levels < 135 mmol/L
Metabolic acidosis	-pH < 7.35 and serum bicarbonate > 30 mmol/L
Metabolic alkalosis	-pH > 7.45 and serum bicarbonate < 24 mmol/L
Respiratory acidosis	-pH < 7.35 and partial pressure of carbon dioxide in arterial blood > 45 mmHg
Respiratory alkalosis	-pH > 7.45 and partial pressure of carbon dioxide in arterial blood < 35 mmHg
Sevoflurane, desflurane, isoflurane	-Recorded the average end-tidal concentration (as indicated on the anesthetic flowsheet) by normalizing over time (i.e., multiplying the end-tidal concentration by the estimated amount of time, and averaging these calculations over the duration of the surgery)
Postoperative hypotension	-At least one occurrence of mean arterial pressure (MAP) being < 60 mmHg lasting 30 minutes or more (Lee and Mark, 2010)
Peak creatinine	-Highest serum creatinine level during the postoperative period until discharge
Renal insufficiency	-An estimated glomerular filtration rate < 90-mL/min/1.73m^2 for an acute period of time within the postoperative period with a full and steady return to the normal range
Renal failure	-Sustained estimated glomerular filtration rate < 90-mL/min/1.73$m^{2,}$ but normally based on a formal diagnosis made by a physician that is clearly stated in the medical chart
Lowest eGFR	-Lowest estimated glomerular filtration rate during the postoperative period until discharge
Hypoxia	-Arterial oxygen saturation level < 90% at a cross-section in time within the postoperative period
Average fractional inspired O2	-The average concentration of inspired oxygen from mechanical ventilation (as indicated on the nursing record), normalized to time (i.e., multiplying the FiO_2 by the estimated amount of time, and averaging these calculated values per day)
Postoperative blood transfusion	-Total amount of blood received during the hospital stay, including units that were transfused during surgery

Table 4. Definitions of specialized categorical variables

Hypoalbuminemia	-Recorded from the abnormal laboratory values in patients' medical charts
Fever	-Body temperature > 37.7°C
Low body temperature	-Body temperature < 32°C
Pain	-Pain rating ≥ 3 from the nurses' notes, or if a note of a patient's complaint of pain was seen
Decreased mobility	-Taken from the discharge summary where it iwas clearly stated by a physician that the patient demonstrated 'decreased mobility'
Exacerbation of CHF	-Worsening of a patient's pre-existing congestive heart failure after surgery; taken from a note made by a physician
New onset atrial fibrillation	-Atrial fibrillation that began in the postoperative period without any indication of pre-existing atrial fibrillation
Sensory disturbance	-Taken from notes that stated that the patient was experiencing focal neurological deficits of auditory, visual, or tactile hallucinations
Low cardiac output syndrome	-Ejection fraction < 50%
Delirium	-Clear diagnosis written in the discharge summary or through psychiatric consultations

In appointments leading up to each patient's procedure, preoperative cognition was routinely assessed with standardized questionnaires that asked about substance use, mental health, and functionality. Often times for patients undergoing transfemoral TAVI, a copy of the Mini-Mental State Examination (MMSE) was also found in the medical records.

The surgical and postoperative management data were abstracted from each patient's discharge summary, physician consultation reports, interdisciplinary notes, progress notes, anesthetic records, perfusion records, operative reports, critical care flowsheets, nurses' notes, and medication administration records. Medications taken in the preoperative period were

recorded from the nurses' preoperative assessments, anesthetic drugs were taken from the anesthetic record, and postoperative medications were taken from the medication administration records. Postoperative medications were recorded at four time points – in the period immediately after surgery, and on postoperative days (POD) #1, 2, and 3. Medications that were received in the period immediately after surgery were given to patients upon their arrival in the Cardiac Surgery Intensive Care Unit (CSICU) in the case of transapical TAVI and open-heart AVR patients, or in the Cardiac Care Unit (CCU) in the case of transfemoral TAVI patients. Medications received on POD #1, 2, and 3 are drugs that were given to patients when they were still in intensive care, or after they were transferred into the Cardiology and Cardiac Surgery Wards.

2.3 Primary Outcome: Diagnosing Delirium

Patients were considered delirious only if a clear diagnosis was made by one of the attending physicians caring for the patients. Abstractors made a dichotomous assessment of delirium for the chart review process (patients were either delirious or not delirious).

Nurses in the CSICU and CCU were trained to use the CAM to screen for delirium. If nurses in the ICU or CCU recognized that a patient might have delirium, then they enlisted the psychiatric consult liason (CL) service to attend to the patient. The CL psychiatrist would then assess the patient with criteria from the DSM-IV-TR to determine if he or she was delirious.

2.4 Secondary Outcomes

A number of secondary outcomes were also recorded. These include the rates of all-cause mortality within 24-hours, 30-days, 1-year and 2-years; time spent in the intensive care unit or the cardiac care unit; total length of surgery; total length of intubation; total lengths of stay; rate of postoperative complications; proportions of individuals with decreased mobility after surgery; and proportions of individuals who were discharge to acute facilities for follow-up treatment or long-term care.

2.5 Statistical Analyses

All analyses were performed on PASW Statistics (SPSS Inc., release 18.0). Continuous variables were analyzed using the Student's t-test for independent samples, while categorical variables were compared using the χ^2 test. Levene's test for equality of variances was used to determine if the variances between comparison groups were equal. Post-hoc analyses for significant variables were performed by running separate comparisons between the three groups; i.e., transfemoral versus transapical, transfemoral versus open-heart, and transapical versus open-heart. In the following, continuous variables are expressed using descriptive statistics (mean ± standard deviation), and categorical variables are expressed as counts and proportions (number (percentage)). Variables were considered to be statistically significant at $p \leq 0.05$.

3 Results

3.1 Demographic, Medical History, and Serum Chemistry Differences Between Surgical Groups

Transfemoral TAVI patients, transapical TAVI patients, and open-heart AVR patients differed on a number of baseline characteristics (**Table 5**). Some notable differences in medical history between transfemoral and transapical patients included a significantly greater proportion of transapical patients having hypertension, pulmonary hypertension, dyslipidemia, peripheral vascular disease, carotid stenosis, and previous myocardial infarctions and coronary artery bypass grafts compared to transfemoral or open-heart patients. Interestingly, the only medical condition that a significantly greater proportion of open-heart patients had compared to TAVI patients was left ventricular hypertrophy.

Open-heart patients were on average younger than TAVI patients by 15 years, and there were more open-heart individuals who were current smokers than in the transfemoral TAVI group. Open-heart patients also had higher body mass index (BMI) than TAVI patients. However, TAVI patients, specifically transapical TAVI patients, had significantly worse cardiac symptoms, as implied by their higher New York Heart Association (NYHA) functional classification scores for heart failure and their Canadian Cardiovascular Society (CCS) angina scores. A greater propotion of TAVI patients compared to open-heart patients

also had porcelain aorta, coronary artery disease, left ventricular dysfunction, prior stents or angioplasties, and pre-existing cognitive impairment.

Table 5. Baseline characteristics

	Transfemoral TAVI (n=45)	Transapical TAVI (n=45)	Open-Heart AVR (n=45)	*P* Value
Demographics				
Age, y	82.1 ± 7.8	80.0 ± 8.2	66.8 ± 14.7	<0.001[b, c]
Male sex, n (%)	24 (53.3)	17 (37.8)	26 (57.8)	0.137
Current smoker, n (%)	0 (0)	1 (2.2)	5 (11.1)	0.003[b]
Regular alcohol use, n (%)	22 (48.9)	20 (44.4)	28 (62.2)	0.214
BMI, kg/m^2	25.4 ± 5.1	24.9 ± 4.7	28.3 ± 6.2	0.007[b, c]
NYHA class ≥ III, n (%)	37 (82.2)	41 (91.1)	22 (48.9)	<0.001[b, c]
Worst CCS score ≥ III, n (%)	4 (8.9)	21 (46.7)	9 (20)	0.014[c]
Medical History				
Primary diagnosis, n (%)				
Bicuspid aortic valve	1 (2.2)	0 (0)	20 (44.4)	<0.001[b, c]
Degenerative aortic stenosis	44 (97.8)	40 (88.9)	23 (51.1)	<0.001[b, c]
Supraventricular tachycardia	0 (0)	0 (0)	5 (11.1)	0.006[b, c]
Atherosclerotic ascending aorta	0 (0)	0 (0)	3 (6.7)	0.047
Inpatient status, n (%)	11 (24.4)	22 (48.9)	36 (80)	<0.001[a, b, c]
Type II diabetes mellitus, n (%)	11 (24.4)	12 (26.7)	10 (22.2)	0.887
Hypertension, n (%)	33 (73.3)	42 (93.3)	32 (71.1)	0.017[a, c]
Pulmonary hypertension, n (%)	19 (42.2)	32 (71.1)	12 (26.7)	<0.001[a, c]
Dyslipidemia, n (%)	32 (71.1)	40 (88.9)	22 (48.9)	<0.001[a, b, c]
Prior stroke, n (%)	10 (22.2)	13 (28.9)	6 (13.3)	0.197
Peripheral vascular disease, n (%)	11 (24.4)	34 (75.6)	2 (4.4)	<0.001[a, b, c]
Porcelain aorta, n (%)	7 (15.6)	10 (22.2)	0 (0)	0.005[b, c]
Carotid stenosis, n (%)	4 (8.9)	11 (24.4)	0 (0)	0.001[a, b, c]
CAD, n (%)	37 (82.2)	38 (84.4)	6 (13.3)	<0.001[b, c]
Atrial fibrillation, n (%)	22 (48.9)	15 (33.3)	23 (51.1)	0.181
Cardiac arrhythmia, n (%)	19 (42.2)	30 (66.7)	26 (57.8)	0.061
Congestive heart failure, n (%)	31 (68.9)	44 (97.8)	28 (62.2)	<0.001[a]
Previous myocardial infarction, n (%)	16 (35.6)	26 (57.8)	6 (13.3)	<0.001[a, b, c]
Left ventricular hypertrophy, n (%)	20 (44.4)	15 (33.3)	31 (68.9)	0.003[b, c]
Left ventricular dysfunction, n (%)	17 (37.8)	17 (37.8)	6 (13.3)	0.014[b, c]
COPD, n (%)	10 (22.2)	11 (24.4)	4 (8.9)	0.121
Prior CABG, n (%)	8 (17.8)	20 (44.4)	1 (2.2)	<0.001[a, b, c]
Prior mitral valve replacement, n (%)	1 (2.2)	5 (11.1)	0 (0)	0.026[c]
Prior stent or angioplasty, n (%)	15 (33.3)	16 (35.6)	2 (4.4)	0.008[b, c]
Memory impairment, n (%)	8 (17.8)	3 (6.7)	0 (0)	0.008[b]
Cognitive deficits, n (%)	15 (33.3)	11 (24.4)	0 (0)	<0.001[b, c]
Hearing impairment, n (%)	24 (53.3)	11 (24.4)	5 (11.1)	<0.001[a, b]
Vision impairment, n (%)	35 (77.8)	40 (88.9)	32 (71.1)	0.110[c]
Renal insufficiency, n (%)	19 (42.2)	19 (42.2)	10 (22.2)	0.073

Table 5. Baseline characteristics

Laboratory Values				
Hemoglobin, g/dL	119.7 ± 17.1	120.2 ± 15.7	134.6 ± 18.2	<0.001[b, c]
Hematocrit, %	36.8 ± 4.5	36.8 ± 4.2	39.8 ± 4.4	0.001[b, c]
Platelets, giga/L	214.7 ± 79.2	218.5 ± 70.8	215.2 ± 61.5	0.962
WBC, giga/L	7.0 ± 2.3	7.5 ± 2.2	10.4 ± 16.8	0.208
INR	1.2 ± 0.2	1.2 ± 0.4	1.1 ± 0.1	0.020[b, c]
Glucose, mmol/L	6.9 ± 2.3	6.5 ± 1.6	6.8 ± 3.3	0.712
Creatinine, μmol/L	111.3 ± 52.7	117.6 ± 63.5	92.8 ± 28.8	0.056
Urea, mmol/L	10.2 ± 4.9	11.7 ± 8.0	9.5 ± 10.0	0.447
eGFR, mL/min	58.2 ± 23.5	51.8 ± 22.1	66.2 ± 23.6	0.042[c]
Troponin, μg/L	0.07 ± 0.08	0.05 ± 0.03	1.0 ± 1.8	0.009[b, c]

[a]$p < 0.05$ between transfemoral, transapical; [b]$p < 0.05$ between transfemoral, open-heart; [c]$p < 0.05$ between transapical, open-heart.
All values represent mean ± standard deviation; frequencies indicate number (proportion).
BMI=b*ody mass index*; NYHA=*New York heart association*; CCS=*Canadian cardiovascular society*; CAD=*coronary artery disease*; COPD=*chronic obstructive pulmonary disease*; CABG=*coronary artery bypass graft*; WBC=*white blood cell*; INR=*international normalized ratio*; eGFR=*estimated glomerular filtration rate*

Some of the differences in the medical histories between the three groups confirmed what was already known about the patients. For instance, a significantly greater proportion of open-heart patients had congenital heart defects than TAVI patients because TAVI procedures are only offered to individuals who are diagnosed with severe aortic stenosis, and the significantly greater proportion of individuals in the TAVI groups with degenerative aortic stenosis reflects this.

There were also significant differences in the three groups in preoperative laboratory values. Preoperative hemoglobin and hematocrit levels were higher for open-heart patients than for TAVI patients, but even these values were on the lower end of the average normal ranges of 131.5-165.5 g/dL for hemoglobin and

39.5-49.0% for hematocrit (all normal ranges reported here were determined by the Medical Council of Canada (2011)). Although there were no significant differences between the groups in terms of white blood cell count, the open-heart group did show slightly elevated levels above the normal range of 2-7 giga/L. Similarly, serum creatinine levels were comparable between all three groups, but both TAVI groups had higher than normal levels which should be on average between 60-105 μmol/L. Accordingly, both TAVI groups had lower than normal eGFR (>59 mL/min), but transapical TAVI patients had significantly lower eGFR compared to open-heart patients. Baseline troponin I and urea levels were both higher than normal for all three groups (troponin I should be less than 0.02 μg/L, and urea should be between 2.5-8.0 mmol/L); however, open-heart patients had much higher troponin I levels than TAVI patients, indicating that on average they were suffering from a greater amount of cardiac ischemia. Platelet count, INR, and glucose levels were all normal in the three groups although open-heart patients did have much lower INRs than TAVI patients even though a higher proportion of TAVI patients were taking the anticoagulants warfarin and clopidogrel as outpatients (see **Table 12** for frequencies of outpatient drug use).

When baseline differences between delirious and non-delirious individuals within each surgical group were compared, the variables that were associated with delirium were different depending on the valve replacement procedure (**Table 6**). Variables that were significantly correlated with the valve replacement

procedures were not necessarily significantly correlated with delirium within each surgical group.

Table 6. Baseline differences between delirious and non-delirious individuals within each surgical group

	Transfemoral TAVI			Transapical TAVI			Open-Heart AVR		
	Delirium (n=7)	No delirium (n=38)	*P*- value	Delirium (n=23)	No delirium (n=22)	*P*- value	Delirium (n=17)	No delirium (n=28)	*P*- value
Baseline Characteristics									
Age, y	85.7 ± 4.9	81.4 ± 8.1	0.182	81.6 ± 7.9	78.3 ± 8.3	0.186	74.6 ± 13.8	62.0 ± 13.3	0.004*
Male sex, n (%)	4 (57)	20 (53)	0.826	10 (43)	7 (32)	0.420	9 (53)	17 (61)	0.609
Married, n (%)	4 (57)	18 (47)	0.780	9 (39)	9 (41)	0.546	8 (47)	17 (61)	0.380
BMI, kg/m^2	24.1 ± 2.2	25.7 ± 5.5	0.233	24.8 ± 4.1	25.0 ± 5.5	0.848	27.8 ± 6.7	28.6 ± 5.9	0.706
Current smoker, n (%)	0 (0)	0 (0)	n/a	0 (0)	1 (5)	0.511	1 (6)	4 (14)	0.679
Regular alcohol use, n (%)	2 (29)	20 (53)	0.242	8 (35)	12 (55)	0.182	9 (53)	19 (68)	0.317
ASA score ≥ 3, n (%)	0 (0)	4 (11)	0.362	5 (22)	4 (18)	0.766	3 (18)	4 (14)	0.765
NYHA class ≥ III, n (%)	5 (71)	32 (84)	0.475	22 (96)	19 (86)	0.218	8 (47)	14 (50)	0.435
Congestive heart failure, n (%)	2 (29)	29 (76)	0.012*	23 (100)	21 (95)	0.301	13 (76)	15 (54)	0.125
Brain injury, n (%)	3 (43)	1 (3)	0.001*	1 (4)	1 (4)	0.974	0 (0)	0 (0)	n/a
History of embolism, n (%)	5 (71)	12 (32)	0.046*	15 (65)	11 (50)	0.302	0(0)	1 (4)	0.431
Porcelain aorta, n (%)	1 (14)	6 (16)	0.920	3 (13)	7 (32)	0.130	0(0)	0 (0)	n/a
Hypertension, n (%)	6 (86)	27 (71)	0.420	22 (96)	20 (91)	0.524	14 (82)	18 (64)	0.195
Dyslipidemia, n (%)	7 (100)	25 (66)	0.066	20 (87)	20 (91)	0.673	8 (47)	14 (50)	0.848
Type II diabetes, n (%)	2 (29)	9 (24)	0.782	7 (30)	5 (23)	0.559	4 (24)	6 (21)	0.869
Renal insufficiency, n (%)	3 (43)	16 (42)	0.970	9 (39)	10 (45)	0.668	6 (35)	4 (14)	0.100
Cardiac arrhythmia, n (%)	5 (71)	14 (37)	0.089	19 (83)	11 (50)	0.02*	15 (88)	11 (39)	0.001*
Atrial fibrillation, n (%)	5 (71)	17 (45)	0.194	10 (43)	5 (23)	0.140	13 (76)	10 (36)	0.008*
Stroke/TIA, n (%)	4 (57)	6 (16)	0.016*	7 (30)	6 (27)	0.815	5 (29)	4 (14)	0.013*
Anxiety, n (%)	2 (29)	1 (3)	0.011*	1 (4)	2 (9)	0.524	0 (0)	1 (4)	0.431

Table 6. Baseline differences between delirious and non-delirious individuals within each surgical group

Memory impairments, n (%)	4 (57)	4 (11)	0.003*	2 (9)	1 (5)	0.577	0(0)	0 (0)	n/a
Cognitive deficits, n (%)	6 (86)	9 (24)	0.002*	8 (35)	3 (14)	0.099	0 (0)	0 (0)	n/a
CAD, n (%)	7 (100)	30 (79)	0.181	22 (96)	16 (73)	0.034*	2 (12)	4 (14)	0.809
PVD, n (%)	2 (29)	9 (24)	0.782	19 (83)	15 (68)	0.260	2 (12)	0 (0)	0.063
LVD, n (%)	3 (43)	14 (37)	0.763	12 (52)	5 (23)	0.042*	2 (12)	4 (14)	0.809
Infection, n (%)	0 (0)	2 (5)	0.535	2 (9)	0 (0)	0.157	5 (29)	0 (0)	0.002*
Hearing impairment, n (%)	6 (86)	18 (47)	0.062	7 (30)	4 (18)	0.339	4 (24)	1 (4)	0.039*
WBC, giga/L	6.98 ± 2.8	6.97 ± 2.2	0.996	7.7 ± 2.3	7.4 ± 2.2	0.590	7.1 ± 3.8	12.3 ± 20.8	0.326
Hemoglobin, giga/L	125.4 ± 26.8	118.4 ± 14.5	0.304	118.7 ± 14.4	121.9 ± 17.1	0.493	132.7 ± 19.1	135.7 ± 17.9	0.592
Hematocrit, %	0.38 ± 0.07	0.37 ± 0.04	0.620	0.37 ± 0.04	0.37 ± 0.05	0.817	0.4 ± 0.05	0.4 ± 0.04	0.965
Platelets, giga/L	180.6 ± 47.4	222.0 ± 83.2	0.183	218.5 ± 72.6	218.5 ± 70.5	0.999	201.2 ± 49.4	223.6 ± 67.3	0.239
Sodium, mmol/L	138.3 ± 4.3	139.3 ± 4.3	0.536	138.9 ± 4.5	139.0 ± 3.3	0.876	139.5 ± 3.3	140.1 ± 3.0	0.583
Potassium, mmol/L	4.29 ± 0.71	4.26 ± 0.52	0.887	4.3 ± 0.4	4.2 ± 0.4	0.313	4.3 ± 0.5	4.1 ± 0.26	0.200
Glucose, mmol/L	6.2 ± 1.6	7.0 ± 2.4	0.507	6.3 ± 1.4	6.6 ± 1.9	0.512	6.1 ± 1.6	7.2 ± 3.9	0.281
Creatinine, μmol/L	101.5 ± 39.5	113.5 ± 55.4	0.567	129.4 ± 77.1	105.3 ± 43.7	0.207	95.4 ± 27.5	91.2 ± 29.9	0.638
Urea, μmol/L	10.9 ± 8.2	10.1 ± 4.1	0.719	11.2 ± 5.4	12.1 ± 10.2	0.707	8.3 ± 5.1	10.2 ± 11.9	0.549
INR	1.39 ± 0.41	1.19 ± 0.18	0.049*	1.3 ± 0.4	1.2 ± 0.4	0.219	1.1 ± 0.15	1.1 ± 0.09	0.013*

*$p \leq 0.05$

All values represent mean ± standard deviation; frequencies indicate number (proportion).

BMI *body mass index;* ASA *American society of anesthesiologists*; NYHA *New York heart association*; TIA *transient ischemic attack*; CAD *coronary artery disease*; PVD *peripheral vascular disease*; LVD *left ventricular dysfunction*; WBC *white blood cell*; INR *international normalized ratio*

For transfemoral TAVI, more delirious patients compared to non-delirious patients currently had, or had histories of brain injuries, episodes of embolism, strokes or transient ischemic attacks, anxiety disorders, cognitive deficits, and memory impairments, and they also had lower preoperative INRs than non-delirious patients. However, congestive heart failure was more common in non-

delirious TAVI patients. Delirious transapical TAVI patients were more likely to have had arrhythmias, coronary artery disease and left ventricular dysfunction in their medical histories. Lastly, delirious open-heart patients tended to be older, and more of them had hearing impairments, arrhythmias, atrial fibrillation, strokes or transient ischemic attacks, and infections. Unlike delirious transfemoral patients, delirious open-heart patients had higher INRs. The association between recent alcohol consumption and delirium that was found in the pilot study by Burns *et al*. (2009) was not dected in any of these three patient samples.

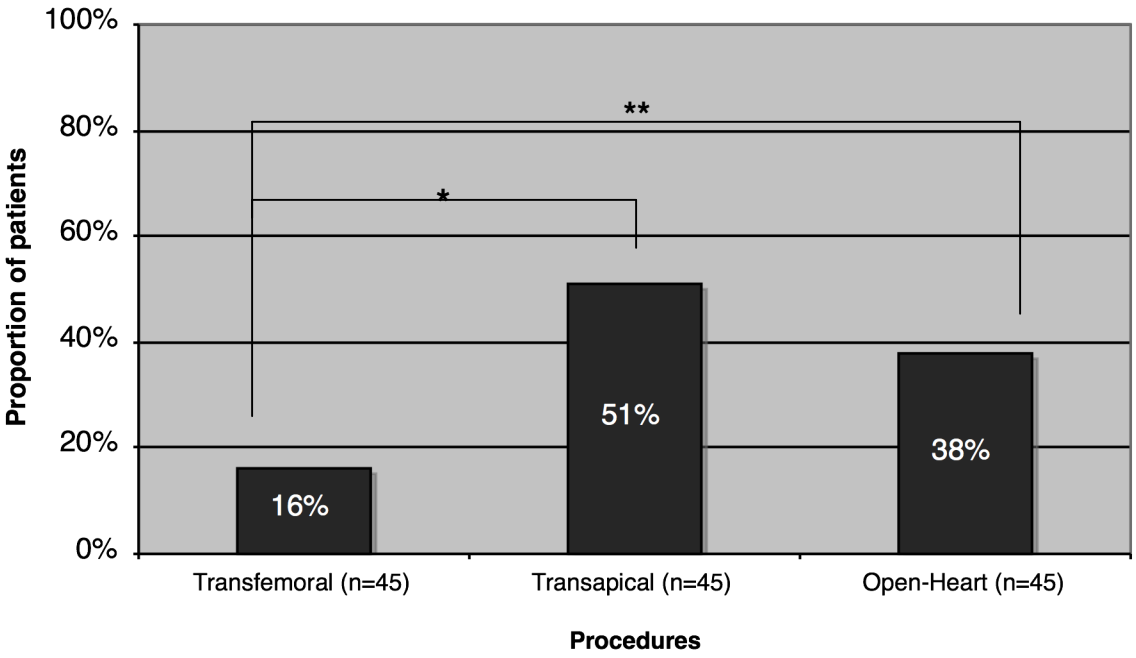
3.2 Transfemoral TAVI has the Lowest Rate of Delirium Compared to Transapical TAVI and Open-Heart AVR

Incidences were calculated by an intention-to-treat analysis. In other words, the incidences were calculated based on a sample size of 45 patients per group, even though deaths did occur during surgery and in the postoperative period (see Section 3.3 for mortality rates).

The rate of postoperative delirium was significantly lower in transfemoral TAVI compared to either transapical TAVI ($p < 0.001$). The rate of delirium after transfemoral TAVI was also significantly lower compared to control ($p = 0.017$). However, incidences of delirium were not significantly different between transapical TAVI and control ($p = 0.203$). Twenty-three transapical patients developed delirium (51%), 17 open-heart patients developed delirium (38%), and

7 transfemoral TAVI patients developed delirium (16%) (**Figure 1**). The proportion of delirium in the control group of open-heart AVR was in the range of the 30% incidence that is frequently reported in the literature for open-heart cardiac surgeries.

Figure 1. Incidences of postoperative delirium after TAVI and open-heart aortic valve replacements based on formal diagnoses.



*$p < 0.001$ (transfemoral vs. transapical)
**$p=0.017$ (transfemoral vs. open-heart)

3.3 All-Cause Mortality After 24-Hours, 30-Days, and 1-Year are Comparable Across Transfemoral TAVI, Transapical TAVI, and Open-Heart AVR

All-cause mortality was not significantly different between the three groups at 24-hours, 30-days, or 1-year after surgery (**Table 7**). However, at 2-years after surgery, significantly greater proportions of transfemoral (18%) and transapical (20%) patients died compared to open-heart patients (p = 0.007 between transapical and open-heart, and p = 0.014 between transfemoral and open-heart). There were no significant differences between mortality rates at any time point between delirious and non-delirious individuals within each surgical group (**Table 8**). Out of the 45 people that received transfemoral TAVI, one died within 24-hours of the procedure; three died within 30-days, one of whom had been delirious; and two died within 1-year. Another two transfemoral patients died within 2-years. Two transapical patients died within 24-hours of the procedure, and one of these patients died during the procedure itself. Two more transapical patients were deceased within 30-days, both of whom had developed delirium, and another 4 died within 1-year. Three of these 4 transapical patients that died within 1-year had been delirious. One more transapical patient passed away after 2-years. No open-heart patients died within 24-hours or 30-days, and only one died within 1-year. No delirious open-heart patients passed away anytime within the 2-year period after surgery. The amounts of time survived by these deceased patients are given in **Table 9**.

Table 7. Cumulative mortality rates for the three surgical groups

	Transfemoral TAVI (n=45)	Transapical TAVI (n=45)	Open-Heart AVR (n=45)	*P* Value
24-hour mortality	1 (2%)	2 (4%)	0 (0%)	0.360
30-day mortality	4 (9%)	4 (9%)	0 (0%)	0.119
1-year mortality	6 (13%)	8 (18%)	1 (2%)	0.054
2-year mortality	8 (18%)	9 (20%)	1 (2%)	0.026[a, b]

[a]$p = 0.014$ (transfemoral vs. open-heart); [b]$p = 0.007$ (transapical vs. open-heart)

Table 8. Mortality rate differences between delirious and non-delriious patients within each surgical group

	Transfemoral TAVI			Transapical TAVI			Open-Heart AVR		
	Delirium (n=7)	No delirium (n=38)	*P*-value	Delirium (n=23)	No delirium (n=22)	*P*-value	Delirium (n=17)	No delirium (n=28)	*P*-value
24-hour mortality	0 (0%)	1 (3%)	0.664	0 (0%)	2 (9%)	0.139	0 (0%)	0 (0%)	n/a
30-day mortality	1 (14%)	3 (8%)	0.585	2 (9%)	2 (9%)	0.963	0 (0%)	0 (0%)	n/a
1-year mortality	1 (14%)	5 (13%)	0.936	5 (22%)	3 (14%)	0.477	0 (0%)	1 (4%)	0.431
2-year mortality	1 (14%)	7 (18%)	0.793	6 (26%)	3 (14%)	0.297	0 (0%)	1 (0%)	0.431

No significant differences.

Table 9. Amounts of time survived by deceased patients

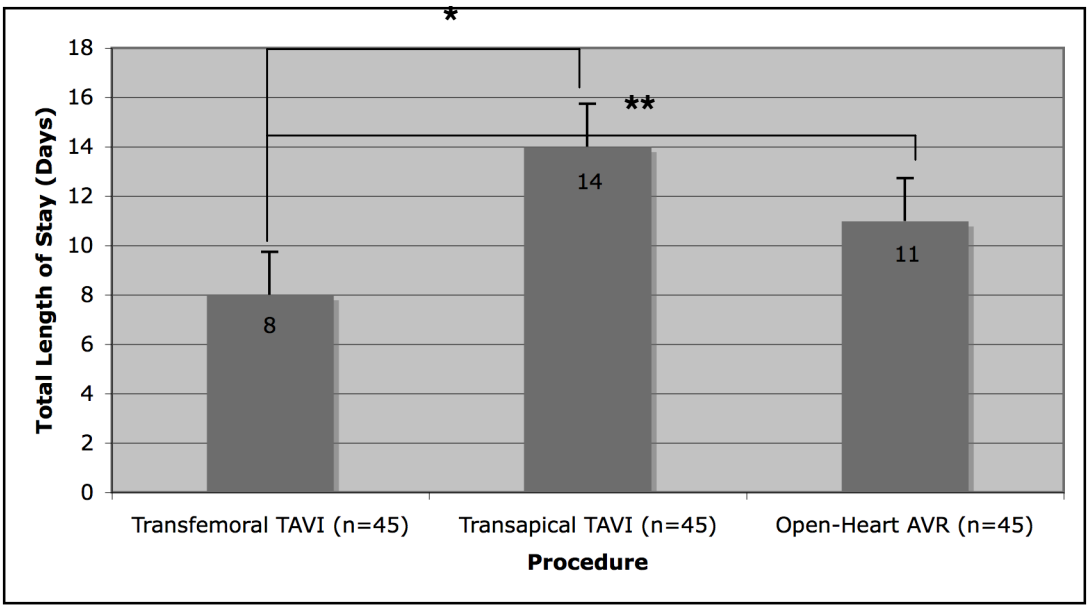
Surgical Group	Deceased Patients' Survival Times	
Transfemoral	24-Hour	Patient 1: 3 hours 12 minutes
	30-Days	Patient 1: 16 days Patient 2: 1 day, 5 hours Patient 3: 9 days (patient was delirious)
	1-Year	Patient 1: 61 days Patient 2: 247 days
	2-Years	Patient 1: 467 days Patient 2: 572 days
Transapical	24-Hour	Patient 1: 1 hour, 38 minutes Patient 2: procedural
	30-Days	Patient 1: 5 days (delirious) Patient 2: 29 days (delirious)
	1-Year	Patient 1: 57 days (delirious) Patient 2: 32 days (delirious) Patient 3: 114 days Patient 4: 67 days (delirious)
	2-Years	Patient 1: 489 days
Open-Heart	24-Hour	None
	30-Days	None
	1-Year	Patient 1: 57 days
	2-Years	None

3.4 Transfemoral TAVI Patients Have the Shortest Length of Stay, Open-Heart Patients Have the Longest Surgeries and Intubation Times, and Transapical TAVI Patients Require the Longest Lengths of Intensive Care

Transfemoral TAVI patients had significantly shorter total lengths of stay compared to either transapical TAVI patients (p = 0.001) or open-heart AVR patients (p = 0.047) (**Figure 2**). On average, transfemoral TAVI patients stay for

approximately 1-week shorter than transapical TAVI patients, and 3-days shorter than open-heart AVR patients.

Figure 2. Comparison of the total lengths of stay between the three procedures

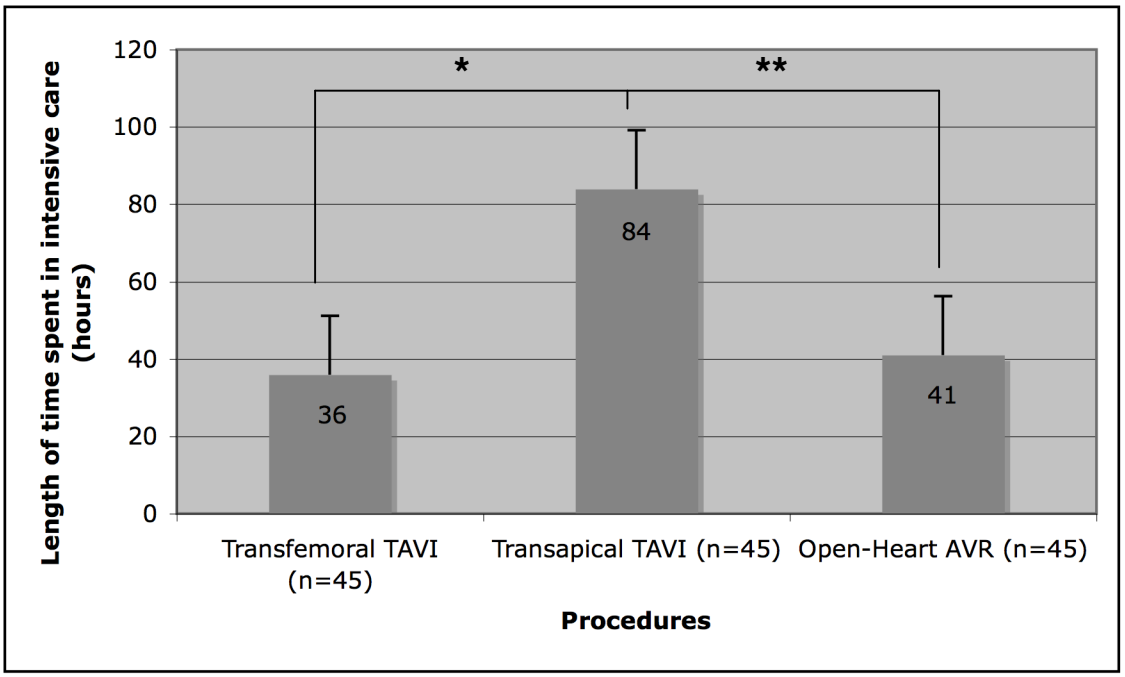


*p = 0.001 (transfemoral TAVI vs. transapical TAVI)
**p = 0.047 (transfemoral TAVI vs. open-heart AVR)
Error bars represent standard error of mean (SEM)

Open-heart patients had the longest surgery times compared to both transfemoral and transapical TAVI (272.5 ± 95.8 minutes for open-heart, verus 195.0 ± 61.3 for transapical and 199.1 ± 57.5 minutes for transfemoral; $p <$ 0.001), and these patients also required the most mechanical ventilation (13.9 ± 10.2 hours for open-heart, versus 9.0 ± 7.8 for transapical and 5.2 ± 6.4 for transfemoral; $p < 0.001$). However, transapical patients had significantly longer intubation times than transfemoral patients, despite no significant differences in surgery length.

The occurrence of delirium affected the total length of time spent in the hospital for open-heart patients (p = 0.041); delirious open-heart patients spent on average 1-week longer in the hospital than non-delirious open-heart patients (13.88 ± 9.0 days versus 8.75 ± 5.0 days, respectively). But the total lengths of stay for patients receiving TAVIs were not affected by the onset of delirium, since there were no significant differences in the length of stay between delirious and non-delirious patients within either TAVI group (p = 0.648 in transfemoral group; p = 0.206 for transapical group). Similarly, delirium affected the length of time spent in intensive care for open-heart patients only (p = 0.028); on average, delirium extended the length of intensive care for 24-hours. Comparing between surgeries, transpaical patients spent a significantly greater amount of time in intensive care than either transfemoral patients or open-heart patients (**Figure 3**). Transapical patients spent an average of a quarter of their total hospital stay in intensive care, while open-heart patients spent 16% and transfemoral patients spent 19% of their overall hospital stays was in the intensive care.

Figure 3. Comparison of the lengths of time spent in intensive care between the three procedures



*p = 0.014 (transfemoral TAVI vs. transapical TAVI)
**p = 0.025 (transapical TAVI vs. open-heart AVR)
Error bars represent standard error of mean (SEM)

3.5 Transapical TAVI and Open-Heart AVR Patients Have the Highest Rate of Complications

There were no significant differences in the proportions of transfemoral patients and transapical patients requiring emergency cardiopulmonary bypass during their procedures. However, transapical TAVI patients fared the worst postoperatively in that they had the highest numbers of complications (see **Table 10** for significant differences between surgical groups). The proportion of patients experiencing postoperative pleural effusion was the highest in transapical TAVI compared to transfemoral TAVI or open-heart AVR, and the

same trend existed for the need for reintubation after extubation from the valve procedure; sodium levels below 135 mmol/L; cardiac arrests; and exacerbation of pre-existing congestive heart failure. Complications that manifested comparably between the two most invasive procedures (transapical TAVI and open-heart AVR) included renal insufficiency; hyperkalemia; respiratory acidosis; and new onset atrial fibrillation. And even though the rates of these complications were not statistically significant between transapical TAVI and open-heart AVR, there was still a greater proportion of transpaical patients who were experiencing renal insufficiency and hypoxia. The two TAVI procedures were comparable in their incidences of postoperative hypotension and renal failure. Transfemoral TAVI patients fared poorer in only one complication that was evaluated, and that was in the frequency of re-explorations for hemorrhage.

Some noteworthy complications that were not significantly different between these procedures were frequencies of postoperative infection, stroke, fever, pneuromonia, or volume overload. Incidentally, a comparison between frequencies of low cardiac output in the postoperative period (i.e., having an ejection fraction less than 50%) was not included in the analysis because postoperative ejection fraction after transfemoral TAVI was often not found in these pateints' medical records.

Table 10. Frequencies of postoperative complications

	Transfemoral TAVI (n=45)	Transapical TAVI (n=45)	Open-Heart AVR (n=45)	*P* Value
Emergency CPB[1]	1 (2.2)	4 (8.9)	0 (0)	0.067
Reintubation	0 (0)	4 (8.9)	0 (0)	0.016[a, c]
Re-exploration for bleeding	10 (22.2)	2 (4.4)	4 (8.9)	0.025[a]
Pleural effusion	2 (4.4)	13 (28.9)	3 (6.7)	0.001[a, c]
Hypotensive episode	19 (42.2)	22 (48.9)	5 (11.1)	<0.001[b, c]
Renal insufficiency	24 (53.3)	36 (80)	29 (64.4)	0.050[a]
Renal failure	5 (11.1)	12 (36.7)	3 (6.7)	0.022[c]
Hypoxia	5 (11.1)	18 (40)	17 (37.8)	0.011[a, b]
Hyponatremia	9 (20)	26 (57.8)	16 (35.6)	0.002[a, c]
Hyperkalemia	17 (37.8)	33 (73.3)	35 (77.8)	<0.001[a, b]
Respiratory acidosis	12 (26.7)	29 (64.4)	34 (75.6)	0.011[a, b]
New onset atrial fibrillation	5 (11.1)	15 (33.3)	20 (44.4)	0.003[a, b]
Cardiac arrest	0 (0)	4 (8.9)	0 (0)	0.016[a, c]
Exacerbation of CHF	0 (0)	7 (15.6)	1 (2.2)	0.003[a,c]
Infection	7 (15.6)	12 (26.7)	9 (20)	0.479
Stroke	3 (6.7)	4 (8.9)	2 (4.4)	0.702
Fever	14 (31.1)	8 (17.8)	8 (17.8)	0.162
Pneumonia	0 (0)	3 (6.7)	4 (8.9)	0.153
Volume overload	3 (6.7)	1 (2.2)	5 (11.1)	0.436

Data represent count (proportion).
[1]Comparison was made between transfemoral and transapical groups only since open-heart patients require bypass for the entire length of the procedure
[a]$p < 0.05$ transfemoral vs. transapical; [b]$p < 0.05$ transfemoral vs. open-heart; [c]$p < 0.05$ transapical vs open-heart
CPB *cardiopulmonary bypass*; CHF *congestive heart failure*

3.6 Frequencies of Decrease in Mobility and Discharge to an Acute Facility Were Comparable Between All Valve Replacement Procedures

Functional independence after valve replacement was affected in these patients after surgery compared to before surgery, since there were a number of individuals from each surgical group with decreased mobility after surgery, and a number of individuals requiring continued care post-discharge at another acute

facility (**Table 11**). However, the type of valve replacement received did not differentially affect functional independence.

Table 11. Decreases in mobility and requirements for continued care at an acute facility post-discharge

	Transfemoral TAVI (n=45)	Transapical TAVI (n=45)	Open-Heart AVR (n=45)	*P* Value
Decreased mobility	10 (22.2)	21 (46.7)	16 (35.6)	0.072
Discharge to acute facility	7 (15.6)	8 (17.8)	5 (11.1)	0.663

Data represent count (proportion).

3.7 Differences in Outpatient Drug Use Between Surgical Groups and Between Delirious and Non-Delirious Patients Within Each Surgical Group

Frequencies of use of each individual outpatient medication that was taken by these patient samples are given in **Table 12**. No statistics were calculated on these frequencies and they are meant solely for illustrative purposes only.

Medications taken preoperatively as outpatients were analyzed by grouping individual medidcations into the drug classes antihypertensives, lipid-lowering agents, antiarrhythmic agents, antidiabetic agents, proton-pump inhibitors, anticoagulants, antibiotics, and psychoactive agents. **Table 13** describes how individual medications were grouped into each of these drug classes.

Table 12. Frequencies of outpatient drug use according to surgery group

Drug	Transfemoral TAVI (n = 45)	Transapical TAVI (n = 45)	Open-Heart AVR (n = 45)	Overall Frequency (n = 135)
Metoprolol	11 (24%)	17 (38%)	6 (13%)	34 (25%)
Bisoprolol	6 (13%)	6 (13%)	5 (11%)	17 (13%)
Atenolol	2 (4%)	4 (9%)	5 (11%)	11 (24%)
Sotalol	0 (0%)	0 (0%)	2 (4%)	2 (1%)
Carvedilol	3 (7%)	3 (7%)	1 (2%)	7 (5%)
Acebutolol	0 (0%)	0 (0%)	2 (4%)	2 (1%)
Salbutamol	7 (16%)	3 (7%)	3 (7%)	13 (10%)
Salmeterol	7 (16%)	2 (4%)	2 (4%)	11 (24%)
Nadolol	1 (2%)	0 (0%)	1 (2%)	21 (16%)
Furosemide	29 (64%)	27 (60%)	15 (33%)	71 (53%)
Metolazone	3 (7%)	1 (2%)	0 (0%)	4 (3%)
Hydrochlorothiazide	8 (18%)	4 (9%)	8 (18%)	20 (15%)
Spironolactone	4 (9%)	7 (16%)	4 (9%)	15 (11%)
Indapamide	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Diltiazem	5 (11%)	0 (0%)	0 (0%)	5 (4%)
Nifedipine	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Felodipine	1 (2%)	1 (2%)	1 (2%)	3 (2%)
Amlodipine	0 (0%)	14 (31%)	2 (4%)	16 (12%)
Verapamil	1 (2%)	1 (2%)	2 (4%)	4 (3%)
Nitroglycerin	5 (11%)	6 (13%)	2 (4%)	13 (10%)
Valsartan	7 (16%)	2 (4%)	1 (2%)	10 (7%)
Candesartan	1 (2%)	3 (7%)	0 (0%)	4 (3%)
Losartan	1 (2%)	1 (2%)	0 (0%)	2 (1%)
Telmisartan	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Irbesartan	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Terazosin	2 (4%)	1 (2%)	1 (2%)	4 (3%)
Clonidine	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Methyldopa	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Ramipril	20 (44%)	9 (20%)	10 (22%)	39 (29%)
Captopril	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Enalapril	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Hydralazine	1 (2%)	1 (2%)	0 (0%)	2 (1%)
Lisonopril	0 (0%)	2 (4%)	1 (2%)	3 (2%)
Cilazopril	0 (0%)	0 (0%)	3 (7%)	3 (2%)
Perindopril	1 (2%)	0 (0%)	3 (7%)	4 (3%)
Trandolapril	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Donepezil	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Quinapril	0 (0%)	3 (7%)	3 (7%)	6 (4%)
Monopril	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Simvastatin	8 (18%)	12 (27%)	12 (27%)	32 (24%)
Atorvastatin	14 (31%)	15 (33%)	6 (13%)	35 (26%)
Rosuvastatin	3 (7%)	4 (11%)	2 (4%)	9 (7%)
Pravastatin	1 (2%)	2 (4%)	0 (0%)	3 (2%)
Ezetimibe	1 (2%)	3 (7%)	0 (0%)	4 (3%)
Loxapine	0 (0%)	2 (4%)	2 (4%)	4 (3%)

Table 12. Frequencies of outpatient drug use according to surgery group

Drug	Transfemoral TAVI (n = 45)	Transapical TAVI (n = 45)	Open-Heart AVR (n = 45)	Overall Frequency (n = 135)
Oxazepam	0 (0%)	0 (0%)	2 (4%)	2 (1%)
Paroxetine	2 (4%)	0 (0%)	0 (0%)	2 (1%)
Fluoxetine	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Venlafaxine	2 (4%)	2 (4%)	1 (2%)	5 (4%)
Domperidone	2 (4%)	1 (2%)	0 (0%)	3 (2%)
Pregabalin	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Levodopa	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Carbidopa	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Lorazepam	4 (9%)	4 (9%)	5 (11%)	13 (10%)
Gabapentin	2 (4%)	1 (2%)	3 (7%)	6 (4%)
Bupropion	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Sertraline	0 (0%)	0 (0%)	2 (4%)	2 (1%)
Citalopram	1 (2%)	1 (2%)	0 (0%)	2 (1%)
Trazodone	1 (2%)	2 (4%)	0 (0%)	3 (2%)
Clonazepam	0 (0%)	2 (4%)	0 (0%)	2 (1%)
Perphenazine	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Nortriptyline	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Trimepramine	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Rabeprazole	8 (18%)	4 (9%)	5 (11%)	17 (13%)
Esomeprazole	2 (4%)	6 (13%)	0 (0%)	8 (6%)
Omeprazole	2 (4%)	3 (7%)	0 (0%)	5 (4%)
Pantoprazole	3 (7%)	2 (4%)	0 (0%)	5 (4%)
Lansoprazole	3 (7%)	1 (2%)	1 (2%)	5 (4%)
Insulin	4 (9%)	3 (7%)	4 (9%)	11 (8%)
Metformin	5 (11%)	6 (13%)	8 (18%)	19 (14%)
Glyburide	1 (2%)	4 (9%)	5 (11%)	10 (7%)
Gliclazide	1 (2%)	2 (4%)	1 (2%)	4 (3%)
Heparin	4 (9%)	4 (9%)	2 (4%)	10 (7%)
Warfarin	8 (18%)	7 (16%)	3 (7%)	18 (13%)
Clopidogrel	14 (31%)	12 (27%)	3 (7%)	29 (21%)
Vancomycin	3 (7%)	0 (0%)	0 (0%)	3 (2%)
Cefazolin	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Cefuroxime	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Digoxin	8 (18%)	11 (24%)	6 (13%)	25 (19%)
Amiodarone	4 (9%)	3 (7%)	3 (7%)	10 (7%)
Propafenone	0 (0%)	1 (2%)	1 (2%)	2 (1%)

Data represent count (proportion).

Table 13. Grouped drug classes for outpatient, anesthetic, and postoperative medications

Antihypertensives	Metoprolol, bisoprolol, atenolol, sotalol, carvedilol, acebutolol, salbutamol, salmeterol, nadolol, labetolol, esmolol, furosemide, metolazone, hydrochlorothiazide, spironolactone, indapamide, diltiazem, nifedipine, felodipine, amlodipine, verapamil, nitroglycerin, nitroprusside, valsartan, candesartan, losartan, telmisartan, irbesartan, terazosin, clonidine, methyldopa, ramipril, captopril, enalapril, hydralazine, lisonopril, cilazopril, perindopril, trandolapril, donepezil, quinapril, monopril
Lipid-Lowering Agents	Simvastatin, atorvastatin, rosuvastatin, pravastatin, ezetimibe
Antiarrhythmic Agents	Digoxin, amiodarone, propafenone
Antidiabetic Agents	Insulin, metformin, gliclazide, glyburide
Proton-Pump Inhibitors	Rabeprazole, pantoprazole, esomeprazole, omeprazole, lansoprazole
Anticoagulants	Warfarin, clopidogrel, integrilin
Antibiotics	Cefazolin, vancomycin, cefuroxime, ciprofloxacin, cephalexin
Psychoactive Agents	Loxapine, oxazepam, paroxetine, fluoxetine, venlafaxine, domperidone, pregabalin, levodopa, carbidopa, lorazepam, gabapentin, bupropion, sertraline, citalopram, trazodone, clonazepam, perphenazine, nortriptyline, trimepramine

Over 80% of patients from each surgical group were taking antihypertensives, but there were no significant differences between the proportions of individuals from each surgical group on antihypertensives, nor were there significant differences in the proportions of patients taking

antiarrythmic, antidiabetic, antibiotic, or psychoactive agents (**Table 14**). However, a significantly greater proportion of transapical patients were on lipid-lowering agents, despite the fact that a greater proportion of these patients were dyslipidemic. Also, more TAVI patients were taking proton-pump inhibitors and anticoagulants compared to open-heart AVR patients.

Table 14. Differences in outpatient drug use according to drug class

	Transfemoral TAVI (n=45)	Transapical TAVI (n=45)	Open-Heart AVR (n=45)	*P* Value
Antihypertensives, n (%)	41 (91.1)	42 (93.3)	38 (84.4)	0.355
Lipid-lowering agents, n (%)	26 (57.8)	35 (77.8)	18 (40)	0.001[a, c]
Antiarrhythmic agents, n (%)	11 (24.4)	13 (28.9)	8 (17.8)	0.459
Antidiabetic agents, n (%)	8 (17.8)	9 (20)	10 (22.2)	0.870
Proton-Pump Inhibitors, n (%)	18 (40)	16 (35.6)	6 (13.3)	0.012[b, c]
Anticoagulants, n (%)	23 (51.1)	21 (46.7)	7 (15.6)	0.001[b, c]
Antibiotics, n (%)	4 (8.9)	1 (2.2)	0 (0)	0.067
Psychoactive agents, n (%)	15 (33.3)	14 (31.1)	14 (31.1)	0.966

Data represent count (proportion).
[a] $p < 0.05$ between transfemoral and transapical; [b] $p < 0.05$ between transfemoral and open-heart; [c] $p < 0.05$ between transapical and open-heart

When outpatient medication differences were compared between delirious and non-delirious patients within each surgical group, no significant differences were found except for with the use of anticoagulants in the open-heart group (**Table 15**)

Table 15. Differences in outpatient medication use between delirious and non-delirious individuals within each surgrical group

	Transfemoral TAVI			**Transapical TAVI**			**Open-Heart AVR**		
	Delirium (**n=7**)	No delirium (**n=38**)	*P*-value	Delirium (**n=23**)	No delirium (**n=22**)	*P*-value	Delirium (**n=17**)	No delirium (**n=28**)	*P*-value
Antihypertensives	6 (86)	35 (92)	0.585	19 (83)	20 (91)	0.607	16 (94)	22 (79)	0.163
Lipid-Lowering Agents	4 (57)	22 (58)	0.970	17 (74)	16 (73)	0.333	7 (42)	11 (39)	0.900
Antiarrhythmic Agents	1 (14)	10 (26)	0.496	6 (26)	6 (27)	0.845	5 (29)	3 (11)	0.112
Antidiabetic Agents	1 (14)	7 (18)	0.793	6 (26)	3 (14)	0.197	4 (24)	6 (21)	0.869
Proton-Pump Inhibitors	1 (14)	17 (45)	0.131	8 (35)	8 (36)	0.808	3 (18)	3 (11)	0.507
Anticoagulants	4 (57)	19 (50)	0.728	11 (48)	10 (45)	0.537	6 (35)	1 (4)	0.004*
Antibiotics	1 (14)	3 (8)	0.585	1 (4)	0 (0)	0.288	0 (0)	0 (0)	N/A
Psychoactive Agents	1 (14)	14 (37)	0.245	6 (26)	6 (27)	0.845	16 (94)	22 (79)	0.163

Data represent count (proportion).
*$p < 0.01$

3.8 Differences in Anesthetic Drug Use Between Surgical Groups and Between Delirious and Non-Delirious Patients Within Each Surgical Group

Frequencies of use of each individual anesthetic medication that was given to these patient samples are given in **Table 16**. No statistics were calculated on these frequencies and they are meant solely for illustrative purposes only.

Table 16. Frequencies of anesthetic drug use according to surgery group

Drug	Transfemoral TAVI (n = 45)	Transapical TAVI (n = 45)	Open-Heart AVR (n = 45)	Overall Frequency (n = 135)
Isoflurane	0 (0%)	0 (0%)	12 (27%)	12 (9%)
Sevoflurane	39 (87%)	45 (100%)	40 (89%)	124 (92%)
Desflurane	3 (7%)	0 (0%)	0 (0%)	3 (2%)
Thiopental	2 (4%)	0 (0%)	1 (2%)	3 (2%)
Succinylcholine	3 (7%)	3 (7%)	4 (9%)	10 (7%)
Cis-Atracurium	3 (7%)	3 (7%)	0 (0%)	6 (4%)
Atracurium	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Midazolam	42 (93%)	44 (98%)	45 (100%)	131 (97%)
Fentanyl	18 (40%)	10 (22%)	6 (13%)	34 (25%)
Sufentanil	23 (51%)	35 (78%)	40 (89%)	98 (73%)
Remifentanil	5 (11%)	3 (7%)	0 (0%)	8 (6%)
Naloxone	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Propofol	32 (71%)	33 (73%)	37 (82%)	102 (76%)
Epinephrine	5 (11%)	13 (29%)	11 (24%)	29 (22%)
Norepinephrine	33 (73%)	38 (84%)	37 (82%)	108 (80%)
Neostigmine	12 (27%)	9 (20%)	0 (0%)	21 (16%)
Glycopyrrolate	9 (20%)	8 (18%)	0 (0%)	17 (13%)
Nitroglycerin	2 (4%)	7 (16%)	4 (9%)	13 (10%)
Hydromorphone	7 (16%)	3 (7%)	4 (9%)	14 (10%)
Milrinone	1 (2%)	13 (29%)	25 (56%)	39 (29%)
Dopamine	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vasopressin	2 (4%)	2 (4%)	2 (4%)	6 (4%)
Desmopressin	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Lidocaine	7 (16%)	1 (2%)	14 (31%)	22 (16%)
Ketamine	32 (71%)	35 (78%)	32 (71%)	99 (73%)
Morphine	2 (4%)	4 (9%)	4 (9%)	10 (7%)
Tranexamic Acid	3 (7%)	24 (53%)	43 (96%)	70 (52%)
Rocuronium	37 (82%)	42 (93%)	44 (98%)	123 (91%)
Protamine	21 (47%)	42 (93%)	39 (87%)	102 (76%)
Heparin	38 (84%)	43 (96%)	44 (98%)	125 (93%)
Ephedrine	6 (13%)	9 (20%)	7 (16%)	22 (16%)
Phenylephrine	36 (80%)	30 (67%)	25 (56%)	91 (67%)
Cefazolin	19 (42%)	1 (2%)	1 (2%)	21 (16%)
Vancomycin	17 (38%)	43 (96%)	44 (98%)	104 (77%)
Ciprofloxacin	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Calcium Chloride	4 (9%)	8 (18%)	21 (47%)	33 (24%)
Magnesium Sulphate	2 (4%)	3 (7%)	4 (9%)	9 (7%)
Amiodarone	1 (2%)	2 (4%)	7 (16%)	10 (7%)
Labetolol	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Esmolol	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Hydrocortisone	2 (4%)	0 (0%)	2 (4%)	4 (3%)
Furosemide	3 (7%)	4 (9%)	1 (2%)	8 (6%)
Ondansetron	10 (22%)	1 (2%)	0 (0%)	11 (8%)
Insulin	1 (2%)	3 (7%)	11 (24%)	15 (11%)

Unlike outpatient medications, anesthetic medications were analyzed individually (**Table 17**). In terms of the anesthetic regimen, differences between maintenance, antibiotic use, and frequency of reversal of neuromuscular blockade within the OR were observed. While sevoflurane was the inhalation agent that was preferentially used in all three procedures for maintenance, there were also a few cases where isoflurane was also used in the open-heart procedure, and desflurane was used in the transfemoral procedure. Maintenance was also managed with the opioid sufenantil in the majority of patients in all three groups, but sufentanil was used in a greater proportion of patients receiving the more invasive transapical and open-heart procedures compared to the transfemoral procedure. Fentanyl was also used during maintenance, but it was preferentially used in transfemoral patients compared to transapical or open-heart patients. The antibiotics that were used for each procedure also differed, and perhaps reflected the different degrees of invasive between transfemoral TAVI and transapical TAVI or open-heart AVR; cefazolin was almost used exclusively in transfemoral patients while vancomycin was used almost exclusively in transapical and open-heart patients. Glycopyrrolate and neostigmine, which are drugs that reverse neuromuscular blockade, were used more often in the TAVI procedures than in the open-heart procedures. There were significant differences in the number of patients in each surgical group that received milrinone and tranexamic acid; both milrinone and tranexamic acid were given to the greatest number of open-heart patients, followed by transapical

patients, and lastly transfemoral patients. Calcium chloride, insulin, and the local anesthetic lidocaine were used in the greatest proportion of open-heart patients compared to either TAVI procedure. The number of patients given heparin, protamine, rocuronium, phenylephrine, and amiodarone only significantly differed between the transfemoral procedure and the open-heart procedure. The use of antibiotics differed between transfemoral TAVI and the more invasive procedures, with more transfemoral TAVI patients receiving cefazolin, and more transapical and open-heart patients receiving vancomycin. Lastly, ondansetron was used almost exclusively in transfemoral TAVI compared to transapical TAVI or open-heart AVR. There were no significant differences in the proportions of patients from each surgical group receiving midazolam, propofol, ketamine, or morphine.

Table 17. Differences between frequencies of intraoperative medications

	Transfemoral TAVI (n=45)	Transapical TAVI (n=45)	Open-Heart AVR (n=45)	*P* Value
Isoflurane, n (%)	0 (0)	0 (0)	12 (27)	<0.001[b, c]
Sevoflurane, n (%)	39 (87)	45 (100)	40 (89)	0.047[a, c]
Desflurane, n (%)	3 (7)	0 (0)	0 (0)	0.047[a, b]
Thiopental, n (%)	2 (4)	0 (0)	1 (2)	0.360
Succinylcholine, n (%)	3 (7)	3 (7)	4 (9)	0.898
Cis-atracurium, n (%)	3 (7)	3 (7)	0 (0)	0.208
Atracurium, n (%)	1 (2)	0 (0)	0 (0)	0.365
Midazolam, n (%)	42 (93)	44 (98)	45 (100)	0.165
Fentanyl, n (%)	18 (40)	10 (22)	6 (13)	0.012[b]
Sufentanil, n (%)	23 (51)	35 (78)	40 (89)	<0.001[a, b]
Remifentanil, n (%)	5 (11)	3 (7)	0 (0)	0.080
Propofol, n (%)	32 (71)	33 (73)	37 (82)	0.431
Epinephrine, n (%)	5 (11)	13 (29)	11 (24)	0.102
Norepinephrine, n (%)	33 (73)	38 (84)	37 (82)	0.378
Neostigmine, n (%)	12 (27)	9 (20)	0 (0)	0.001[b, c]
Glycopyrrolate, n (%)	9 (20)	8 (18)	0 (0)	0.007[b, c]
Nitroglycerin, n (%)	2 (4)	7 (16)	4 (9)	0.198
Hydromorphone, n (%)	7 (16)	3 (7)	4 (9)	0.355
Milrinone, n (%)	1 (2)	13 (29)	25 (56)	<0.001[a, b, c]
Dopamine, n (%)	0 (0)	0 (0)	0 (0)	1.00
Vasopressin, n (%)	2 (4)	2 (4)	2 (4)	1.00
Desmopressin, n (%)	0 (0)	1 (2)	0 (0)	0.365
Lidocaine, n (%)	7 (16)	1 (2)	14 (31)	0.001[a, c]
Ketamine, n (%)	32 (71)	35 (78)	32 (71)	0.711
Morphine, n (%)	2 (4)	4 (9)	4 (9)	0.649
Tranexamic Acid, n (%)	3 (7)	24 (53)	43 (96)	<0.001[a, b, c]
Rocuronium, n (%)	37 (82)	42 (93)	44 (98)	0.028[b]
Protamine, n (%)	21 (47)	42 (93)	39 (87)	<0.001[b]
Heparin, n (%)	38 (84)	43 (96)	44 (98)	0.035[b]
Ephedrine, n (%)	6 (13)	9 (20)	7 (16)	0.684
Phenylephrine, n (%)	36 (80)	30 (67)	25 (56)	0.047[b]
Cefazolin, n (%)	19 (42)	1 (2)	1 (2)	<0.001[a, b]
Vancomycin, n (%)	17 (38)	43 (96)	44 (98)	<0.001[a, b]
Calcium Chloride, n (%)	4 (9)	8 (18)	21 (47)	<0.001[b, c]
Magnesium Chloride, n (%)	2 (4)	3 (7)	4 (9)	0.700
Amiodarone, n (%)	1 (2)	2 (4)	7 (16)	0.035[b]
Ondansetron, n (%)	10 (22)	1 (2)	0 (0)	<0.001[a, b]
Insulin, n (%)	1 (2)	3 (7)	11 (24)	0.002[b, c]

Data represent count (proportion).

Anesthetic drugs did not affect delirium in any procedure (**Table 18**), except for the use of ketamine in transapical TAVI. A greater proportion of non-delirious transpical patients were given ketamine during surgery compared to delirious patients ($p = 0.038$).

Table 18. Differences between delirious and non-delirious individuals in frequency of anesthetic drug use within each surgical group

	Transfemoral TAVI			**Transapical TAVI**			**Open-Heart AVR**		
	Delirium (**n=7**)	No delirium (**n=38**)	*P*-value	Delirium (**n=23**)	No delirium (**n=22**)	*P*-value	Delirium (**n=17**)	No delirium (**n=28**)	*P*-value
Sevoflurane	6 (86)	33 (87)	0.936	23 (100)	22 (100)	1.00	17 (100)	23 (82)	0.065
Fentanyl	2 (29)	16 (42)	0.502	3 (13)	7 (32)	0.130	2 (12)	4 (14)	0.809
Sufentanil	4 (57)	19 (50)	0.728	20 (87)	15 (68)	0.130	15 (88)	25 (89)	0.913
Tranexamic Acid	1 (14)	2 (5)	0.379	13 (57)	11 (50)	0.667	17 (100)	26 (93)	0.260
Ketamine	4 (57)	8 (21)	0.375	15 (65)	20 (91)	0.038*	10 (59)	22 (79)	0.156
Rocuronium	7 (100)	30 (79)	0.181	22 (96)	20 (91)	0.524	17 (100)	27 (96)	0.431
Protamine	2 (29)	19 (50)	0.296	21 (91)	21 (95)	0.577	14 (82)	25 (89)	0.507
Phenylephrine	7 (100)	29 (76)	0.150	17 (74)	13 (59)	0.292	10 (59)	15 (54)	0.731
Vancomycin	3 (43)	14 (37)	0.763	22 (96)	21 (95)	0.974	16 (94)	28 (100)	0.194
Calcium Chloride	0 (0)	4 (11)	0.368	5 (22)	3 (14)	0.477	9 (53)	12 (43)	0.511

Data represent count (proportion).
*$p < 0.05$

3.9 Differences in Postoperative Drug Use Between Surgical Groups and Between Delirious and Non-Delirious Patients Within Each Surgical Group

Frequencies of use of each drug used in the postoperative period immediately after surgery, that is, in the duration of time immediately following surgery till eight o'clock the next morning, are given in **Table 19**, and those that were used between postoperative days #1-3 are given in **Table 20**. No statistics were calculated on these frequencies and they are meant solely for illustrative purposes.

Table 19. Frequencies of postoperative drug use immediately following surgery, according to surgery group

Drug	Transfemoral TAVI (n = 45)	Transapical TAVI (n = 44*)	Open-Heart AVR (n = 45)	Overall Frequency (n = 134)
Metoprolol	6 (13%)	2 (5%)	3 (7%)	11 (8%)
Bisoprolol	1 (2%)	1 (2%)	1 (2%)	3 (2%)
Atenolol	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Labetolol	2 (4%)	1 (2%)	6 (13%)	9 (7%)
Sotalol	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nadolol	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Carvedilol	2 (4%)	0 (0%)	0 (0%)	2 (1%)
Esmolol	0 (0%	1 (2%)	0 (0%)	1 (1%)
Furosemide	10 (22%)	20 (45%)	16 (36%)	46 (34%)
Metolazone	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Spironolactone	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hydrochlorothiazide	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ramipril	3 (7%)	1 (2%)	0 (0%)	4 (3%)
Captopril	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Lisonopril	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Trandolapril	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Donepezil	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Perindopril	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Nitroglycerin	11 (24%)	29 (66%)	29 (64%)	69 (51%)
Nitroprusside	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Clonidine	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Hydralazine	5 (11%)	10 (23%)	14 (31%)	29 (22%)
Trazodone	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Methyldopa	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Candesartan	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Losartan	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Amlodipine	3 (7%)	3 (7%)	1 (2%)	7 (5%)
Diltiazem	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Felodipine	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Verapamil	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Simvastatin	14 (31%)	2 (5%)	0 (0%)	16 (12%)
Pravastatin	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Atorvastatin	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Heparin	3 (7%)	4 (9%)	1 (2%)	8 (6%)
Warfarin	1 (2%)	0 (0%)	1 (2%)	2 (1%)
Clopidogrel	7 (16%)	0 (0%)	0 (0%)	7 (5%)
Ranitidine	1 (2%)	18 (41%)	17 (38%)	36 (27%)
Rabeprazole	2 (4%)	1 (2%)	1 (2%)	4 (3%)
Pantoprazole	3 (7%)	2 (5%)	0 (0%)	5 (4%)
Lansoprazole	2 (4%)	2 (5%)	0 (0%)	4 (3%)
Esomeprazole	0 (0%)	2 (5%)	0 (0%)	2 (1%)
Omeprazole	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ondansetron	8 (18%)	8 (18%)	26 (58%)	42 (31%)
Prochlorperazine	1 (2%)	1 (2%)	8 (18%)	10 (7%)

Table 19. Frequencies of postoperative drug use immediately following surgery, according to surgery group

Drug	Transfemoral TAVI (n = 45)	Transapical TAVI (n = 44*)	Open-Heart AVR (n = 45)	Overall Frequency (n = 134)
Dimenhydrinate	4 (9%)	3 (7%)	2 (4%)	9 (7%)
Metoclopramide	1 (2%)	1 (2%)	0 (0%)	2 (1%)
Ipratropium	5 (11%)	1 (2%)	0 (0%)	6 (4%)
Tiotropium	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Salbutamol	2 (4%)	4 (9%)	1 (2%)	7 (5%)
Salmeterol	3 (7%)	1 (2%)	0 (0%)	4 (3%)
Fluticasone	2 (4%)	1 (2%)	0 (0%)	3 (2%)
Budesonide	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Formeterol	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Beclomethason	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Insulin	10 (22%)	26 (59%)	41 (91%)	77 (57%)
Dextrose Solution	3 (7%)	34 (77%)	40 (89%)	67 (50%)
Morphine	17 (38%)	31 (70%)	44 (98%)	92 (69%)
Hydromorphone	20 (44%)	22 (50%)	34 (76%)	76 (57%)
Acetaminophen	24 (53%)	36 (82%)	44 (98%)	104 (78%)
Lorazepam	2 (4%)	1 (2%)	8 (18%)	11 (8%)
Midazolam	6 (13%)	23 (52%)	36 (80%)	65 (49%)
Propofol	10 (22%)	25 (57%)	45 (100%)	80 (60%)
Norepinephrine	7 (16%)	22 (50%)	35 (78%)	64 (48%)
Epinephrine	3 (7%)	10 (23%)	11 (24%)	24 (18%)
Milrinone	1 (2%)	12 (27%)	24 (53%)	37 (28%)

No statistics were calculated on these data.
*One patient who received the transapical procedure died during the procedure and was never transferred into CSICU.
Data represent count (proportion).

Table 20. Frequencies of postoperative drug use anytime from postoperative days 1-3, according to surgery group

Drug	Transfemoral TAVI (n = 44)*	Transapical TAVI (n = 43)**	Open-Heart AVR (n = 45)	Overall Frequency (n = 131)
Metoprolol	14 (32%)	20 (47%)	21 (47%)	55 (42%)
Bisoprolol	12 (27%)	7 (16%)	3 (7%)	22 (17%)
Atenolol	2 (5%)	4 (9%)	13 (29%)	19 (15%)
Labetolol	1 (2%)	2 (5%)	0 (0%)	3 (2%)
Sotalol	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Nadolol	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Carvedilol	3 (7%)	2 (5%)	1 (2%)	6 (5%)
Esmolol	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Furosemide	30 (68%)	41 (95%)	44 (98%)	115 (88%)
Metolazone	2 (5%)	6 (14%)	2 (4%)	10 (8%)
Spironolactone	3 (7%)	3 (7%)	0 (0%)	6 (1%)
Hydrochlorothiazide	4 (9%)	1 (2%)	0 (0%)	5 (4%)
Ramipril	19 (43%)	11 (26%)	16 (36%)	46 (35%)
Captopril	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Lisonopril	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Trandolapril	2 (5%)	1 (2%)	1 (2%)	4 (3%)
Donepezil	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Perindopril	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Nitroglycerin	9 (20%)	16 (37%)	18 (40%)	43 (33%)
Nitroprusside	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Clonidine	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Hydralazine	2 (5%)	13 (30%)	13 (29%)	28 (21%)
Trazodone	3 (7%)	0 (0%)	0 (0%)	3 (2%)
Methyldopa	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Candesartan	4 (9%)	5 (12%)	0 (0%)	9 (7%)
Losartan	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Amlodipine	4 (9%)	14 (33%)	5 (11%)	23 (18%)
Diltiazem	3 (7%)	1 (2%)	0 (0%)	4 (3%)
Felodipine	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Verapamil	1 (2%)	1 (2%)	1 (2%)	3 (2%)
Simvastatin	33 (75%)	28 (65%)	23 (51%)	84 (64%)
Pravastatin	2 (5%)	1 (2%)	1 (2%)	4 (3%)
Atorvastatin	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Heparin	11 (25%)	39 (91%)	45 (100%)	95 (73%)
Warfarin	13 (30%)	12 (28%)	12 (27%)	37 (28%)
Clopidogrel	33 (75%)	24 (56%)	1 (2%)	58 (44%)
Ranitidine	1 (2%)	10 (23%)	27 (60%)	38 (29%)
Rabeprazole	7 (16%)	7 (16%)	10 (22%)	24 (18%)
Pantoprazole	5 (12%)	3 (7%)	0 (0%)	8 (6%)
Lansoprazole	13 (30%)	19 (44%)	14 (31%)	46 (35%)
Esomeprazole	0 (0%)	12 (28%)	0 (0%)	12 (9%)
Omeprazole	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Ondansetron	5 (11%)	7 (16%)	5 (11%)	17 (13%)
Prochlorperazine	1 (2%)	7 (16%)	6 (13%)	14 (11%)

Table 20. Frequencies of postoperative drug use anytime from postoperative days 1-3, according to surgery group

Drug	Transfemoral TAVI (n = 44)*	Transapical TAVI (n = 43)**	Open-Heart AVR (n = 45)	Overall Frequency (n = 131)
Dimenhydrinate	7 (16%)	1 (2%)	4 (9%)	12 (9%)
Metoclopramide	3 (7%)	1 (2%)	3 (7%)	7 (5%)
Ipratropium	7 (16%)	4 (9%)	7 (16%)	18 (14%)
Tiotropium	4 (9%)	2 (5%)	0 (0%)	6 (5%)
Salbutamol	3 (7%)	8 (19%)	11 (24%)	22 (17%)
Salmeterol	9 (20%)	3 (7%)	1 (2%)	13 (10%)
Fluticasone	6 (14%)	3 (7%)	1 (2%)	10 (8%)
Budesonide	0 (0%)	0 (0%)	1 (2%)	1 (1%)
Formeterol	0 (0%)	1 (2%)	1 (2%)	2 (2%)
Beclomethason	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Insulin	11 (25%)	20 (47%)	31 (69%)	62 (47%)
Dextrose Solution	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Morphine	7 (16%)	11 (26%)	28 (62%)	46 (35%)
Hydromorphone	19 (43%)	26 (60%)	44 (98%)	89 (68%)
Acetaminophen	41 (93%)	40 (93%)	44 (98%)	125 (95%)
Lorazepam	4 (9%)	4 (9%)	9 (20%)	17 (13%)
Midazolam	0 (0%)	4 (9%)	2 (4%)	6 (5%)
Propofol	0 (0%)	5 (12%)	2 (4%)	7 (5%)
Norepinephrine	2 (5%)	9 (21%)	8 (18%)	19 (15%)
Epinephrine	2 (5%)	2 (5%)	1 (2%)	5 (4%)
Milrinone	0 (0%)	7 (16%)	13 (29%)	20 (15%)

*One patient died 3 hours after receiving transfemoral TAVI, and another died 18 hours after; however, partial drug consumption data was accrued for POD #1 for the latter, patient which is why n=44 instead of 43 for this group.
**One patient died during transapical TAVI, and another died 2 hours after.
All data represent count (proportion).

When drugs that were administered postoperatively were grouped into classes according to the same classification scheme described in **Table 13**, there were significant differences in the proportions of transfemoral patients and open-heart patients being given lipid-lowering agents and anti-emetics; unlike the trend seen preoperatively, a greater number of transfemoral rather than transapical patients were being given lipid-lowering agents, while a greater number of open-

heart patients were being given ant-emetic agents. A smaller proportion of transfemoral patients were given postoperative proton-pump inhibitors and dextrose compared to the more invasive procedures, while a larger proportion of open-heart patients were given hydromorphone compared to either TAVI procedure. And finally, similar to milrinone and tranexamic acid given during anesthesia, there were significant differences between all three surgical groups in the number of patients being given postoperative insulin, midazolam, propofol, and norepinephrine, with the largest proportion being patients that received open-heart AVR, followed by transapical TAVI, and lastly, by transfemoral TAVI.

Table 21. Differences in postoperative medication use

	Transfemoral TAVI (n=45)	Transapical TAVI (n=45)	Open-Heart AVR (n=45)	*P* Value
Antihypertensives, n (%)	43 (98)	43 (98)	45 (100)	0.595
Lipid-Lowering Agents, n (%)	36 (82)	29 (66)	24 (53)	0.017[b]
Anticoagulants, n (%)	41 (93)	42 (96)	45 (100)	0.204
Proton-Pump Inhibitors, n (%)	22 (50)	42 (96)	44 (98)	<0.001[a,b]
Antiemetics, n (%)	17 (39)	20 (46)	28 (62)	0.046[b]
Insulin, n (%)	13 (30)	27 (61)	41 (91)	<0.001[a,b,c]
Dextrose Solution, n (%)	3 (7)	34 (77)	40 (89)	<0.001[a,b]
Morphine, n (%)	18 (41)	31 (71)	44 (98)	<0.001[a,b,c]
Hydromorphone, n (%)	26 (59)	32 (73)	44 (98)	<0.001[b,c]
Acetaminophen, n (%)	41 (93)	40 (91)	44 (98)	0.381
Lorazepam, n (%)	6 (14)	5 (11)	12 (27)	0.119
Midazolam, n (%)	6 (14)	23 (52)	36 (80)	<0.001[a,b,c]
Propofol, n (%)	10 (23)	25 (57)	35 (78)	<0.001[a,b,c]
Norepinephrine, n (%)	7 (16)	22 (50)	35 (78)	<0.001[a,b,c]
Epinephrine, n (%)	4 (9)	10 (23)	11 (24)	0.129
Milrinone, n (%)	1 (2)	13 (30)	24 (53)	<0.001[a,b,c]

Data represent count (proportion).
[a] $p < 0.05$ between transfemoral and transapical; [b] $p < 0.05$ between transfemoral and open-heart; [c] $p < 0.05$ between transapical and open-heart

Drugs given to patients postoperatively from the period immediately following surgery until POD #3 are shown in **Table 22.** Warfarin given on POD #2 was associated with delirium; a significantly greater proportion of delirious patients were given warfarin on POD #2 than non-delirious patients. And while lorazepam given immediately after surgery and on POD #3, morphine given on POD #2, and hydralazine given on POD #3 seemed to be significantly associated with delirium, there was only one individual who was taking each of those drugs on these days; therefore, these associations are probably underpowered and are likely not indicative of a true trend. Epinephrine given immediately after surgery, dopamine given on POD #1, and rabeprazole and insulin given on POD #3 was associated with delirium in the transapical group. For all these drugs, the proportions of delirious individuals taking those drugs were higher than the proportions of non-delirious individuals. Similarly, epinephrine given immediately after surgery reflected the same trend in open-heart patients. Interestingly, zopiclone given on POD #1, 2, and 3 was significantly negatively associated with delirium in transapical and open-heart patients. Zopiclone usage was higher in non-delirious patients receiving these procedures, but had no correlation with delirium in the transfemoral procedure.

Table 22. Differences between frequency of postoperative drug use between delirious and non-delirous individuals within each surgical group

	Transfemoral TAVI			Transapical TAVI			Open-Heart AVR		
	Delirium (**n=7**)	No delirium (**n=38**)	*P*-value	Delirium (**n=23**)	No delirium (**n=22**)	*P*-value	Delirium (**n=17**)	No delirium (**n=28**)	*P*-value
Medications Received Immediately After Surgery									
Lorazepam, n (%)	1 (14)	0 (0)	0.022*	2 (9)	0 (0)	0.157	2 (12)	6 (21)	0.411
Epinephrine, n (%)	1 (14)	1 (3)	0.186	9 (39)	2 (9)	0.019*	7 (41)	4 (14)	0.042*
Medications Received on POD #1									
Dopamine, n (%)	0 (0)	1 (3)	0.655	4 (17)	0 (0)	0.040*	1 (6)	1 (4)	0.715
Zopiclone, n (%)	0 (0)	10 (26)	0.111	2 (9)	10 (45)	0.005*	2 (12)	12 (43)	0.029*
Medications Received on POD #2									
Morphine, n (%)	1 (14)	0 (0)	0.022*	2 (9)	3 (13)	0.598	3 (18)	1 (4)	0.108
Warfarin, n (%)	4 (57)	4 (11)	0.004*	6 (26)	4 (18)	0.524	4 (24)	6 (21)	0.869
Zopiclone, n (%)	0 (0)	11 (29)	0.090	4 (17)	10 (45)	0.042*	3 (18)	17 (61)	0.005*
Medications Received on POD #3									
Lorazepam, n (%)	1 (14)	0 (0)	0.022*	1 (4)	0 (0)	0.323	3 (18)	3 (11)	0.507
Hydralazine, n (%)	1 (14)	0 (0)	0.022*	2 (9)	5 (23)	0.194	3 (18)	6 (21)	0.758
Rabeprazole, n (%)	1 (14)	3 (8)	0.620	7 (30)	1 (5)	0.023*	6 (35)	7 (25)	0.460
Insulin, n (%)	1 (14)	3 (8)	0.620	7 (30)	1 (5)	0.023*	6 (35)	7 (25)	0.460
Zopiclone, n (%)	0 (0)	11 (29)	0.090	2 (9)	8 (36)	0.026	1 (6)	16 (57)	0.001*

*$p < 0.05$
Data represent count (proportion).

White cells in **Table 23** indicate surgeries where > 50% of delirious patients compared to non-delirious patients were taking a certain drug. The percentages in the brackets indicate the proportions of patients that were taking each drug that became delirious or did not become delirious; bolded fonts indicate surgeries where > 50% of the individuals taking the drug became delirious. For instance, the white cells for transapical patients taking metoprolol

as outpatients mean that a greater proportion of delirious transapical patients were taking metoprolol as outpatients compared to non-delirious patients (9/23 = 39% versus 8/22 = 36%), and the bolded font indicates that most transapical patients who were taking metoprolol as outpatients developed delirium (9/17 = 53%). A larger proportion of delirious patients versus the proportion of non-delirious patients in all three surgical groups were taking nitroglycerin, lorazepam, metformin and warfarin as outpatients; propofol, epinephrine, tranexamic acid, rocuronium, heparin, and phenylephrine during anesthesia; furosemide and heparin immediately after surgery; and metoprolol and warfain during POD #1-3. Thus, the class of drugs that was taken by a greater proportion of delirious patients from all three surgical groups throughout the perioperative period was anticoagulant agents (namely, warfarin and heparin).

Surprisingly, there were no drugs where more than 50% of patients taking those drugs became delirious in all three surgical groups. However, more than 50% of transapical and open-heart patients using the outpatient medications metoprolol, furosemide, glyburide, and digoxin; the opioid analgesic morphine; as well as the postoperative drugs heparin, epinephrine and norepineprhine, became delirious. This also appeared to be true for outpatient use of felodipine, terazosin, and lansoprazole, but there were only frequency counts of 1 for these drugs, so they are probably not reflective of a true correlation. In transfemoral TAVI, only the use of preoperative gliclazide and candesartan, and intraoperative labetolol were associated with delirium in more than 50% of patients taking these

drugs; but just like outpatient use of felodipine, terazosin, and lansoprazole for transapical TAVI and open-heart AVR, the frequency counts were only 1 for these drugs.

A 2x2 construct can be obtained from the results of this table, and each drug may fit into the description given in a single quadrant listed as such:

i) A greater proportion of delirious versus non-delirious patients were on drug *x*, and a greater proportion of drug *x* users became delirious, compared to the proportion of drug *x* users who did not become delirious (white cells, bold font)

ii) A greater proportion of delirious versus non-delirious patients were on drug *x*, but a greater proportion of drug *x* users did not become delirious compared to the proportion of drug *x* users who did become delirious (white cells, normal font)

iii) A greater proportion of non-delirious versus delirious individuals were taking drug *x*, and a greater proportion of drug *x* users did not become delirious compared to the proportion of drug *x* users who did become delirious (grey cells, normal font)

iv) A greater proportion of non-delirious versus delirious patients were taking drug *x*, but a greater proportion of drug *x* users became delirious compared to the proportion of drug *x* users who did not become delirious (grey cells, bold font)

Table 23. Drugs that were used more frequently in patients with delirium (white cells) and the proportions of individuals who were taking those drugs that became delirious

Drug	Transfemoral TAVI		Transapical TAVI		Open-Heart AVR		Overall Frequency	
	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium
Outpatient Drugs	**(n=7)**	**(n=38)**	**(n=23)**	**(n=22)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=88)**
Metoprolol	1 (9%)	10 (91%)	**9 (53%)**	**8 (47%)**	**4 (67%)**	**2 (33%)**	14 (41%)	20 (59%)
Bisoprolol	1 (17%)	5 (83%)	2 (33%)	4 (67%)	2 (40%)	3 (60%)	5 (29%)	12 (71%)
Atenolol	0 (0%)	2 (100%)	1 (25%)	3 (75%)	**3 (60%)**	**2 (40%)**	4 (36%)	7 (64%)
Carvedilol	1 (33%)	2 (67%)	**2 (67%)**	**1 (33%)**	0 (0%)	1 (100%)	3 (43%)	4 (57%)
Sotalol	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**2 (100%)**	**0 (0%)**	2 (100%)	0 (0%)
Acebutolol	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**2 (100%)**	**0 (0%)**	2 (100%)	0 (0%)
Salbutamol	0 (0%)	7 (100%)	1 (33%)	2 (67%)	**2 (67%)**	**1 (33%)**	3 (23%)	10 (77%)
Salmeterol	0 (0%)	7 (100%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	2 (18%)	9 (82%)
Furosemide	3 (10%)	26 (90%)	**15 (56%)**	**12 (44%)**	**8 (53%)**	**7 (47%)**	26 (37%)	45 (63%)
Hydrochlorothiazide	2 (25%)	6 (75%)	1 (25%)	3 (75%)	1 (25%)	3 (75%)	4 (25%)	12 (75%)
Spironolactone	1 (25%)	3 (75%)	3 (43%)	4 (57%)	2 (50%)	2 (50%)	6 (40%)	9 (60%)
Diltiazem	1 (20%)	4 (80%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	4 (80%)
Felodipine	0 (0%)	1 (100%)	**1 (100%)**	**0 (0%)**	**1 (100%)**	**0 (0%)**	2 (67%)	1 (33%)
Amlodipine	0 (0%)	0 (0%)	7 (50%)	7 (50%)	1 (50%)	1 (50%)	8 (50%)	8 (50%)
Verapamil	0 (0%)	1 (100%)	**1 (100%)**	**0 (0%)**	1 (50%)	1 (50%)	2 (50%)	2 (50%)
Nitroglycerin	1 (20%)	4 (80%)	**6 (100%)**	**0 (0%)**	1 (50%)	1 (50%)	8 (62%)	5 (38%)
Terazosin	0 (0%)	2 (100%)	**1 (100%)**	**0 (0%)**	**1 (100%)**	**0 (0%)**	2 (50%)	2 (50%)
Valsartan	2 (29%)	5 (71%)	0 (0%)	2 (100%)	**1 (100%)**	**0 (0%)**	3 (30%)	7 (70%)
Telmisartan	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	1 (100%)	0 (0%)
Candesartan	**1 (100%)**	**0 (0%)**	1 (33%)	2 (67%)	0 (0%)	0 (0%)	2 (50%)	2 (50%)
Ramipril	2 (10%)	18 (90%)	**7 (78%)**	**2 (22%)**	3 (30%)	7 (70%)	12 (31%)	27(69%)
Donepezil	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Quinapril	0 (0%)	0 (0%)	**2 (67%)**	**1 (33%)**	1 (33%)	2 (67%)	3 (50%)	3 (50%)
Simvastatin	1 (13%)	7 (87%)	5 (42%)	7 (58%)	5 (42%)	7 (58%)	11 (34%)	21 (66%)
Rosuvastatin	1 (33%)	2 (67%)	**3 (75%)**	**1 (25%)**	0 (0%)	2 (100%)	4 (44%)	5 (56%)
Atorvastatin	2 (14%)	12 (86%)	**10 (67%)**	**5 (33%)**	3 (50%)	3 (50%)	15(43%)	20 (57%)
Loxapine	0 (0%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	2 (50%)	2 (50%)
Oxazepam	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
Lorazepam	1 (25%)	3 (75%)	**3 (75%)**	**1 (25%)**	2 (40%)	3 (60%)	6 (46%)	7 (54%)
Sertraline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
Trazodone	0 (0%)	1 (100%)	**2 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	1 (33%)	2 (67%)
Trimipramine	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Rabeprazole	0 (0%)	8 (100%)	0 (0%)	4 (100%)	2 (40%)	3 (60%)	2 (12%)	15 (88%)
Omeprazole	1 (50%)	1 (50%)	1 (33%)	2 (67%)	0 (0%)	0 (0%)	2 (40%)	3 (60%)

Table 23. Drugs that were used more frequently in patients with delirium (white cells) and the proportions of individuals who were taking those drugs that became delirious

Drug	Transfemoral TAVI		Transapical TAVI		Open-Heart AVR		Overall Frequency	
	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium
Outpatient Drugs	**(n=7)**	**(n=38)**	**(n=23)**	**(n=22)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=88)**
Esomeprazole	0 (0%)	2 (100%)	**4 (67%)**	**2 (33%)**	0 (0%)	0 (0%)	4 (50%)	4 (50%)
Pantoprazole	0 (0%)	3 (100%)	**2 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	2 (40%)	3 (60%)
Lansoprazole	0 (0%)	3 (100%)	**1 (100%)**	**0 (0%)**	**1 (100%)**	**0 (0%)**	2 (40%)	3 (60%)
Insulin	1 (25%)	3 (75%)	1 (33%)	2 (67%)	1 (25%)	3 (75%)	3 (27%)	8 (73%)
Metformin	1 (20%)	4 (80%)	**4 (67%)**	**2 (33%)**	4 (50%)	4 (50%)	9 (47%)	10 (53%)
Glyburide	0 (0%)	1 (100%)	**3 (75%)**	**1 (25%)**	**3 (60%)**	**2 (40%)**	6 (60%)	4 (40%)
Gliclazide	**1 (100%)**	**0 (0%)**	1 (50%)	1 (50%)	0 (0%)	1 (100%)	2 (50%)	2 (50%)
Digoxin	0 (0%)	8 (100%)	**9 (64)**	**5 (36%)**	**5 (83%)**	**1 (17%)**	11 (44%)	14 (56%)
Amiodarone	1 (25%)	3 (75%)	**2 (67%)**	**1 (33%)**	1 (33%)	2 (67%)	4 (40%)	6 (60%)
Propafenone	0 (0%)	0 (0%)	0 (0%)	1 (100%)	**1 (100%)**	**0 (0%)**	1 (50%)	1 (50%)
Heparin	0 (0%)	4 (100%)	0 (0%)	4 (100%)	**2 (100%)**	**0 (0%)**	2 (20%)	8 (80%)
Warfarin	3 (38%)	5 (62%)	**4 (57%)**	**3 (43%)**	**3 (100%)**	**0 (0%)**	10 (56%)	8 (44%)
Clopidogrel	1 (7%)	13 (93%)	**8 (67%)**	**4 (33%)**	**2 (67%)**	**1 (33%)**	11 (38%)	18 (62%)
Vancomycin	1 (33%)	2 (67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	2 (67%)
Cefuroxime	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Intraoperative Drugs	**(n=7)**	**(n=38)**	**(n=23)**	**(n=22)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=88)**
Sevoflurane	6 (16%)	32 (84%)	**23 (51%)**	**22 (49%)**	17 (43%)	23 (57%)	46 (37%)	77 (63%)
Thiopental	1 (50%)	1 (50%)	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	2 (67%)	1 (33%)
Sufentanil	4 (18%)	18 (82%)	**20 (57%)**	**15 (43%)**	15 (38%)	25 (62%)	39 (40%)	58 (60%)
Remifentanil	0 (0%)	5 (100%)	**2 (67%)**	**1 (33%)**	0 (0%)	0 (0%)	2 (25%)	6 (75%)
Propofol	6 (19%)	25 (81%)	**18 (55%)**	**15 (45%)**	16 (43%)	21 (57%)	40 (40%)	61 (60%)
Morphine	0 (0%)	2 (100%)	**3 (75%)**	**1 (25%)**	**3 (75%)**	**1 (25%)**	6 (60%)	4 (40%)
Midazolam	6 (15%)	35 (85%)	23 (48%)	21 (52%)	17 (38%)	28 (62%)	46 (35%)	84 (65%)
Hydromorphone	1 (14%)	6 (86%)	**2 (67%)**	**1 (33%)**	1 (25%)	3 (75%)	4 (29%)	10 (71%)
Milrinone	0 (0%)	1 (100%)	**7 (54%)**	**6 (46%)**	11 (44%)	14 (56%)	18 (46%)	21 (54%)
Epinephrine	1 (20%)	4 (80%)	**8 (62%)**	**5 (38%)**	5 (45%)	6 (55%)	14 (48%)	15 (52%)
Nitroglycerin	1 (50%)	1 (50%)	2 (29%)	5 (71%)	2 (50%)	2 (50%)	5 (42%)	7 (58%)
Vasopressin	1 (50%)	1 (50%)	1 (50%)	1 (50%)	0 (0%)	2 (100%)	2 (33%)	4 (67%)
Tranexamic Acid	1 (33%)	2 (67%)	**13 (54%)**	**11 (46%)**	17 (40%)	26 (60%)	31 (44%)	39 (56%)
Rocuronium	7 (19%)	29 (81%)	**22 (52%)**	**20 (48%)**	17 (39%)	27 (61%)	46 (38%)	76 (62%)
Lidocaine	0 (0%)	7 (100%)	**1 (100%)**	**0 (0%)**	4 (29%)	10 (71%)	5 (23%)	17 (77%)
Heparin	6 (16%)	31 (84%)	**23 (53%)**	**20 (47%)**	17 (39%)	27 (61%)	43 (36%)	78 (64%)
Phenylephrine	7 (20%)	28 (80%)	**17 (57%)**	**13 (43%)**	10 (40%)	15 (60%)	34 (38%)	56 (62%)
Ephedrine	0 (0%)	6 (100%)	**6 (67%)**	**3 (33%)**	3 (43%)	4 (57%)	9 (41%)	13 (59%)
Cefazolin	2 (11%)	17 (89%)	0 (0%)	1 (100%)	**1 (100%)**	**0 (0%)**	3 (14%)	18 (86%)

Table 23. Drugs that were used more frequently in patients with delirium (white cells) and the proportions of individuals who were taking those drugs that became delirious

Drug	Transfemoral TAVI		Transapical TAVI		Open-Heart AVR		Overall Frequency	
	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium
Intraoperative Drugs	**(n=7)**	**(n=38)**	**(n=23)**	**(n=22)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=88)**
Vancomycin	3 (19%)	13 (81%)	**22 (51%)**	**21 (49%)**	16 (36%)	28 (64%)	41 (40%)	62 (60%)
Hydrocortisone	0 (0%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (50%)	2 (50%)
Labetolol	**1 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Furosemide	1 (33%)	2 (67%)	2 (50%)	2 (50%)	0 (0%)	1 (100%)	3 (37%)	5 (63%)
Ondansetron	2 (20%)	8 (80%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	2 (18%)	9 (82%)
Calcium Chloride	0 (0%)	4 (100%)	**5 (63%)**	**3 (37%)**	9 (43%)	12 (57%)	14 (17%)	19 (83%)
Magnesium Sulphate	0 (0%)	2 (100%)	**2 (67%)**	**1 (33%)**	0 (0%)	4 (100%)	2 (22%)	7 (78%)
Postoperative Drugs Taken Immediately After Surgery	**(n=7)**	**(n=38)**	**(n=23)**	**(n=21)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=87)**
Bisoprolol	0 (0%)	1 (100%)	**1 (100%)**	**0 (0%)**	**1 (100%)**	**0 (0%)**	2 (67%)	1 (33%)
Labetolol	1 (50%)	1 (50%)	**1 (100%)**	**0 (0%)**	1 (17%)	5 (83%)	3 (33%)	6 (67%)
Esmolol	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	0 (%)	0 (0%)	1 (100%)	0 (0%)
Carvedilol	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)
Ramipril	0 (0%)	3 (100%)	**1 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	1 (25%)	3 (75%)
Furosemide	2 (20%)	8 (80%)	**11 (55%)**	**9 (45%)**	7 (44%)	9 (56%)	20 (43%)	26 (57%)
Nitroglycerin	2 (18%)	9 (82%)	**16 (55%)**	**13 (45%)**	**10 (53%)**	**19 (47%)**	28 (41%)	41 (59%)
Hydralazine	2 (40%)	3 (60%)	**6 (60%)**	**4 (40%)**	5 (36%)	9 (64%)	13 (45%)	16 (55%)
Amlodipine	0 (0%)	0 (0%)	**2 (67%)**	**1 (33%)**	0 (0%)	0 (0%)	2 (67%)	1 (33%)
Heparin	1 (33%)	2 (67%)	**3 (75%)**	**1 (25%)**	**1 (100%)**	**0 (0%)**	5 (62%)	3 (38%)
Warfarin	0 (0%)	1 (100%)	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	1 (50%)	1 (50%)
Ranitidine	0 (0%)	1 (100%)	**11 (61%)**	**7 (39%)**	7 (41%)	10 (59%)	18 (50%)	18 (50%)
Rabeprazole	0 (0%)	2 (100%)	**1 (100%)**	**0 (0%)**	0 (0%)	1 (100%)	2 (50%)	2 (50%)
Esomeprazole	0 (0%)	0 (0%)	**2 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	2 (100%)	0 (0%)
Ondansetron	2 (25%)	6 (75%)	**7 (88%)**	**1 (12%)**	7 (27%)	19 (73%)	16 (38%)	26 (62%)
Dimenhydrinate	1 (25%)	3 (75%)	1 (33%)	2 (67%)	0 (0%)	2 (100%)	2 (22%)	7 (78%)
Ipratropium	1 (20%)	4 (80%)	**1 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	2 (33%)	4 (67%)
Insulin	3 (30%)	7 (70%)	**16 (62%)**	**10 (38%)**	15 (37%)	26 (63%)	34 (44%)	43 (56%)
Dextrose Solution	1 (33%)	2 (67%)	16 (47%)	18 (53%)	14 (35%)	26 (65%)	31 (40%)	46 (60%)
Hydromorphone	4 (20%)	16 (80%)	**13 (59%)**	**9 (41%)**	11 (32%)	23 (68%)	28 (37%)	48 (63%)
Norepinephrine	0 (0%)	7 (100%)	11 (50%)	11 (50%)	14 (40%)	21 (60%)	25 (39%)	39 (61%)
Acetaminophen	5 (21%)	19 (79%)	17 (47%)	19 (54%)	16 (36%)	28 (64%)	38 (37%)	66 (63%)
Midazolam	1 (17%)	5 (83%)	11 (48%)	12 (52%)	14 (39%)	22 (61%)	26 (40%)	39 (60%)
Postoperative Drugs Taken Anytime Between POD #1-3	**(n=7)**	**(n=37)**	**(n=23)**	**(n=20)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=85)**
Metoprolol	3 (21%)	11 (79%)	**12 (60%)**	**8 (40%)**	1 (50%)	1 (50%)	16 (44%)	20 (56%)

Table 23. Drugs that were used more frequently in patients with delirium (white cells) and the proportions of individuals who were taking those drugs that became delirious

Drug	Transfemoral TAVI		Transapical TAVI		Open-Heart AVR		Overall Frequency	
	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium
Postoperative Drugs Taken Anytime Between POD #1-3	**(n=7)**	**(n=37)**	**(n=23)**	**(n=20)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=85)**
Bisoprolol	3 (25%)	9 (75%)	3 (43%)	4 (57%)	1 (33%)	2 (67%)	7 (32%)	15 (68%)
Atenolol	0 (0%)	2 (100%)	0 (0%)	4 (100%)	6 (46%)	7 (54%)	6 (32%)	13 (68%)
Labetolol	1 (100%)	0 (0%)	**2 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	3 (100%)	0 (0%)
Sotalol	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	1 (100%)	0 (0%)
Carvedilol	1 (33%)	2 (67%)	**2 (100%)**	**0 (0%)**	0 (0%)	1 (100%)	3 (50%)	3 (50%)
Furosemide	4 (13%)	26 (87%)	**22 (54%)**	**19 (46%)**	16 (36%)	28 (64%)	42 (37%)	73 (63%)
Spironolactone	1 (33%)	2 (67%)	**2 (67%)**	**1 (33%)**	0 (0%)	0 (0%)	3 (50%)	3 (50%)
Hydrochlorothiazide	1 (25%)	3 (75%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (20%)	4 (80%)
Ramipril	2 (11%)	17 (89%)	**6 (55%)**	**5 (45%)**	6 (38%)	10 (62%)	14 (30%)	32 (70%)
Donepezil	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Verapamil	0 (0%)	1 (100%)	**1 (100%)**	**0 (0%)**	0 (0%)	1 (100%)	1 (33%)	2 (67%)
Nitroglycerin	2 (22%)	7 (78%)	7 (44%)	9 (56%)	7 (39%)	11 (61%)	16 (37%)	27 (63%)
Hydralazine	1 (50%)	1 (50%)	5 (38%)	8 (62%)	4 (31%)	9 (69%)	10 (36%)	18 (64%)
Terazosin	1 (33%)	2 (67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	2 (67%)
Candesartan	1 (25%)	3 (75%)	1 (20%)	4 (80%)	0 (0%)	0 (0%)	2 (22%)	7 (78%)
Amlodipine	1 (25%)	3 (75%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	3 (75%)
Diltiazem	1 (33%)	2 (67%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (25%)	3 (75%)
Simvastatin	5 (15%)	28 (85%)	**15 (54%)**	**13 (46%)**	9 (39%)	14 (61%)	29 (35%)	55 (65%)
Pravastatin	0 (0%)	2 (100%)	0 (0%)	1 (100%)	**1 (100%)**	**0 (0%)**	1 (25%)	3 (75%)
Heparin	1 (33%)	2 (67%)	**21 (54%)**	**18 (46%)**	17 (38%)	28 (62%)	39 (45%)	48 (55%)
Warfarin	4 (31%)	9 (69%)	**7 (58%)**	**5 (42%)**	5 (42%)	7 (58%)	16 (43%)	21 (57%)
Clopidogrel	5 (15%)	28 (85%)	**14 (58%)**	**10 (42%)**	1 (100%)	0 (0%)	20 (34%)	38 (66%)
Ranitidine	0 (0%)	1 (100%)	4 (40%)	6 (60%)	13 (48%)	14 (52%)	17 (45%)	21 (55%)
Rabeprazole	0 (0%)	7 (100%)	**5 (71%)**	**2 (29%)**	2 (20%)	8 (80%)	7 (29%)	17 (71%)
Pantoprazole	0 (0%)	5 (100%)	**2 (67%)**	**1 (33%)**	0 (0%)	0 (0%)	2 (25%)	6 (75%)
Esomeprazole	0 (0%)	0 (0%)	**7 (58%)**	**5 (42%)**	0 (0%)	0 (0%)	7 (58%)	5 (42%)
Ondansetron	2 (40%)	3 (60%)	**4 (57%)**	**3 (43%)**	1 (20%)	4 (80%)	7 (41%)	10 (59%)
Prochlorperazine	1 (100%)	0 (0%)	**4 (57%)**	**3 (43%)**	1 (17%)	5 (83%)	6 (43%)	8 (57%)
Salbutamol	0 (0%)	3 (100%)	4 (50%)	4 (50%)	5 (45%)	6 (55%)	9 (41%)	13 (59%)
Tiotropium	1 (25%)	3 (75%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)	1 (17%)	5 (83%)
Formeterol	0 (0%)	0 (0%)	**1 (100%)**	**0 (0%)**	0 (0%)	1 (100%)	1 (50%)	1 (50%)
Insulin	2 (18%)	9 (82%)	9 (45%)	11 (55%)	15 (48%)	16 (52%)	26 (42%)	36 (58%)
Morphine	2 (29%)	5 (71%)	**6 (55%)**	**5 (45%)**	8 (29%)	20 (71%)	16 (35%)	30 (65%)
Hydromorphone	3 (16%)	16 (84%)	**15 (58%)**	**11 (42%)**	17 (39%)	27 (61%)	35 (39%)	54 (61%)

Table 23. Drugs that were used more frequently in patients with delirium (white cells) and the proportions of individuals who were taking those drugs that became delirious

Drug	Transfemoral TAVI		Transapical TAVI		Open-Heart AVR		Overall Frequency	
	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium	Delirium	No delirium
Postoperative Drugs Taken Anytime Between POD #1-3	**(n=7)**	**(n=37)**	**(n=23)**	**(n=20)**	**(n=17)**	**(n=28)**	**(n=47)**	**(n=85)**
Propofol	0 (0%)	0 (0%)	1 (20%)	4 (80%)	1 (50%)	1 (50%)	2 (29%)	5 (71%)
Norepinephrine	0 (0%)	2 (100%)	**5 (56%)**	**4 (44%)**	**6 (75%)**	**2 (25%)**	11 (58%)	8 (42%)
Epinephrine	0 (0%)	2 (100%)	**2 (100%)**	**0 (0%)**	**1 (100%)**	**0 (0%)**	3 (60%)	2 (40%)
Acetaminophen	7 (17%)	34 (83%)	21 (53%)	19 (47%)	16 (36%)	28 (64%)	44 (35%)	81 (65%)
Lorazepam	2 (50%)	2 (50%)	2 (50%)	2 (50%)	4 (44%)	5 (56%)	8 (47%)	9 (53%)
Midazolam	0 (0%)	0 (0%)	2 (50%)	2 (50%)	**2 (100%)**	**0 (0%)**	4 (67%)	2 (33%)
Milrinone	0 (0%)	0 (0%)	2 (29%)	5 (71%)	6 (46%)	7 (54%)	8 (40%)	12 (60%)

Statistics were not performed on these data.
All values represent number of individuals with/without delirium on the drug (proportion of individuals who were on the drug that became /did not become delirious).
White cells = proportion of delirious patients on the drug > proportion of non-delirious patients on the drug
Bold font = proportion of individuals taking the drug who became delirious > proportion of individuals taking the drug who did not become delirious

4 Discussion

4.1 Transfemoral TAVI is Superior to Transapical TAVI or Open-Heart AVR for Reducing Postoperative Delirium

This study presents data showing that transfemoral TAVI was associated with a significantly lower rate of delirium than transapical TAVI or open-heart AVR. This contrasts with what was hypothesized, which was a comparable rate of delirium across all three surgeries. Although the rate of delirium after transapical TAVI appeared to be higher than after open-heart AVR, this difference was not statistically significant; thus, it cannot be said that in terms of delirium, the transapical procedure is worse than the open-heart procedure. On the other hand, since the *p*-value for this difference was slight greater than 20% ($p = 0.203$), there is a chance that this may reflect a Type II error, and the sample sizes may not be large enough to detect a true difference. Nevertheless, this does suggest that transfemoral TAVI could offer benefits to patients with severe aortic stenosis (who may or may not be surgical candidates) over transapical TAVI or open-heart AVR in terms of delirium.

The benefits of transfemoral TAVI that were observed in this study were not just limited to the rate of delirium, but also had implications for better postoperative patient health and overall well-being, and suggested economic advantages over the more invasive transapical and open-heart procedures. Transfemoral patients spent less time under intensive care in the CCU, indicating that costs for such services are reduced, and they had total hospital stays that

were on average 1-week shorter than transapical or open-heart patients. Also, transfemoral TAVI patients had shorter intubation times compared to transapical TAVI and open-heart AVR. This observation could reflect an important benefit of the procedure, since weaning from mechanical ventilation represents a reduction in patients' dependencies on drugs for sedation, and suggests that patients regain homeostasis sooner, and are able to be transferred out of intensive care (Shehabi *et al*., 2009). And while these data showed that TAVI procedures were associated with greater mortality rates 2-years after surgery, the mortality rates 24-hours, 30-days, and 1-year after surgery did not significantly differ. Considering that TAVI patients were, on average, 15 years older than open-heart patients, this may just reflect the normal life expectancy rather than a consequence of the surgeries.

4.2 Risk Factors for Postoperative Delirium are Weighed Differently Depending on the Patient Population and the Aortic Valve Replacement Procedure Performed

Postoperative delirium was observed to be associated with a number of non-modifiable and modifiable risk factors present in these patients. But rather than finding that modifiable risk factors were more important in open-heart patients, and non-modifiable risk factors were more important in TAVI patients as it was hypothesized, it was observed that different aortic valve replacement procedures were described with different sets of both types of risk factors. The non-modifiable risk factors for each surgical group were different because the

baseline characteristics of the patient samples were different, and there was not a single non-modifiable factor that was associated with delirium in all three surgical groups. Modifiable risk factors were slightly different in this respect, because there were some obvious inherent differences about the procedures that were found to be significantly associated with delirium. Probably the most salient modifiable risk factor that was observed was intubation time, which was found to be significantly different between all three procedures. Earlier weaning from endotracheal intubation after cardiac surgery may be promoted with the use of thoracic epidural anesthesia (Preistley *et al*., 2002), or by giving intercostal local anesthetic injections before chest closure (Fox and Hughes, 2002). Regrettably, since the use of more sophiscated linear regression modeling was not performed on data from this present study, it cannot be determined if these non-modifiable and modifiable risk factors are independently predictive of postoperative delirium in these patient populations, or whether they are confounded by other risk factors.

4.3 Drug Consumption in the Perioperative Period is Associated with Postoperative Delirium

Out of all the drugs that were studied, there were only a few key distinctive relationships. One drug variable that reappeared time and time again was anticoagulant usage in all three valve replacement procedures. Preoperative anticoagulant agents (as a class of drugs including warfarin, heparin, and

clopidogrel) were used in a significantly greater proportion of delirious patients versus non-delirious patients receiving open-heart AVR. More than 50% of open-heart AVR and transapical TAVI patients who were taking heparin immediately after surgery also developed delirium. A larger proportion of delirious patients versus non-delirious patients from all three surgical groups were taking warfarin and heparin as outpatients, during anesthesia, immediately after surgery, and in the postoperative period between POD #1-3, and although the statistical significance of these correlations was not determined, such repetitiveness implies that there may be some clinical relevance. It is possible that warfarin may have central anticholinergic effects that are causing patients, specially elderly patients, to become delirious after surgery (Mulsant *et al.*, 2003), but the central anticholinergic activity of warfarin is only speculated and there have been studies that have not been able to demonstrate measurable anticholinergic effects (Chew *et al.*, 2008). Also, there have been no studies published on the real or potential relationship between blood clotting and postoperative delirium, but the data obtained in this study can aid in conjecturing a possible explanation for this observation.

Cerebral perfusion is normally autoregulated within 50-60 mmHg as the lower boundary and 150-160 mmHg as the upper boundary to maintain regular blood flow to nourish the brain tissue (Hudetz, 1997). Since one of the theories of delirium etiology point to cerebral hypoperfusion as being one cause, it is necessary that blood flow be maintained at a steady, uninterrupted velocity in

order to prevent delirium. However, it is important to not forget that excessive blood flow might also lead to neuronal cell death via edema and blood-brain barrier dysfunction (Banaji *et al*., 2005). While cerebral blood flow is normally regulated by changes in blood pressure, changes in blood viscosity may also modify cerebral autoregulation; however, the compensatory constriction or dilation of cerebral capillaries will not occur if the autoregulatory mechanisms are defective (Mulzelaar *et al*., 1986), such as in the case of excessive blood loss during cardiac surgery. It may the case that in these patients who are underoing valve repair, perioperative anticoagulant usage and/or drugs of anesthesia are influencing blood viscosity, which affects blood flow to the brain. In our patient samples, preoperative platelet levels in all three surgeries were comparable, and levels did not differ between those that developed delirium and those that did not develop delirium; moreover, platelet levels for patients in all three surgical procedures were within the normal range of 130-400 giga/L. Where the difference is reflected is in these patients' INR levels. Delirious patients in the transfemoral group and open-heart group had significantly higher INR values than non-delirious patients receiving these surgeries, and the same trend existed in the transapical procedure although the difference did not reach significance, and a higher INR level indicates a greater chance of bleeding. Importantly, the average INR values for delirious transfemoral and transapical patients were above the normal range, while the average values for both delirious and non-delirous open-heart patients were within the normal range. These data, taken

together with the data showing that a greater proportion of delirious patients from all three surgical groups were taking warfarin and heparin throughout the perioperative period, this suggests that perhaps excessive blood flow rather than hypoperfusion is the cause of postoperative delirium in TAVI patients. Whether differences in INR levels reflect the differences in the incidences of delirium observed between surgeries is not so straightforward. Average INR levels before surgery for patients in both TAVI groups were significantly lower than for open-heart patients, even though greater proportions of TAVI patients were taking warfarin and clopidogrel preoperatively as outpatients, which should have reduced the viscosity of their blood. A similar trend was seen for transapical patients taking lipid-lowering agents – a greater proportion of transapical patients were on lipid-lowering agents, despite the fact that a greater proportion of them were dyslipidemic. Perhaps the explanation for the differences observed in the incidences of delirium between these three surgical groups lies in the reason why warfarin, clopidogrel, and lipid-lowering agents did not seem to be effective in patient populations receiving transfemoral and transapical TAVI.

These data also seem to provide some support for the cholinergic hypothesis of delirium etiology. More than 50% of transapical and open-heart patients who were on digoxin and furosemide as outpatients became delirious, and these drugs have been shown to have minimal anticholinergic effects and low distribution in the CNS (Chew *et al*., 2008). Sixty-one percent of transapical patients who were taking ranitidine in the period immediately after surgery

became delirious. Ranitidine is a proton-pump inhibitor with low anticholinergic effects and low distribution in the CNS at typical doses (Chew *et al.*, 2008), and was shown to be one of the most commonly used drugs in inpatients with delirium by Han et al. (2001). A greater proportion of delirious TAVI patients compared to non-delirious patients were also taking the drugs ipratropium, dimenhydrinate, and metformin, and these have also been suspected to have some anticholinergic activity (Mintzer and Burns, 2000; Chew *et al.*, 2008).

Likewise, there is some support in this study for the physiological stress response hypothesis of delirium etiology as well. The proportions of patients in each group receiving insulin significantly differed between the procedures during surgery, and in the postoperative period. Specifically, the numbers of patients requiring insulin during and after surgery could be thought of as being related to the intensity of the procedure they were undergoing; the greatest number of patients to receive insulin had open-heart AVR, which on average took the longest time to complete and required a sternotomy and cardiopulmonary bypass; the second greatest number of patients to take insulin had transapical TAVI, which requires a mini-thoracotomy, and took the second longest time to complete; and the smallest number of patients to require insulin had transfemoral TAVI, the least invasive of all the procedures. A greater need for insulin suggests that open-heart patients were experiencing greater surgical stress than transapcial or transfemoral TAVI patients, since the proportion of patients with

diabetes and those that were taking insulin preoperatively did not significantly differ.

One anesthetic drug, ketamine, was found to be negatively correlated with the incidence of delirium in this study. This finding supports the study by Hudetz *et al*. (2009), which demonstrated protective effects of ketamine for delirium after cardiac surgery.

Another drug that was negatively correlated with the incidence of delirium was the orally administered non-benzodiazepine hypnotic agent, zopiclone, which was used in the postoperative period. Zopiclone is a first generation cyclopyrrolone, which is a drug class that has high efficacy and low toxicity with similar effects to benzodiazepines (Goa and Heel, 1986). It has a half-life of about 5 hours, and it does not form active metabolites (Goa and Heel, 1986). Zopiclone is given through the oral route to patients after surgery on a *pro re nata* (PRN, or "as needed") basis to regulate their sleep-wake cycles because it is not unusual for patients to experience dysfunction in their circadian rhythms after general anesthesia or cardiopulmonary bypass (Chenevard *et al*., 2008). Zopiclone was given significantly more frequently to non-delirious transapical and open-heart patients on POD #1, 2, and 3, and the same trend was seen for transfemoral patients, although this did not reach significance. In the CSICU, the protocol dictates that patients who are at risk for delirium are not to be given zopiclone. However, in this study, it was not confirmed whether the symptoms of delirium appeared before or after the administration of zopiclone in these patient

samples. The initial onset of symptoms was not reliably noted in the patients' medical records, so it was difficult to determine the temporal sequence of these events. Also, because zopiclone is given orally, it requires that patients be extubated in order to be able to consume the drug; therefore, a confounding factor in this relationship could be intubation time. Nevertheless, the possibility does exist for zopiclone to render a protective effect against delirium, since it must be able to cross the blood-brain barrier to exert its sedative effects. If this were indeed the case, then these data would offer support that regulation of the sleep-wake cycle is important for preventing postoperative delirium. It would be interesting to conduct a prospective interventional study where sleep prior to cardiac surgery is induced by zopiclone rather than by a benzodiapene like diazepam to determine if there is a protective effect of zopiclone against delirium after cardiac surgery.

4.4 Threats to Validity

There were a number of factors that limited the strength of this study. Firstly, the lack of robust statistics in this study hinders the conclusions that may be drawn from its results. The statistics that were used did not identify independently associated risk factors, since logistic regression or multivariate analysis were not performed. The reason why these more sophisticated statistics were not calculated is because the primary aim of this study was to

determine the incidences of delirium after TAVI procedures, so less of the focus was placed on determining salient risk factors in these populations.

Secondly, since postoperative management of transfemoral and transapical patients differed in terms of where the intensive care took place (in the CCU and the CSICU, respectively), this might contribute to the differences in the rates of delirium that were observed. It is possible that the nurses in the CCU, who looked after transfemoral patients, were not as rigorous with using the consult liason (CL) service provided by psychiatry as the nurses in the CSICU were, and thus this may have resulted in the lower rate of formally diagnosed delirium that was seen in the transfemoral group.

One operative variable that may have affected the rates of delirium is the fact that there is currently only one surgeon at St. Paul's who performs transfemoral TAVI, while there are a number of different surgeons who perform transapical TAVI and open-heart AVR. This introduces a bias in the study that was not controlled.

Lastly, besides the fact that Type II errors may have been made due to the small sample sizes, the likelihood of Type I errors are also high in this study because of the large number of comparisons that were made. Thus, it is best to consider the results of this study as a preliminary measurement of what is clinically seen.

4.5 Significance of the Present Findings

The two transcatheter aortic valve implantation techniques are associated with exorbitant differences in the incidence of postoperative delirium in relation to one other. While the incidence of postoperative delirium was not significantly different between transapical TAVI and open-heart AVR, there were highly significant differences between the incidence of delirium after transfemoral TAVI and open-heart AVR. The benefits of transfemoral TAVI extended beyond the incidence of delirium because it demonstrated significant advantages in overall patient health and well-being compared to the transapical and open-heart procedures. Furthermore, the differences in the apparent influence of certain medications on the incidence of delirium for each valve replacement procedure could potentially reflect differences in the etiology of delirium for these patient populations; however, without more sophisticated statistics and further prospective interventional studies, this cannot be ascertained.

This study promotes the following clinical considerations. Firstly, the benefits endowed by transfemoral aortic valve implantations suggest that this procedure should be studied in both surgical as well as non-surgical patients. Despite the lack of predictable ability of the risk factors identified in this study, the incidences of delirium and the associated outcomes that were obtained offer great support for the use of transfemoral TAVI over conventional open-heart AVR in both types of patients. Lastly, the results from this study suggest that preoperative, intraoperative, and postoperative management of elderly cardiac

surgery patients with pharmacological agents should be considered with delirium etiology in mind, since many of the drugs that were found to be significantly correlated with delirium in these patient samples can be related to such pathophysiology. In conclusion, strategies to reduce the incidence of postoperative delirium after cardiac surgery should include consideration of less stressful, less invasive surgical alternatives and the careful use of all types of medications.

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