FRAILTY AND DELRIUM IN OLDER PATIENTS UNDERGOING CARDIAC PROCEDURES

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ABSTRACT

BACKGROUND: Frailty, a state of decreased physiological reserve predisposing to adverse health events, including delirium, is prevalent in older patients undergoing cardiac procedures. In turn, delirium, an acute confusional state, predisposes to frailty in a vicious cycle. So far, most promising measures to prevent delirium, and potentially frailty, in medical and surgical patients, are non-pharmacological in nature. In the context of cardiac surgery, such interventions have infrequently been studied and no standard of care has been established.

AIMS: Using a Delphi Consensus Survey, we sought to determine which components should be included in a non-pharmacologic intervention bundle aiming at delirium prevention and treatment in patients undergoing cardiac surgery.

METHODS: Twenty multidisciplinary experts with knowledge and experience in delirium management in patients undergoing cardiac surgical procedures were approached to provide five suggestions of components to include in a non-pharmacologic delirium prevention and treatment intervention specific to this population. These suggestions were analyzed in duplicate by two independent investigators who grouped them into categories of components. A second iteration was then distributed to the same experts, asking them to rate each category of components on a 7-point Likert scale with regards to its importance, feasibility, and risk for adverse events.

RESULTS: Thirteen and eleven out of the twenty experts respectively answered the two iterations of our survey. Ten categories of components were generated from the participants' propositions. Aside from components known to be effective in other clinical settings, our panel identified pain and anxiety management, family and healthcare workers education as well as delirium screening and treatment planning to be of specific interest to cardiac surgical patients. After two rounds of the Delphi Survey, consensus was reached on the high importance and the low risk of adverse events of most categories. No consensus was achieved with regards to the feasibility of the different categories of components, as it was felt by many respondents to rely excessively on individual institutions' cultures and practices.

CONCLUSION: Our work allowed us to identify ten categories of components to potentially include in a multicomponent non-pharmacologic delirium prevention and treatment intervention specific to cardiac surgical patients.

RÉSUMÉ

CONTEXTE: La fragilité, un état de diminution des réserves physiologiques prédisposant à des effets néfastes sur la santé, dont le délirium, est prévalente chez les patients âgés qui subissent une intervention cardiaque. Dans un cercle vicieux, le délirium, un état confusionnel aigu, prédispose à son tour à la fragilité. Jusqu'à présent, les mesures les plus prometteuses pour prévenir le délirium, voire la fragilité, auprès des patients hospitalisés en médecine et en chirurgie sont de nature non-pharmacologique. Dans le contexte de la chirurgie cardiaque, de telles interventions ont rarement été étudiées et aucune norme de soins n'a été établie.

OBJECTIFS : À l'aide d'une enquête Delphi, nous souhaitions déterminer les catégories de composantes non-pharmacologiques à inclure dans une intervention multifacette visant la prévention et le traitement du délirium chez les patients subissant une chirurgie cardiaque.

MÉTHODES : Vingt experts multidisciplinaires avec expérience au niveau de la prise en charge du délirium chez les patients subissant une chirurgie cardiaque ont été invités à fournir cinq suggestions de composantes à inclure dans une intervention multifacette non-pharmacologique de prévention et de traitement du délirium dans cette population. Ces suggestions ont été analysées en parallèle par deux chercheurs indépendants qui les ont regroupées en catégories de composantes. Un second questionnaire a ensuite été distribué aux mêmes experts, leur demandant d'évaluer chaque catégorie de composantes sur une échelle de Likert en 7 points en fonction de son importance, de sa faisabilité et de son risque d'effets indésirables.

RÉSULTATS: Treize et onze des vingt participants ont respectivement répondu aux deux étapes de notre enquête. Dix catégories de composantes ont été générées à partir des propositions des participants. Outre les composantes connues pour être efficaces dans d'autres contextes cliniques, notre panel a déterminé que la gestion de l'anxiété, l'éducation de la famille et du personnel soignant, ainsi que le dépistage du délirium et la planification de son traitement présentaient un intérêt particulier pour les patients ayant subi une chirurgie cardiaque. Après deux cycles de l'enquête Delphi, un consensus a été atteint sur la grande importance et le faible risque d'effets indésirables de presque toutes les catégories proposées. Aucun consensus n'a été atteint quant à la faisabilité des différentes catégories de composantes, de nombreux répondants

ayant estimé qu'il était trop ardu de se prononcer sur le sujet étant donné les différences importantes de pratiques et de mentalités d'un programme de chirurgie cardiaque à l'autre.

CONCLUSION: Nos travaux nous ont permis d'identifier dix catégories de composantes à inclure dans une intervention multi-facette non-pharmacologique visant la prévention et le traitement du delirium, spécifique aux patients ayant subi une chirurgie cardiaque.

CONTRIBUTION OF AUTHORS

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Thesis candidate. Initiated study concept. Designed and wrote the protocols for both the systematic review of the literature and the Delphi consensus Survey. Performed literature search, data analysis, critical appraisal of studies for the scoping review on frailty and transcatheter aortic valve replacement. Performed the literature search, abstract screening, full text screening, quality appraisal of included articles for the systematic review of delirium prevention in cardiac surgical patients. Prepared and submitted application for research ethics approval of the modified Delphi survey. Analyzed data from its different iterations. Produced manuscripts of the systematic review and the Delphi studies. Co-authored review article on frailty in patients undergoing transcatheter aortic valve replacement. Wrote this thesis document.

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Collaborator. Reviewed ethics board submission for the Delphi consensus survey. Provided input on methodology of Delphi survey.

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LIST OF ABBREVIATIONS

ABCDEF: Assess, Prevent, and Manage Pain, Both Spontaneous Awakening Trials and Spontaneous Breathing Trials, Choice of analgesia and sedation, Delirium: Assess, Prevent, and Manage, Early mobility and Exercise, and Family engagement and empowerment

ACC: American College of Cardiology

ACCM: American College of Critical Care Medicine

BADLs: Basic Activities of Daily Living

CABG: Coronary Artery Bypass Graft

CAM: Confusion Assessment Method

CAM-ICU: Confusion Assessment Method – Intensive Care Unit version

CHSA: Canadian Study of Health and Aging

CI: Confidence Interval

CRP : C-Reactive Protein

CVD: Cardiovascular Diseases

DSM-V: Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition

GDS: Geriatric Depression Scale

HR: Hazard Ratio

IADLs : Instrumental Activities of Daily Living

ICD-11: International Classification of Diseases – 11^{th} revision

ICDSC :Intensive Care Delirium Screening Checklist

ICU: Intensive-Care Unit

IL-6 : Interleukin 6

IQR : interquartile range

KCCQ : Kansas City Cardiomyopathy Questionnaire

HELP : Hospital Elder Life Program

MI: myocardial infarction

MMSE: Mini Mental State Examination

MNA: Mini Nutritional Assessment

NS: Non Statistically Significant

OR: Odds Ratio

RCT: Randomized Controlled Trial

PCI: Percutaneous Coronary Intervention

SIP: Sickness Impact Profile

STS: Society of Thoracic Surgeons

STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

TAVR : Transcatheter Aortic Valve Replacement

TUG: Timed Up and Go

USD: United States Dollar

INTRODUCTION

"… inside every old person is a young person wondering what happened."

- Terry Pratchett

The aging process is a complex and fascinating one that has yet to be completely understood. It is responsible for atypical disease presentation in older individuals and is associated with the increasing prevalence of geriatric syndromes, defined as "clinical conditions in older persons that do not fit into discrete disease categories"[1].

In the following work conducted between Fall 2016 and Summer 2018, we sought to examine the importance, and to explore the prevention and treatment of two interconnected geriatric syndromes, frailty and delirium, in patients undergoing cardiac procedures. After reviewing basic concepts related to aging in general as well as important age-related changes of the cardiovascular system, we will review the evidence for the frailty syndrome in patients with cardiovascular disease, with special attention given to the role of frailty in patient selection prior to transcatheter aortic valve replacement. We will then discuss the association of frailty and delirium in older patients at large and in those undergoing cardiac procedures. This will allow us to better introduce the second part of our work pertaining to the prevention and treatment of delirium in older patients undergoing open-heart surgeries.

In the second part of this thesis, we will first present the results of a systematic review of randomized controlled trials of non-pharmacologic interventions for the prevention and treatment of delirium in patients undergoing cardiac procedures. This work was performed to confirm the perceived paucity of high-quality evidence regarding delirium prevention and treatment interventions in this patient population, despite the syndrome's high incidence in this context. The results from this review have led us to question what specific non-pharmacologic intervention components should be implemented and studied in delirium prevention and treatment in cardiac surgical patients. We were interested in knowing whether these interventions should differ from those already shown to be effective in other clinical contexts.

The last section of our work will therefore detail the process and results of a Delphi Consensus Survey designed with the intention of identifying most important non-pharmacologic components for delirium prevention and treatment in cardiac surgery, to be included in a patient-centered multicomponent intervention to be implemented and studied in the future. Important results and methodological concerns regarding this last piece of our work will then be discussed. Finally, future steps related to this project will be presented.

LITERATURE REVIEW

SECTION I: ON AGING AND HOMEOSTENOSIS

1.1 INTRODUCTION

From a semantic point of view, aging refers to the "state of someone growing old", to "showing the effects or the characteristics of increasing age"[2]. If the increase in life expectancy seen in the past century can be considered a victory of modern medicine, many continue to fear the aging process, which is often thought to invariably be associated with disease and disability[3]. But these preconceived ideas, often referred to as ageists, do not reflect adequately the aging experience of many individuals. For instance, 28% of individuals aged 85 and above describe their health status as very good or excellent, and more than half of this same cohort of individuals report no health-related housework or work-limitations[4], showing that aging affects individuals in a heterogeneous manner, and that chronological age alone is unlikely to be the best correlate of one's overall health and functional status.

There are multiple biological changes thought to be responsible for the aging process which will be briefly discussed below. We will also describe the relation between aging and a state of increased vulnerability termed homeostenosis. A quick overview of the epidemiology of old age will be made subsequently, setting the table for further discussions throughout this paper.

1.2 AGING BIOLOGY AND THE CONCEPT OF HOMEOSTENOSIS

There is no consensus among scientists so far as to what exact mechanisms are responsible for initiating and maintaining the aging process in humans. Many theories, including oxidative stress damage, auto-immune processes, neuroendocrine dysregulations and chronic inflammation, chromosomal damage, as well as genetic programming, have been suggested to explain human aging, but none was confirmed as the unique root cause of this phenomenon[5]. Further adding to this uncertainty, aging does not seem to affect cells and components of different organs systems in the same way. Far from thoroughly describing the impact of aging on all organs and systems in this work, some important changes related to aging of the

cardiovascular system will be discussed in the following chapter, to better detail concepts most relevant to this work.

What is agreed upon is that through aging occurs a loss of homeostasis, or a breakdown in maintenance of specific molecular structures[6]. Homeostasis was first defined by Cannon as "the coordinated physiological processes which maintain most of the steady states in the organism"[7]. The phenomenon of homeostatic impairments occurring with aging is termed homeostenosis[8]. Behind this concept lies the belief that, with the multiple changes caused by aging, an increasing amount of a person's physiologic reserves need to be in use to maintain a physiological steady state. Therefore, there are fewer reserves available to face potential threats to the body's intrinsic balance. When such threats occur in an older person who does not have enough physiological stores to face the challenge, clinically evident decline may occur. This is illustrated in figure 1 below, where clinical decline is represented by the individual crossing over "the precipice":

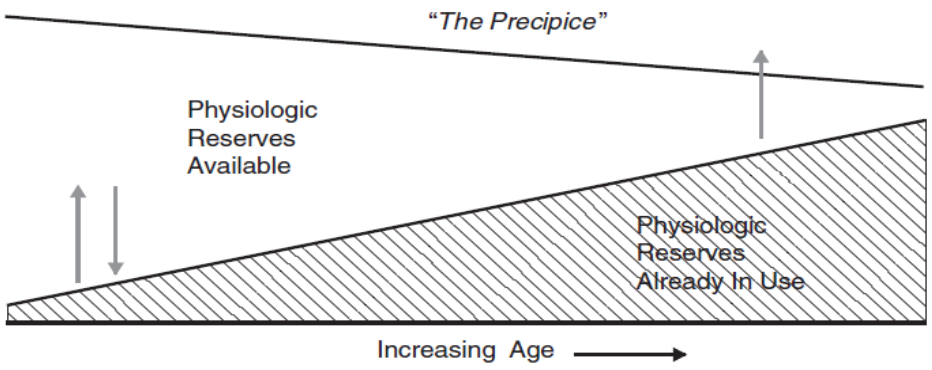

Figure 1: Homeostenosis occurs when, with age, physiologic reserves are increasingly used to maintain normal body functions, leaving little physiologic reserves available in case of acute perturbations (from Cassel, 2003, p.28).

Similarly, homeostenosis means that, when facing a similar health threat, an older individual is more likely to show clinical signs of decompensation than a younger one, due to decreased available physiological reserves.

1.3 AGING: THE GLOBAL AND CANADIAN PERSPECTIVES

Aging of the population has been a much-discussed subject over the past years, and with reason: it touches most societies in the world, regardless of their income status, and has important social, economic and health-related consequences. In 2010, the global number of individuals aged 65 and above was estimated at around 524 million[9]. In 2050, a projected 1.5 billion individuals worldwide will be considered seniors[9]. This represents an increase in the overall proportion of seniors from 8 to 16% of the world's total population[9]. Life expectancy at birth, which did not exceed 50 years in 1900, is now above 80 years in most developed countries, and individuals aged 85 and above, also known as the oldest old, are the fastest growing group of the world's population[9]. Indeed, their numbers are projected to increase by 351% between 2010 and 2050, and the number of centenarians is expected to increase by 10-fold over the same period[9]. In parallel to the aging of the population, there are major changes in the predominant patterns of illness, with the increasing prevalence of chronic, non-communicable diseases, an example of which would be cardiovascular diseases, both in developed and non-developed countries, where they will soon become the leading cause of death and disability, mirroring the current situation in high income countries[10]. Finally, aging is already changing healthcare delivery models and costs, with older individuals generating higher per-capita annual expenditures than their younger counterparts[9]. Consequently, aging is currently causing increased pressure on healthcare spending, especially in developed countries, although its direct impact is thought to be lower compared to cost increments related to the application of technological advances in medical care delivery[9].

With respect to aging of the population, Canada's situation is very similar to that of other developed countries. From 1971 to 2010, the proportion of seniors has risen from 8 to 14% of its total population, with the absolute number of individuals aged 65 years and above reaching close to 5 million[11]. Since then, the number of senior citizens has continued to increase and, in 2016, Canada registered a generational shift, as the number of seniors (5.9 million) exceeded the number of children aged 14 years and younger (5.8 million)[12]. It is expected that by 2031, close to 25% of the Canadian population will be composed of senior citizens.[12] Similar to the situation in other parts of the world, the oldest old (85 years and above)[6] are growing at a fast rate[13]. In

this age group, there is nearly twice the number of women than men, but this ratio is decreasing[13]. The majority of Canadian seniors live in the community, with 7% only living in long term and residential care facilities[14]. Many are affected by chronic conditions, with heart diseases affecting more than one fifth[14].

SECTION 2 : AGING AND THE CARDIOVASCULAR SYSTEM

2.1 INTRODUCTION

In the previous section, we reviewed the epidemiology of aging and touched on its hypothesized biological underpinnings. This second section is dedicated to further detailing the impact of advancing age on the structure and function of the cardiovascular system. The role of aging as a risk factor for cardiovascular diseases will also be discussed.

2.2 STRUCTURAL CHANGES

Aging causes structural changes affecting the myocardium, cardiac valves, conduction system, as well as the vessels. At the level of the cardiac muscle itself, aging is associated with the loss of myocytes due to necrosis, apoptosis and possibly to autophagy. A 30-35% loss in the absolute number of cardiomyocytes is observed between the ages of 17 to 90[15]. This cellular loss is compensated by an increase in size of the adjacent myocardial cells[15]. Left ventricular hypertrophy, even in the absence of systemic arterial hypertension or any other cause of afterload increase, is also commonly seen with aging[16].

The cardiac valves also undergo structural changes with aging. The aortic valve leaflets stiffen, scar and calcify, leading to aortic valve sclerosis, present in 26% of individuals aged 65 years and above[17], and in 50% of those aged over 80 years[18]. Calcification of the aortic annulus and leaflets also predisposes to aortic regurgitation, with just above 2% of individuals 70 years and above suffering from moderate or severe aortic valve insufficiency[19]. Other valves may also be affected by calcification, notably the mitral valve annulus, causing mitral annulus calcification, more prevalent in older women (52%) than men (36%)[20].

At the level of the conduction system, multiple changes are observed. One of the most important ones is the loss of pacemaker cells at the level of the sinoatrial node. Indeed, by the age of 70, only around 10% of an individual's pacemaker cells remain[21]. Similar cellular loss occurs at a lesser degree at the level of the atrioventricular node and at the level of the bundle of Hiss. Important cellular loss occurs at the level of the bundle branches, predisposing older individuals, to cardiac conduction abnormalities, as will be detailed below.[21]

Finally, vessels are affected by the aging process. There is widespread arterial dilatation, most evident at the level of the large arteries. There is also enlargement of the vascular lumen, and thickening of the vascular wall[22], leading to decreased vascular compliance or elasticity.

2.3 FUNCTIONAL CHANGES

As a result of these structural changes, and of alterations in cellular metabolism and neuroendocrine signaling, the function of all the above-mentioned components of the cardiovascular system changes with increasing age.

Left ventricular hypertrophy and stiffening described in the sub-section above, as well as prolonged ventricular contraction due to longer cytoplasmic calcium release, tends to cause impaired ventricular relaxation during diastole, while older individuals' systolic function remains normal at rest[23]. Impaired ventricular relaxation interferes with early ventricular filling, forcing a more important contribution from atrial contraction to achieve adequate filling and stroke volume. Progressive left ventricular hypertrophy predisposes to (often silent) subendocardial ischemia and fibrosis, which further impedes left ventricular relaxation and increases left ventricular diastolic dysfunction in older individuals[24].

Exercise tolerance worsens with age, due to both decreased maximum heart rate as well as impaired left ventricular ejection fraction during effort, causing reduced cardiac reserve with aging[25]. Indeed, maximum heart rate tends to decrease on average by one beat per minute with every one year increase in age[26]. Furthermore, on effort, left ventricular ejection fraction during exercise tends to decrease from an average of 85% in the third decade to 70% in the ninth[27]. This last number is very close to that of a normal ejection fraction at rest, leading again to impaired cardiac reserves in older individuals, who fail to increase their ejection fraction significantly to respond to the increased demand during effort.

Dysfunction in the autonomic nervous system, related to aging, provokes a decrease in maximum heart rate that is proportional to age, as well as a decreased heart rate variability[28]. This interferes with older persons' exercise tolerance, as stroke volume is dependent on heart rate and cardiac output, both decreased on exercise secondary to the aging process.

At the level of the vessels, impaired compliance or elasticity is seen as a result of the hypertrophy, proliferation and migration of small muscle fibers in the subendothelial space which is also infiltrated by collagen. Furthermore, at the cellular level, the increased expression of vasoconstrictive factors, and the impaired expression of vasodilating factors, leads to further arterial stiffness and high pulse wave velocity, a phenomenon referred to as arteriosclerosis[29]. There is also a secondary increase in systolic blood pressure, and a decrease in diastolic blood pressure, such that the pulse pressure increases with aging[30].

2.4 AGE AS A RISK FACTOR FOR CARDIOVASCULAR DISEASE

In this sub-section and for the rest of this work, the term cardiovascular disease (CVD) will be used to refer to a wide array of clinical entities encompassing ischemic heart disease, cerebrovascular disease, heart failure, arrhythmia, and valvular heart disease[31].

Cardiovascular diseases are extremely prevalent in our societies, and, due to increasing prevalence in developing countries, they now are globally the most important cause of mortality from non-communicable diseases[32]. As detailed above, aging causes multiple structural and functional changes in the cardiovascular system, which participate in the development of CVD in older individuals. In fact, age is the single most important risk factor for CVD. This is in part reflected by the high prevalence of these disease types in the aged population. Indeed, CVD is estimated to be present in more than 70% of Americans aged 60 to 79, and in more than 80% of those aged 80 years and above[33].

All structural and functional changes related to aging that were mentioned in previous sections predispose older individuals to develop different clinical forms of CVD. Impaired diastolic filling, for example, predisposes older patients to suffer from congestive heart failure. In fact, in this age group, the most important causal mechanism for heart failure is diastolic dysfunction, leading to the recognition of a distinct entity: heart failure with preserved ejection fraction, responsible for 40-80% of heart failure cases in this patient population[34], and is present in 10% of women aged 80 and above[35].

Aortic valve calcification and stiffening from aging also predisposes to the development of aortic stenosis, whose prevalence increases from 1% in individuals aged 60-69 years, to 10% in those aged 80 to 89[36].

Increased arterial stiffness, measured by pulse wave velocity is recognized as an independent predictor of cardiovascular morbidity and mortality, as well as overall mortality in many populations[30]. Interestingly, exercise has favorable outcomes on arterial stiffening secondary to aging[29]. Arterial stiffness is also associated with increased prevalence of ischemic heart disease, peripheral vascular disease as well as cerebrovascular disease. Indeed, a one standard deviation increase in objective measures of arterial stiffness has been associated with a 48% increase in the risk of cardiovascular events in the Framingham Heart Study[37].

Cerebrovascular disease's prevalence increases with age, with stroke rates doubling each decade after age 55[38]. Furthermore, 75-89%[39] of all strokes occur in individuals aged 65 years and above.

Finally, changes to the conduction system increase older patients' risk of suffering from arrhythmia. For example, atrial fibrillation is present in only 0.1% of individuals aged less than 55 years but affects 9% of individuals 80 years and above[40]. Sick sinus syndrome, from sinoatrial node dysfunction, is also more prevalent in the older population. In fact, every 5 years increment in age confers a 73% increase in the risk of developing sick sinus syndrome[41]. In the 85 years and above, incidence of sick sinus syndrome is between 0.3-0.4 per 100 person-years, while it is below 0.04 per 100 person-years in the less than 65 years of age[41].

2.5 CONCLUSION

The aging process is responsible for multiple structural and functional changes in the cardiovascular system, which in turn predispose older individuals to suffer from CVD. Various forms of CVD – including atherosclerotic coronary artery disease, cerebrovascular disease, systemic hypertension, calcific aortic valve stenosis, heart failure with preserved ejection fraction, atrial fibrillation, and sick sinus syndrome – are closely linked to age both causally and epidemiologically.

SECTION 3: ON FRAILTY

3.1 INTRODUCTION

In previous sections, we explored the physiopathology of aging, as well as its consequence: homeostenosis. We also detailed the more specific age-related changes occurring in the cardiovascular system, and their relation to CVD. In this third chapter, we will introduce the concept of frailty, central to this thesis work, and explain its relation to aging and homeostenosis. Two important clinical frailty models will be reviewed, and the prevalence and outcomes related to this syndrome in community dwelling older individuals will be presented. Finally, potential treatments for alleviating frailty will be reviewed. The more specific association of frailty with CVD's prevalence and outcomes will be discussed in Section 4.

3.2 FRAILTY: DEFINITION AND PHYSIOPATHOLOGY

Frailty refers to an increased vulnerability to adverse health outcomes, reflecting an age-associated decline in multiple physiological systems [42,43]. If this widely accepted definition entails that frailty is correlated to aging, it is important to note that frailty experts differentiate between chronological age, which is merely the measure of one's time spent on Earth, and biological age, which refers to the active rate at which the body is aging[44]. Biological age may thus be better to estimate life expectancy, quality of life and current health status[45]. In some way, frailty is a measure of biological age[46].Thus, frailty has to be seen as a continuum from fitness to pre-frailty, and then to frailty itself[47]. For certain experts, frailty is the clinical state of someone who has reached the far end of the figure of homeostenosis (cf. figure 1, Section 1), regardless of their age, making any perturbation likely to provoke adverse outcomes[8]. Importantly, frailty differs from chronological age in that its progression may happen faster or slower than chronological age, and in that, unlike the aging process, it appears to be at least partially reversible.

The precise physiopathology of frailty is still poorly understood. Inflammation seems to be playing a role, as pre-frail and frail individuals were found to have increased levels of inflammatory markers such as Interleukin-6 (IL-6) and C-reactive protein (CRP) compared to their non-frail counterparts[48]. However, frailty is most likely multifactorial, and other biomarkers of hormonal dysregulation, oxidative damage, and other clinical parameters irregularities (signs,

symptoms, comorbidities and disabilities) have been associated with the syndrome, speaking to its intrinsic complexity[49]. All these dysregulations lead to a catabolic state with ensuing fatigue, sarcopenia, malnutrition and low levels of physical activity, as seen in figure 2 below[50].

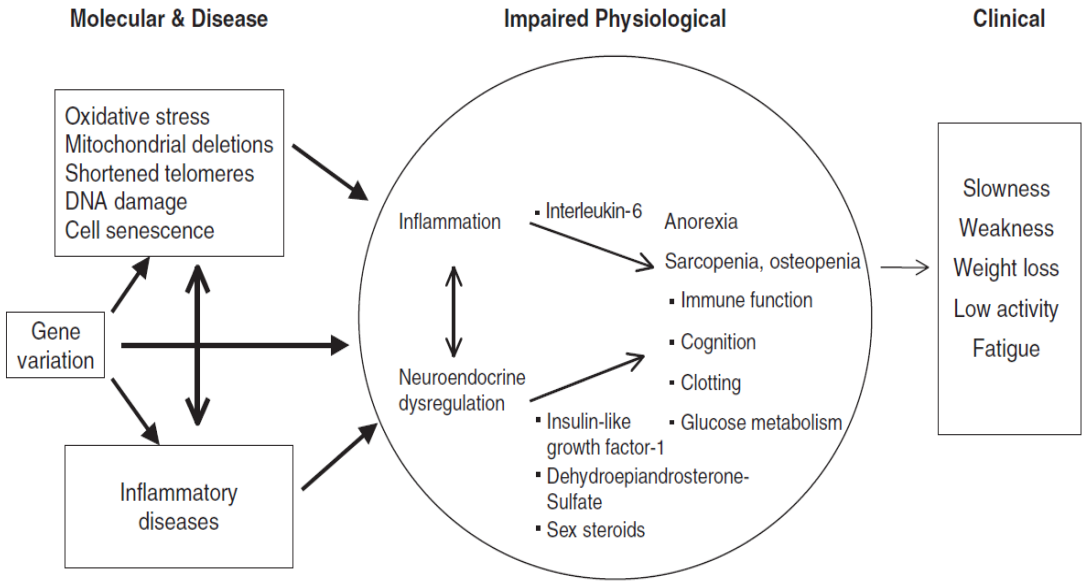

Figure 2: Hypothesized molecular, physiological and clinical pathways to frailty (Wilson, 2006, p. 993).

3.3 CLINICAL MODELS OF FRAILTY

Many clinical models and scales operationalizing the definition of frailty have been published, but none has been adopted so far as a gold standard. This lack of consensus on a unique frailty concept and measurement tool is one of the criticisms of this field of study. Two models have been used more consistently in the literature: Fried's phenotypic model of frailty and Rockwood's Frailty Index, based on the theory of accumulation of deficits[51], in which frailty is considered more a state than a syndrome[45].

In Fried's model[42], frailty is defined by the presence of three of the following characteristics: low grip strength, slow gait speed, exhaustion, weight loss and low levels of physical activity. The presence of one or two characteristics differentiates the pre-frail state, emphasizing the fact that frailty occurs on a continuum. Of note, disability/functional impairment is absent from this model, emphasizing that frailty can exist without comorbid disability[42].

In Rockwood's Frailty Index, impairments in multiple domains are summed and compared to a pre-defined number of impairments (70 items in the original index) [52]. This is in accordance to the theory of aging via accumulation of deficits. Weights of different deficits are considered equal. It differs from Fried's approach in that it includes multiple dimensions, such as comorbidities, functional status, signs and symptoms, as well as laboratory abnormalities. [51]

Some studies have compared the ability of both scales to identify frail individuals as well as to predict mortality, morbidity and cognitive decline in older individuals and found them to be equal in that regard[53,54], while other studies have found slight superiority of the Frailty Index[55-57]. Finally, some have pleaded that both models were to be considered as complementary, rather than opposed, with Fried's model being useful to screen for frailty, especially in non-disabled older individuals, and the Frailty Index, being best at quantifying losses and disabilities and at summarizing results of a comprehensive geriatric assessment[58].

3.4 EPIDEMIOLOGY OF FRAILTY IN COMMUNITY DWELLERS

Allowing for some variations depending on the measurement tool used, it is estimated that frailty affects 11% of all community dwellers aged 65 years and above[59]. Frailty seems to affect more the oldest old, as it is present in 26% of those 85 years and older[59]. The syndrome is more common in women[60], and in individuals of low socio-economic status[61]. Furthermore, the syndrome seems to be more frequent in patients suffering from chronic conditions, such as congestive heart failure or chronic obstructive pulmonary disease, where it may affect more than one individual out of two[62,63]. Cognitive impairment seems often associated with frailty, with 22-40% of frail patients suffering from cognitive difficulties[64]. In nursing homes, frailty is highly prevalent, affecting more than one individual out of two[65].

3.5 OUTCOMES RELATED TO FRAILTY

In observational studies of large samples of community dwelling older adults, the presence of frailty has independently been associated with worsening mobility, falls, incident dependency in basic activities of daily living (BADLs) and instrumental activities of daily living (IADLs) as well as institutionalization[42,66,67]. Furthermore, in those same studies, frailty was

associated with the need for hospitalization, institutionalization, as well as overall survival. In fact, frailty was shown to better correlate with survival than chronological age alone[52].

Other studies, this time of hospitalized patients, have demonstrated the predictive value of frailty in terms of hospital readmission[68], in-hospital complications as well as in-hospital mortality[69]. In surgical patients, the presence of frailty was associated with postoperative complications, in-hospital mortality, institutional discharge and poor survival[70-73]. Finally, frailty is associated with increased healthcare costs as well as poorer quality of life[74].

3.6 FRAILTY: APPROACH TO TREATMENT

As previously mentioned, frailty is a syndrome occurring on a continuum. Based on this, much hope has been placed into its potential reversibility. The first step into achieving this, passes through frailty recognition, especially by primary care practitioners, which remains a challenge[75].

To date, only a few studies have looked at potential interventions to alleviate frailty, and they varied in quality. [76] A recent systematic review looking at exercise interventions to improve frailty-related outcomes such as mobility and disability showed some benefit of multicomponent exercise programs (i.e. including resistance, endurance, flexibility, balance training in different combinations) performed regularly over a three month period. [77] Importantly, none of the included studies reported frailty as an outcome. Nutritional interventions have also been given a special interest in the frailty community, with protein and/or amino-acid supplementation having been studied in a small number of randomized controlled trials, combined with exercise or alone, with modest benefits[78]. Studies on testosterone supplementation have also shown promise, mostly when administered to men with low testosterone levels[79]. Hormonal replacement in women has also been studied[78]. Finally, multidimensional assessments and interventions, usually involving assessment and individualized treatment planning by an interdisciplinary team, also showed benefit in alleviating the consequences of frailty[78]. The comprehensive geriatric assessment, a form of patient-centered multidimensional assessment, is currently considered to be the gold standard in frailty treatment[80]. Although time and labor intensive, it is gaining popularity in multiple disciplines, including cardiology.

3.7 CONCLUSION

Frailty is a syndrome characterized by increased vulnerability to stressors. Its prevalence increases with age. Despite many different methods developed to operationalize frailty, it seems to invariably be associated with poor outcomes, both in community dwellers and in hospitalized older adults. There is room for improvement in frailty screening in primary care, which will become even more important, as a number of studies under way will potentially assist clinicians in choosing the best therapeutic approach for their frail patients[75]. To date, the most promising interventions to alleviate frailty remain multifactorial in nature.

SECTION 4: ON FRAILTY AND CARDIAC PROCEDURES

4.1 INTRODUCTION

In our last section, we described frailty and went over its physiopathology and consequences on the health of community dwelling seniors. In the following lines, we will review the strong association between frailty and cardiovascular diseases (CVD) in the older population. We will also discuss the prognostic value of frailty in CVD and review its growing role in risk stratification and treatment planning for patients undergoing cardiac surgery. Finally, we will introduce our next section containing our own work reviewing the usefulness and methods of frailty screening prior to transcatheter aortic valve replacement (TAVR), a minimally invasive procedure which has gained much popularity in the recent years for the treatment of older patients suffering from aortic stenosis.

4.2 FRAILTY AND CARDIOVASCULAR DISEASE

Frailty is closely linked to CVD. Vascular inflammation has an important role in the physiopathology of atherosclerosis and hypertension, two important risk factors for ischemic heart disease and cerebrovascular disease[81]. It also has a role in promoting valvular calcification seen in calcific aortic valve disease[82]. High levels of inflammatory markers and hormonal dysregulations are also found in patients with heart failure[83]. This shows how both frailty and CVD share common causal mechanisms.

Many risk factors for CVD are also more prevalent in frail and in pre-frail individuals[84], although the direction of this association remains unknown. Frailty and heart disease seem linked to each other in a vicious cycle, with frailty being a risk factor for the development of certain forms of CVD[85-87], which in turn are involved in causing and exacerbating frail states[67,88]. Considering this, it is not surprising to see that an important proportion of individuals with CVD, from 10 to 60 % depending on the frailty definition considered, are also frail[89]. Moreover, in patients with CVD, the presence of frailty is associated with a two-fold increase in mortality, independent of age and comorbidities[89]. Throughout the large spectrum of CVD, frailty is also associated with increased risks of hospitalization, with disability, and with poor health-related quality of life (HRQOL)[89].

This ability to predict poor outcomes beyond that of traditional tools based on age and comorbidities alone, has rendered frailty an important part of the preoperative assessment of patients undergoing cardiac procedures, as will be discussed in the following sections.

4.3 FRAILTY AND CARDIAC SURGERY

With the aging of the population and medical technological advances, open-heart surgeries are increasingly performed on older individuals, with contemporary patients' median age being around 73 years[90]. Unfortunately, despite technical advances, older individuals (80 years and above) undergoing these procedures continue to have poorer prognoses than their younger counterparts[91]. To better inform preoperative decisions, many traditional postoperative risk scores have been validated, but tend to perform poorly for older individuals[73,92]. Of note, the two most studied and used cardiac surgical risk stratification models incorporate chronological age and comorbidities as major determinants of the patient's overall score[93-96].

With the need to better predict postoperative risk to inform patient decision, some authors have decided to study the value of frailty as an outcome predictor in this population. Their studies have shown that objective frailty measures, such as gait speed, tend to complement or outperform traditional age-based risk prediction models[72,97,98].

Other studies have found that preoperative frailty was associated with postoperative mortality at 30 days, one and two years[71,99,100] in patients undergoing cardiac surgery. A systematic review and meta-analysis revealed that frailty increased by almost five-fold the risk of postoperative major adverse cardiac and cerebrovascular events[101] in this patient population. More recently, researchers have shown the association of preoperative frailty to the onset of postoperative delirium in patient undergoing cardiac procedures[102-104]. This last association will be further detailed in Section 6. Lastly, preoperative frailty also seems to be associated with lower risks of being discharged home and a higher risk to require rehabilitation and/or institutionalization after cardiac surgery[89].

4.4 CONCLUSION

In conclusion, when considering invasive cardiac procedures, frailty is an important predictor of mortality and morbidity, refining prognostic estimates from more traditional risk calculators mostly based on chronological age and comorbidities. In our next section, we will discuss the role of frailty in the preoperative assessment of patients undergoing transcatheter aortic valve replacement, a minimally invasive procedure initially designed to assist in the treatment of patients at higher risk for conventional cardiac surgery.

SECTION 5: MANUSCRIPT 1 - FRAILTY IN PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

5.1 PREFACE

The field of cardiac surgery is currently going through an important revolution with the arrival and dissemination of minimally invasive procedures, allowing for interventions to be performed on candidates with much higher preoperative risk profiles than before, with relative success. One of these novel interventions is transcatheter aortic valve replacement (TAVR). The following article is a scoping review of the literature on the prevalence and prognostic value of frailty in cohorts of patients undergoing TAVR. It was written during Fall 2016 as an invited article with the goal of informing an audience mainly constituted of specialists in the care of older individuals, on the TAVR procedure itself and its outcomes as well as on the role and importance of incorporating frailty measurements in the preoperative assessments of older individuals undergoing this procedure. It was published in the Journal of the American Geriatrics Society in April 2017, after being first published online in February of the same year. Of note, the most recent American College of Cardiology Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis now recommends systematic preoperative frailty screening for patients to undergo aortic valve replacement, to better inform the ensuing shared decision-making process.[105]

5.2 MANUSCRIPT COVER PAGE

Transcatheter Aortic Valve Replacement in the Care of Older Persons with Aortic Stenosis

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Introduction

This past decade has certainly been one of great innovation in the treatment of heart valve disease, most importantly in the treatment of severe aortic stenosis with the arrival and dissemination of transcatheter aortic valve replacement (TAVR)c as a viable alternative to surgical aortic valve replacement (SAVR) in high-risk patient populations. Due to its natural history, calcific degenerative aortic stenosis tends to be a disease of the aged, and it is only natural that it should draw the attention of the geriatric community as the care of patients with this condition is prone to be shared between cardiologists and geriatricians. In the following lines, we will review the existing body of literature on TAVR, focusing on (i) seminal randomized clinical trials that have proven the effectiveness and safety of this procedure, and observational studies that have highlighted the importance of geriatric domains, mainly frailty, on prognosis and decision making.

Major Randomized Control Trials of TAVR

Two major randomized clinical trial programs, PARTNER and CoreValve, have evaluated TAVR as compared to the standard-of-care; the former using Edwards Sapien devices and the latter using Medtronic CoreValve devices. Both included patients with severe calcific aortic stenosis and NYHA class II or greater symptoms, and excluded patients with congenitally abnormal valves, left ventricular ejection fraction <20%, recent myocardial infarction <1 month, recent GI bleed <3 months, recent stroke <6 months, limited life expectancy <12 months, and severe dementia resulting in inability to provide informed consent, to live independently outside of a chronic care facility, or to be compliant with rehabilitation or follow-up visits.

Patients deemed to be at very high “prohibitive” surgical risk, defined as >50% predicted likelihood of death or serious irreversible morbidity at 30 days, were enrolled in the PARTNER 1B and CoreValve Extreme Risk trials wherein TAVR was compared to conservative therapy (which, in many cases, involved balloon valvuloplasty)[1-3]. Frailty was cited as the main reason for prohibitive risk in 31% of patients[4]. Patients deemed to be at high surgical risk, defined as >15%

predicted likelihood of death at 30 days, were enrolled in the PARTNER 1A and CoreValve U.S. Pivotal trials wherein TAVR was compared to SAVR in order to demonstrate non-inferiority of the two procedures[5-8]. More recently, patients deemed to be at intermediate surgical risk, defined as 4-8% predicted likelihood of death at 30 days, were enrolled in the PARTNER 2 and SURTAVI trials wherein TAVR was compared to SAVR in a non-inferiority design[9,10].

No age-specific cutoff was used for enrollment and participants' mean age was 82-84 years with a standard deviation of 7-9 years[1,2,5,6]. Few geriatric measures aside from frailty were reported, with the available data confirming that the population undergoing TAVR was indeed frail and had on average 5 comorbid chronic conditions[1,2,5,6]. Disability and cognitive function were collected at baseline with the Katz Activities of Daily Living (ADL) and Mini-Mental Status Examination (MMSE) instruments, but these were not always reported in the published manuscripts. In the CoreValve trials, 80-84% of patients had slow 5-meter gait speed, 67% had weak handgrip strength, 10-22% had ADL disability, 18% had recent falls, and 28% had MMSE scores ≤24[1,5]. In the PARTNER 1A and 1B trials, the median gait speed was strikingly low at 0.38 m/s, handgrip strength was 23.6 kg in men and 12.2 kg in women, and 29% had ADL disability[11].

The primary endpoint was death from any cause at 1 year, and pre-specified secondary endpoints included: stroke, acute kidney injury, vascular complications, bleeding complications, echocardiographic valve performance, NYHA class, 6-minute walk distance, and need for repeat hospitalization. Patient-reported outcomes were collected, in particular, quality-of-life (QOL). Results for these endpoints are summarized in Table 1. In summary, for patients at prohibitive risk, TAVR was markedly superior to conservative therapy in terms of symptomatic improvement, repeat hospitalizations, and survival at 1 year; at the expense of a higher risk of peri-procedural stroke, bleeding, and vascular complications[1,2]. For patients at intermediate or high risk, TAVR was as equivalent (if not slightly superior) to SAVR in terms of survival at 1 year, superior for bleeding complications, postoperative atrial fibrillation, length of stay, and short-term symptomatic improvement, and inferior for vascular complications, residual aortic regurgitation, and permanent pacemaker implantation (mainly due to CoreValve-associated heart block)[5,6]. The benefits of TAVR were similar among subgroups >85 and ≤85 years of age.

Patient-Centered Outcomes in TAVR Trials

Several sub-studies[12-15] have shed light on QOL outcomes from the PARTNER and CoreValve trials, which, for a geriatric population, are measures of great interest. In these studies, QOL was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) as well as with the SF-12 and EQ-5D instruments. Results showed that prohibitive risk patients who underwent TAVR enjoyed better QOL at 1, 6, and 12 months as compared to those treated conservatively. Nevertheless, 1 out of 3 patients still suffered very poor or worsening QOL or death at 6 months, collectively termed "poor outcomes", and this increased to 1 out of 2 patients at 12 month[16,17]. High risk patients who underwent TAVR via a trans-femoral approach enjoyed better QOL at 1 month and similar QOL at 6 and 12 months as compared to those who underwent SAVR or TAVR via a more invasive trans-apical approach. Improvement in QOL scores were generally of a large magnitude (+23 to 33 KCCQ points), and were noted across sub-scales pertaining to symptoms, physical limitations, social limitations, and mental functioning.

Predicting Outcome in TAVR

The Society of Thoracic Surgeons (STS) risk score is the most commonly used tool to predict risk (http://riskcalc.sts.org/), although one of its blind spots is frailty. To better identify older adults at greater risk of adverse outcomes after TAVR, Hermillier et al.[18] analyzed data from the CoreValve trials and identified the following predictors of death at 1 year: falls in the past 6 months, Charlson comorbidity index ≥5, low serum albumin level at baseline (<3.3 g/dL), high STS risk score (≥7.0%), and use of home oxygen. The following predictors were not retained in the final model: gait speed, handgrip strength, weight loss, Katz ADL, and being wheelchair bound. Rather than focusing solely on mortality, Arnold et al.[13,16,17] analyzed data from the PARTNER and CoreValve trials and identified the following predictors of "poor (patient-centered) outcomes" at 6 months: low 6-minute walk distance, low mean aortic gradient, use of home oxygen, renal dysfunction, cardiac arrhythmia, cognitive dysfunction as measured by the MMSE, frailty as measured by the Fried scale (with weight loss being the most predictive domain in the scale), and disability as measured by the Katz ADL index.

Observational Studies of Frailty in TAVR

From early on, investigators interested in outcomes post-TAVR have studied frailty as one of its key predictors. The reasons for this interest are multiple and pertain to (i) the high burden of frailty in this complex geriatric population, the proven ability of frailty to improve risk prediction and thus guide decision making in cardiac surgery and other settings[19], the ease of use of certain measures of frailty such as gait speed and grip strength, and (iv) the potential ability of frailty to serve as a therapeutic target and improve outcomes. Our systematic review of the literature found 20 studies that focused on the implications of frailty in patients undergoing TAVR; these are reviewed in Table 2 and discussed below.

The studies reviewed were published between 2011-2016 and consisted of prospective and retrospective cohort studies. Sample sizes ranged between 100-460 patients, with the exception of two studies containing 2,830-3,687 patients from the CoreValve trials[16,18] and one study containing 8,039 patients from the STS/American College of Cardiology Transcatheter Valve Therapy registry (STS/ACC TVT registry)[20]. Much between-study variability was observed with respect to the operating definition of frailty, which contributed to discrepancies in the proportion of frail patients encountered in each individual study, ranging from 33% to 76% using objective scales. Frailty scales were generally based on variations of the phenotype of frailty construct[21,22], encompassing domains of physical performance (gait speed, handgrip strength), sarcopenia (CT-measured muscle area, self-reported weight loss), malnutrition (mini nutritional assessment, serum albumin), and often amalgamating ADL disability within the scale – even though disability is a distinct concept that most would argue should be disentangled from frailty[23].

Using a traditional cutoff of ≤6 seconds to walk 5 meters, gait speed was found to be ubiquitously slow in >75% of patients, rendering its sensitivity high but its specificity very low to identify high-risk patients[20]. A cutoff of >10 seconds to walk 5 meters, or worse yet, being wheelchair bound or unable to complete the 5-meter gait speed test were found to be more predictive in this patient population[14]. Other high-risk frailty indicators were low serum albumin (<3.5-3.5 g/dL), ADL disability (≥1-2 dependencies), and unintentional weight loss. Given the

limitations of self-reported weight loss as a surrogate for muscle loss, investigators have used CT images to measure muscle area (CT scans are routinely acquired as part of the pre-TAVR work-up), and the McGill-Munich Study was among the first to report the prognostic value of measuring psoas muscle area on a single axial image at the level of the L4 vertebrae using a web-based software tool (https://www.coreslicer.com)[24].

The recently completed Frailty-AVR study compared the prognostic value of the various frailty scales in 1,010 older adults undergoing TAVR and SAVR, and found that the short physical performance battery (SPPB) outperformed other scales to predict 1-year mortality and disability[25]. The SPPB, which has been extensively validated in the geriatric literature[26,27], consists of 5-meter gait speed, timed chair rises, and timed standing balance. Prediction was further improved by considering serum albumin, hemoglobin, and cognitive function. Despite the multitude of frailty scales used in the studies from our systematic review, similar observations have been made across studies. Frailty has consistently been associated with a two-to-threefold greater risk of death 1-2 years after TAVR. Frailty has variably been associated with short-term risk of death and complications, with some studies reporting a positive association[20,28-30] and others failing to demonstrate it in a statistically significant fashion[11,31-35]. When major complications did arise, these were more likely to be fatal in frail patients[29]. Furthermore, frailty has been associated with lengthier hospital stays, a lower likelihood of being discharged home[20,29,32], and a greater risk of functional decline 6-12 months after TAVR[31,36].

Conclusion

Geriatric domains play a central role in the evaluation of older adults with severe symptomatic aortic stenosis, who may accordingly be counselled and guided towards SAVR, TAVR, or conservative medical management when an intervention is likely to be futile[37]. Based on the evidence to-date, our recommendation is to adopt a tiered approach starting with the SPPB and a screening test for cognitive impairment; when deficits are encountered, deeper phenotypic characterization is indicated including comprehensive geriatric assessment. Through gains in operator expertise and valve design, the technical success of the TAVR procedure has

reached 96% and the unmet challenge has become achieving QOL success which is subpar in 50% of patients. Thus, geriatric domains will likely shift from prognostic markers to therapeutic targets, earmarking frail patients that could benefit from pre- or post-procedural interventions aimed at optimizing physical recovery and preventing progressive disability. Multi-faceted interventions combining structured exercise and nutritional supplementation have shown promising results[38,39] and are being investigated in frail TAVR patients. Optimization of patient-centered outcomes will undoubtedly require the close collaboration of cardiovascular and geriatric specialists as well as allied health professionals.[40-44]

References

1. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
3. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696-704.
4. Makkar RR, Jilaihawi H, Mack M, et al. Stratification of outcomes after transcatheter aortic valve replacement according to surgical inoperability for technical versus clinical reasons. J Am Coll Cardiol 2014;63:901-11.
5. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
6. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
7. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686-95.
8. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2015;66:113-21.
9. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374:1609-20.
10. Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. JACC Cardiovasc Interv 2013;6:443-51.
11. Green P, Arnold SV, Cohen DJ, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). The American journal of cardiology 2015;116:264-9.
12. Reynolds MR, Magnuson EA, Lei Y, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. Circulation 2011;124:1964-72.
13. Arnold SV, Reynolds MR, Wang K, et al. Health Status After Transcatheter or Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis at Increased Surgical Risk: Results From the CoreValve US Pivotal Trial. JACC Cardiovasc Interv 2015;8:1207-17.
14. Osnabrugge RL, Arnold SV, Reynolds MR, et al. Health status after transcatheter aortic valve replacement in patients at extreme surgical risk: results from the CoreValve U.S. trial. JACC Cardiovasc Interv 2015;8:315-23.
15. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol 2012;60:548-58.

16. Arnold SV, Afilalo J, Spertus JA, et al. Prediction of Poor Outcome After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2016;68:1868-77.
17. Arnold SV, Reynolds MR, Lei Y, et al. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. Circulation 2014;129:2682-90.
18. Hermiller JB, Jr., Yakubov SJ, Reardon MJ, et al. Predicting Early and Late Mortality After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2016;68:343-52.
19. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol 2014;63:747-62.
20. Alfredsson J, Stebbins A, Brennan JM, et al. Gait Speed Predicts 30-Day Mortality After Transcatheter Aortic Valve Replacement: Results From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation 2016;133:1351-9.
21. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
22. Afilalo J. Conceptual Models of Frailty: The Sarcopenia Phenotype. Can J Cardiol 2016;32:1051-5.
23. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255-63.
24. Mamane S, Mullie L, Piazza N, et al. Psoas Muscle Area and All-Cause Mortality After Transcatheter Aortic Valve Replacement: The Montreal-Munich Study. Can J Cardiol 2016;32:177-82.
25. Afilalo J, Lauck S, Kim DH, et al. Frailty assessment in older adults undergoing transcatheter or surgical aortic valce remplacement: The FRAILTY-AVR study. J Am Coll Cardiol 2016;67:8-.
26. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556-61.
27. Volpato S, Cavalieri M, Sioulis F, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. J Gerontol A Biol Sci Med Sci 2011;66:89-96.
28. Cockburn J, Singh MS, Rafi NH, et al. Poor mobility predicts adverse outcome better than other frailty indices in patients undergoing transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2015;86:1271-7.
29. Puls M, Sobisiak B, Bleckmann A, et al. Impact of frailty on short- and long-term morbidity and mortality after transcatheter aortic valve implantation: risk assessment by Katz Index of activities of daily living. EuroIntervention 2014;10:609-19.
30. Paknikar R, Friedman J, Cron D, et al. Psoas muscle size as a frailty measure for open and transcatheter aortic valve replacement. J Thorac Cardiovasc Surg 2016;151:745-50.
31. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv 2012;5:974-81.
32. Huded CP, Huded JM, Friedman JL, et al. Frailty Status and Outcomes After Transcatheter Aortic Valve Implantation. The American journal of cardiology 2016;117:1966-71.

33. Kamga M, Boland B, Cornette P, et al. Impact of frailty scores on outcome of octogenarian patients undergoing transcatheter aortic valve implantation. Acta Cardiol 2013;68:599-606.
34. Mok M, Allende R, Leipsic J, et al. Prognostic Value of Fat Mass and Skeletal Muscle Mass Determined by Computed Tomography in Patients Who Underwent Transcatheter Aortic Valve Implantation. The American journal of cardiology 2016;117:828-33.
35. Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080-90.
36. Schoenenberger AW, Stortecky S, Neumann S, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J 2013;34:684-92.
37. Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. JACC Cardiovasc Interv 2014;7:707-16.
38. Bibas L, Levi M, Bendayan M, Mullie L, Forman DE, Afilalo J. Therapeutic interventions for frail elderly patients: part I. Published randomized trials. Prog Cardiovasc Dis 2014;57:134-43.
39. Bendayan M, Bibas L, Levi M, Mullie L, Forman DE, Afilalo J. Therapeutic interventions for frail elderly patients: part II. Ongoing and unpublished randomized trials. Prog Cardiovasc Dis 2014;57:144-51.
40. Bogdan A, Barbash IM, Segev A, et al. Albumin correlates with all-cause mortality in elderly patients undergoing transcatheter aortic valve implantation. EuroIntervention 2016;12:e1057-e64.
41. Ewe SH, Ajmone Marsan N, Pepi M, et al. Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis. Am Heart J 2010;160:1113-20.
42. Saji M, Lim DS, Ragosta M, et al. Usefulness of Psoas Muscle Area to Predict Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement. The American journal of cardiology 2016;118:251-7.
43. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. JACC Cardiovasc Interv 2012;5:489-96.
44. Seiffert M, Sinning JM, Meyer A, et al. Development of a risk score for outcome after transcatheter aortic valve implantation. Clin Res Cardiol 2014;103:631-40.

Table 1: Patient Characteristics and Outcomes in Major Clinical Trials of Transcatheter Aortic Valve Replacement

	Very High Risk		*High Risk*		*Intermediate Risk*
	PARTNER 1B Trial[2,3]	**CoreValve Extreme Risk Trial**[1]	**PARTNER 1A Trial**[6,7]	**CoreValve US Pivotal Trial**[5,8]	**PARTNER 2 Trial**[9]
Year	2010	2014	2011	2014	2016
Sample size	358	489	699	795	2,032
Intervention	TAVR vs. medical	TAVR (single arm)	TAVR vs. SAVR	TAVR vs. SAVR	TAVR vs. SAVR
Age, years	83 ± 8	83 ± 9	84 ± 7	83 ± 7	82 ± 7
Females	192 (54%)	255 (52%)	300 (43%)	372 (47%)	1014 (50%)
STS-PROM, %	11.6 ± 6.0	10.3 ± 5.5	11.8±3.4	7.4 ± 3.1	5.8 ± 2.0
30-day outcomes					
Mortality	5.0 vs. 2.8	9.8	3.4 vs. 6.5	3.3 vs. 4.5	3.9 vs. 4.1
Stroke	6.7 vs. 1.7*	4.0	4.6 vs. 2.3	4.9 vs. 6.2	5.5 vs 6.1
Major bleed	16.8 vs. 3.9*	36.7	9.3 vs. 19.5*	28.1 vs. 34.5*	10.4 vs 43.4*
Vascular complication	30.7 vs 5.0*	8.2	17.0 vs. 3.8*	5.9 vs. 1.7*	7.9 vs. 5.0*
Acute kidney injury	1.1 vs. 2.2	11.8	4.0 vs. 4.0	6.0 vs. 15.1*	1.3 vs. 3.1*
New atrial fibrillation	0.6 vs. 1.1	-	8.6 vs. 16.0*	11.7 vs. 30.5*	9.1 vs. 26.4*
New pacemaker	3.4 vs. 5.0	21.6	3.8 vs. 3.6	19.8 vs. 7.1*	8.5 vs 6.9
Length of stay, days	-	7	8 vs. 12*	-	6 vs 9*
Change in KCCQ	24.8 vs. 10.4*	23.9	23.7 vs. 12.2*	21.6 vs. 3.8 *	-
1-year outcomes					
Mortality	30.7 vs.49.7*	26.0	24.3 vs. 26.8	14.2 vs. 19.1*	12.3 vs. 12.9
Stroke	10.6 vs. 4.5*	7.0	5.7 vs 2.8*	8.8 vs. 12.6	8.0 vs. 8.1
Readmission	22.3 vs. 44.1*	-	18.6 vs. 17.7	-	14.8 vs. 14.7
Change in KCCQ	31.8 vs. 4.1*	27.4	28.7 vs. 25.2	24.0 vs. 21.9	-
2-year outcomes					
Mortality	43.3 vs. 68.0	-	33.9 vs. 35.0	22.2 vs. 28.6*	16.7 vs. 18.0
Stroke	13.8 vs.5.5*	-	7.7 vs 4.9	10.9 vs. 16.6*	9.5 vs. 8.9

Where * indicates a statistically significant finding with P≤0.05. Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 2: Results of a Systematic Review of the Literature on Frailty in TAVR

STUDY	N	DESIGN	FRAILTY TOOL	% FRAIL	MAIN OUTCOME(S)
Alfredsson, 2016[20]	8,039	Prospective multi-center registry from STS/ACC TVT	5-meter gait speed	28% >10s 76% >6s	**30-day mortality**: 8.4% vs. 5.4% (>10s vs. <6s) **In-hospital morbidity**: nonsignificant except vascular complications **Discharge to a facility**: 47% vs. 22% **Length of stay**: 7 vs. 5 days
Arnold, 2016[16]	2,830	Secondary analysis of TAVR patients in the CoreValve trials	Fried scale Katz ADL disability	60% 17%	**1-year "poor outcome"**: frailty OR 1.42, disability OR 1.19 per ADL
Bogdan, 2016[40]	150	Retrospective single-center cohort	Albumin <4.0	53%	**2.1-year mortality**: HR 2.28
Cockburn, 2015[28]	312	Prospective single-center cohort	Poor mobility	-	**30-day mortality**: OR 4.03 **2.2-year mortality**: OR 2.15 * Katz, Karnofsky, CHSA, Brighton scales nonsig.
Ewe, 2010[41]	147	Prospective two-center cohort	Fried scale	33%	**9-month death, MI, stroke, heart failure**: HR 4.20
Green, 2012[31]	159	Prospective single-center cohort	Custom scale (grip, gait, albumin, ADL)	48%	**1-year mortality**: 17% vs. 7%, HR 3.51 **30-day mortality/morbidity**: nonsignificant except major bleeding complications **Length of stay**: 9 vs. 6 days
Green, 2015[11]	244	Secondary analysis of TAVR patients at 3 sites in the PARTNER 1A and 1B trials	Custom scale (grip, gait, albumin, ADL)	45%	**1-year mortality**: 33% vs. 16%, HR 2.5 **6-month "poor outcome"**: 42% vs. 28%, OR 2.21 **30-day mortality/morbidity**: nonsignificant
Hermiller, 2016[18]	3,687	Secondary analysis of TAVR patients in the CoreValve trials	Albumin <3.3 Recent fall <6 months	17% 20%	**1-year mortality**: low albumin OR 1.40, recent fall OR 1.36
Huded, 2016[32]	191	Retrospective single-center cohort	Custom scale (grip, gait, weight loss, ADL)	33%	**3-month mortality**: nonsignificant **30-day mortality/morbidity**: nonsignificant **Discharge to facility**: 39% vs. 14%, OR 4.80
Kamga, 2013[33]	30	Prospective single-center cohort	SHERPA scale	-	**1-year mortality**: 60% vs. 11%, HR 2.74 per point **In-hospital mortality/morbidity**: nonsignificant * ISAR scale nonsig.
Mamane, 2016[24]	208	Retrospective two-center cohort	Psoas muscle area at L4	-	**1.4-year mortality**: HR 0.88 per cm^2 in females
Mok, 2016[34]	460	Retrospective two-center cohort	Total muscle area at L3	64%	**1-year mortality**: HR 1.49 **30-day mortality**: nonsignificant

Osnabrugge, 2015[14]	436	Secondary analysis of femoral TAVR patients in the CoreValve Extreme Risk Trial	Albumin <3.3 Wheelchair bound	18% 16%	**6-month "poor outcome"**: low albumin OR 1.8, wheelchair bound OR 2.6
Paknikar, 2016[30]	295	Retrospective single-center cohort of TAVR and SAVR patients	Psoas muscle area at L4	-	**2-year mortality**: OR 0.56 per sex-stratified SD **30-day mortality/morbidity**: OR 0.52 **ICU LOS >7d, LOS >14d, or readmission**: OR 0.56
Puls, 2014[29]	300	Prospective single-center cohort	Katz ADL disability	48%	**1.5-year mortality**: HR 2.67 **30-day mortality**: 17% vs. 6% **30-day complications**: nonsignificant except acute kidney injury and need for PRBC **Length of stay >14d**: 32% vs. 22% **Discharge to facility/nursing**: 53% vs. 9%
Rodes, 2010[35]	345	Retrospective multi-center cohort	Subjective judgment	25%	**8-month mortality**: nonsignificant **30-day mortality**: nonsignificant **Procedural complications**: nonsignificant except need for dialysis
Saji, 2016[42]	232	Retrospective single-center cohort	Psoas muscle area at L4	-	**6-month mortality:** OR 1.53 per cm^2/m^2
Schoenenberger, 2013[36]	119	Prospective single-center cohort (extension of Stortecky)	Custom scale (TUG, MNA, MMSE, ADL, IADL)	50%	**6-month ADL change ≥1**: OR 3.34 **6-month mortality**: 18.6% vs. 3.3%
Stortecky, 2012[43]	100	Prospective single-center cohort	Custom scale (TUG, MNA, MMSE, ADL, IADL)	49%	**1-year mortality**: OR 2.93 **1-year cardiovascular/cerebral events**: OR 4.89
Seiffert, 2014[44]	347	Retrospective cohort	Subjective judgment	5%	**1-year mortality**: HR 1.41

Abbreviations: ADL, Activities of Daily Living; CHSA, Canadian Study of Health and Aging; HR, Hazard Ratio; IADL, Instrumental Activities of Daily Living; MI, myocardial infarction; MNA, Mini-Nutritional Assessment; OR, Odds Ratio; PCI, Percutaneous Coronary Intervention; STS, Society of Thoracic Surgeons; TAVR, Transcatheter Aortic Valve Replacement; TUG, Timed Up & Go.

SECTION 6: ON FRAILTY AND DELIRIUM

6.1 INTRODUCTION

The previous sections allowed us to better understand the concept of frailty and its relation to the aging process. We also were able to appreciate the importance of frailty with regards to treatment planning and prognostication in patients undergoing cardiac procedures, from the less invasive transcatheter aortic valve replacement (TAVR) to open-heart surgery. In the following lines, we will introduce another geriatric syndrome: delirium, as it is central to this thesis. We will define delirium and discuss its prevalence in the older population. We will go over its physiopathology and clinical characteristics, as well as its diagnostic criteria. General prevention and treatment measures for delirium will be presented as well. We will conclude by presenting the growing evidence on the association between the frailty and delirium syndromes. This will allow us to set the table for the remainder of our work, pertaining to delirium prevention and treatment in patients undergoing cardiac surgery.

6.2 DELIRIUM: DEFINITION AND IMPORTANCE

Delirium, a geriatric syndrome, is an acute change in attention and cognition, often compared to "acute brain failure"[106]. Its prevalence varies depending on studied settings, but is invariably high, with the syndrome affecting up to one third of patients admitted to medical inpatient units, 15% of patients presenting to emergency rooms, and up to 50% of patients undergoing cardiac and non-cardiac surgeries[107]. Its prevalence is even higher in intensive care units, where it may affect up to 60-80 % of patients receiving mechanical ventilation[108]. These are perhaps under-estimates of an even higher prevalence of the syndrome, as delirium tends to be underrecognized and undertreated[109,110].

The importance of delirium lies in its high prevalence, as detailed above, in its potential to be prevented (and therefore used as an indicator of quality of care), which will be discussed later, but also in its association with important adverse outcomes including death[107]. In an important meta-analysis, delirium was associated with a hazard ratio for mortality of 1.95 (95% CI 1.51-2.52) at two years, and a higher risk of institutionalization (HR 2.41, 95% CI 1.77-3.29) [111]. Patients with delirium also seem to be at much higher risk to develop a major neurocognitive

disorder (dementia) at four years of follow-up (HR 12.52, 95% CI 1.86-84.2)[111]. While in hospital, patients who experience delirium are at a 3-5 fold greater risk of developing nosocomial complications[106]. In patients treated on intensive care units, delirium has been linked to longer duration of mechanical ventilation, to prolonged lengths of stay both in the intensive care and in hospital, as well as to in-hospital mortality (RR for mortality 2.19, 94% CI 1.78-2.70)[112]. This syndrome has also been associated with lower physical performance and with increased functional dependence lasting at least 30 days in most patient populations[107]. Finally, delirium also has an impact on health care expenditures, with estimated annual costs of 6.9 billion dollars (in 2004 USD)[113].

If delirium had been portrayed early on as largely reversible, accumulating evidence suggests that up to 45% of patients still have delirium upon their discharge from hospital, and that the syndrome may persist for longer than 6 months[114]. Cognitive, functional and vital outcomes tend to be consistently worse in these patients suffering from what is referred to as persistent delirium. [115]

6.3 DELIRIUM PHYSIOPATHOLOGY AND RISK FACTORS

The underlying physiopathology of delirium is still not well understood. Just like frailty and other geriatric syndromes, it is considered to be multifactorial in nature[116]. Accumulating evidence suggests that delirium is caused by the interaction of various biological imbalances involving neurotransmitters and inflammatory markers as well as physiological stressors, metabolic and electrolyte disorders and possibly genetic factors, all resulting in the overt disruption of major cerebral neuronal networks, to provoke the clinical manifestations we will describe later[106].

Multiple potential triggers of the above-mentioned biological imbalances have been identified as potential causes of delirium in at-risk individuals. In most cases, more than a single trigger may be found. It is suggested to view delirium as resulting from the interaction between predisposing factors, responsible for an individual's intrinsic vulnerability for the syndrome, and precipitating factors, activating the pathological changes described above. In this model,

individuals with high vulnerability require less noxious insults in order to develop the full syndrome, and vice-versa, such as illustrated in figure 3 below:

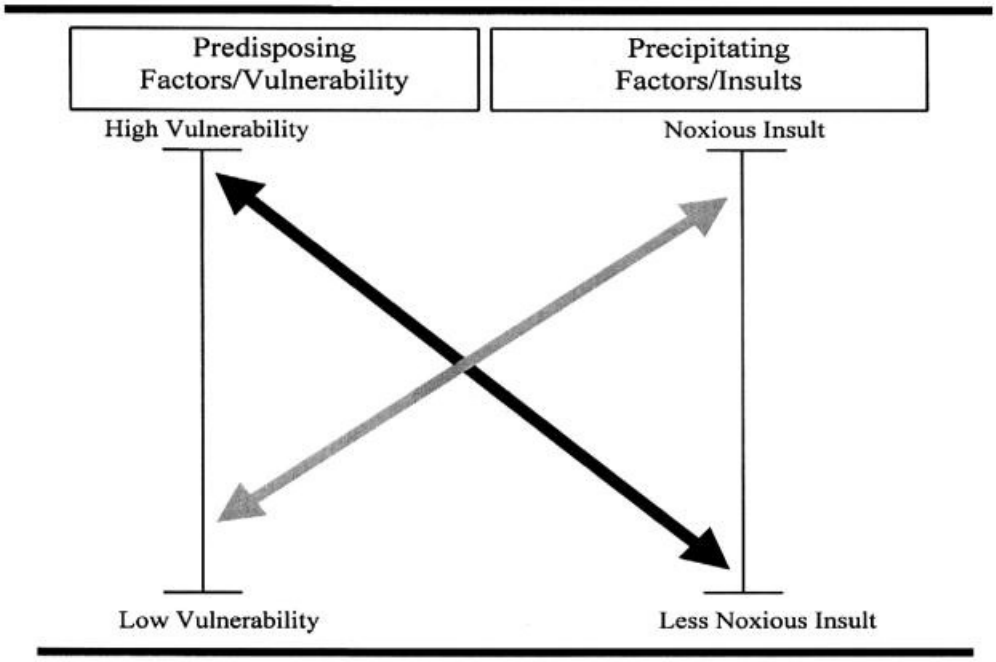

Figure 3: Multifactorial model of delirium. (from Inouye, 2014, p.912)
As shown above, the development of delirium depends on the complex interaction of patient-related predisposing factors (or vulnerability) and precipitating factors, where more vulnerable individuals (shown in upper left corner) need less noxious stimuli to provoke the syndrome, than less vulnerable ones (lower left corner).Highly noxious insults can be caused either by the addition of multiple smaller insults, or by one severe pathological process.

Identified risk factors for delirium in most clinical setting are numerous and include: older age (75 years and above), baseline cognitive impairment and major neurocognitive disorder (formerly dementia), functional impairment, history of delirium, sensory impairment (vision and/or hearing), comorbidity or severe illness, alcohol misuse, and history of cerebrovascular accident[107,110].

Precipitating factors, on the other hand, vary across patient populations. In medical inpatients, the leading ones are polypharmacy and use of psychoactive medications, physical restraints, bladder catheterization and electrolyte abnormalities. In surgical populations, electrolyte imbalances, type of surgery (thoracic, vascular), and pain are the most important

precipitants reported in the literature[107,110]. Nevertheless, it should be remembered that almost any medical and neurological condition, either alone or with others, may contribute to precipitating delirium[110]. Of note, many of the above-mentioned precipitating factors are preventable and are makers of quality of care (ex. use of physical restraints, bladder catheterization, use of psychoactive medications). Hence, it has been suggested that delirium incidence could serve as a proxy for hospital quality of care[117].

6.4 DELIRIUM DIAGNOSIS

Delirium is a clinical entity, with no reliable auxiliary test to prove its presence or absence. The current standard for diagnosis are the criteria found in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)[118] and in the World Health Organization's International Classification of Diseases, 11th revision (ICD-11)[119].

Core diagnostic features for delirium include an acute onset and fluctuating symptoms, inability to maintain attention, impaired level of consciousness and disturbance of cognition[120]. Features supportive of the diagnosis include disturbances of the sleep/wake cycle, hallucinations and/or delusions, emotional lability and abnormal behavior[115]. Of note, delirium exists in hyperactive, mixed, and hypoactive forms, the latter conferring poorer prognosis[121].

Clinical screening tools have been developed to improve delirium detection in all settings, but one tool, the Confusion Assessment Method [122], was found to have the best characteristics, with a pooled sensitivity of 86% and specificity of 93%[123]. Furthermore, multiple variations of the CAM were developed and validated, such as one for ICU (CAM-ICU)[124] and one for emergency rooms[125], for example.

6.5 DELIRIUM PREVENTION AND TREATMENT

Once delirium is recognized, a thorough assessment of the patient must be undertaken to identify and, if possible, reverse all predisposing, precipitating, and perpetuating factors of the syndrome through history taking, review of medications, physical examination and ancillary testing, as indicated[110].

There is no specific treatment for delirium, aside from the above and, in some cases, symptomatic relief, which is why the available research has focused on its prevention, either through non-pharmacologic or pharmacologic approaches. If non-pharmacologic interventions aim at preventing delirium by targeting previously mentioned risk factors, pharmacologic interventions aim to prevent or treat this syndrome by normalizing neurotransmitters levels in the brain[117].

An important systematic review studied the effectiveness of single and multicomponent interventions for the prevention of delirium in hospitalized, non-ICU patients, and found that multicomponent non-pharmacologic interventions were effective in reducing delirium incidence by about 30% in both medical and surgical patients[117]. Similar interventions were however not effective in reducing delirium incidence in patients with underlying major neurocognitive disorder, nor were they found to reduce delirium duration or severity. No serious adverse events were reported in excess in studies of non-pharmacologic interventions.

The Hospital Elder Life Program (HELP)[126] is the most widely spread prototype of non-pharmacologic intervention for delirium prevention in the world, using a multidisciplinary and multifaceted approach, delivered in part by volunteers. In a recent meta-analysis looking at the effectiveness of HELP in both medical and surgical patient populations, this program was linked to lower delirium incidence (OR 0.47, 95% CI 0.37-0.59) and to lower in hospital falls rates[127]. Furthermore, the implementation of the HELP program is thought to be cost-effective, with savings around 1600-3800 USD (in 2018 USD) per patient, and 16000$ per person per year in long term care costs in the post-delirium year[127]. Another interesting form of non-pharmacologic intervention for delirium prevention is a proactive geriatric medicine consultation program, which has proven to be very effective in decreasing delirium incidence, duration and severity in a surgical population[128].

Looking at pharmacologic delirium prevention studies, there was no convincing evidence that cholinesterase inhibitors, typical or atypical antipsychotics, melatonin or melatonin agonists decrease the incidence of delirium[117]. If one study found Onlanzapine, an atypical antipsychotic, to have benefit on the incidence of delirium in a cohort of patients undergoing orthopedic

surgery, this was at the detriment of higher delirium severity and longer delirium duration[129]. Risks of developing side effects were also significantly higher in patients receiving pharmacologic interventions[117].

To date, non-pharmacologic interventions for delirium prevention remain first line in the approach to the syndrome and appear in dedicated society guidelines[130]. It is suggested that the interventions be delivered by trained multidisciplinary teams as soon as possible after a patient's admission. Suggested components to include in a non-pharmacologic bundle are: performing frequent reorientation and cognitive stimulation, addressing dehydration and constipation, avoiding hypoxia (low levels of oxygen), screening for and treating infections, encouraging mobilization, encouraging presence of family and friends, addressing pain, carrying out a medication review, avoiding unnecessary catheterization, addressing poor nutrition, palliating to sensory impairment and promoting normal sleep/wake cycles, as well as others. The same guidelines also suggest that antipsychotic use be reserved for agitated patients at risk for themselves or others, when de-escalation maneuvers fail.

In patients treated on intensive care units, data has shown different results regarding the effectiveness of delirium prevention and treatment interventions. A systematic review showed that, in surgical ICU patients, the use of dexmedetomidine instead of benzodiapezines, and that of antipsychotics, may help in decreasing delirium incidence, but not duration[131]. This however is not reflected in the guidelines from the American College of Critical Care Medicine (ACCM) in which only the use of dexmedetomidine is encouraged to decrease delirium duration in the same population[132]. These guidelines were however written preceding some of the studies include in the above-mentioned systematic review. On the other hand, ACCM guidelines do recommend early mobilisation as means to prevent and reduce the duration of delirium in ICU patients.

6.6 DELIRIUM AND FRAILTY: THE CONCEPT OF VULNERABILITY

Now that we briefly reviewed delirium, we would like to propose that this geriatric syndrome is linked, in many ways, to the frailty syndrome which has been the subject of our thesis so far. At first glance, frailty, a state of increased vulnerability to stress due to decreased physiologic reserves, and delirium, an acute confusional state, do not have much in common.

Looking closer however, there are several commonalities between these two geriatric syndromes. These will be presented in the following paragraphs.

6.6.1 Continuum of risk. Both frailty and delirium occur on a continuum, with frailty being at the end of the progression from fitness to pre-frailty to overt frailty, and delirium having the potential to present in a subsyndromal form, where some of the essential diagnostic criteria are missing to fulfill the definition of the entire syndrome[115]. Moreover, we have learned earlier that the acute nature of delirium is not representative of the experience of many patients, suffering from chronic, more persistent forms of the syndrome.

6.6.2 Vulnerability. Conceptually, both frailty and delirium are linked to the concept of vulnerability. In frailty, vulnerability ensues from the individual's state of decreased physiological reserve. In delirium, vulnerability is conferred by the accumulation of risk factors for the condition, such as depicted in figure 3.

6.6.3 Inflammation. Physiopathologically, frailty and delirium share similarities, with inflammation playing an important role in the onset and perpetuation of both syndromes. Indeed, levels of peripheral inflammatory cytokines are chronically elevated in frail patients, and acutely elevated in delirium. Chronic peripheral inflammation is also seen in cognitive impairment, an important risk factor for delirium[133].

6.6.4 Common risk factors. Frailty and delirium also share common risk factors: malnutrition and atherosclerosis. As seen in section 3, malnutrition is one of the hallmarks of frailty, with both macronutrient and micronutrient deficiencies having been associated with the syndrome[134]. We also saw that multicomponent interventions to alleviate frailty including a nutritional intervention tented to show promising results[78]. Similarly, malnutrition is an important risk factor for delirium[135] and is targeted in most of its prevention and treatment interventions[107,115]. Finally, atherosclerosis, mainly small vessel disease, may also contribute to the onset of both syndromes[136].

6.6.5 Prognosis and complications. Delirium and frailty are risk factors for mortality, morbidity and functional decline in a variety of settings. Both can therefore be used as prognostic

tools, useful in engaging with treatment planning decisions with patients and their families. Another important finding is that when both present, frailty and delirium seem to interact to confer patients a much worse prognosis in terms of survival[35]. Interestingly, in medical patients, delirium seems to be particularly adverse in terms of mortality in those suffering from lighter levels of frailty[137], possibly reflecting the severity of the insult required to produce delirium in fitter individuals.

6.6.6 Approach to treatment. As previously mentioned, frailty and delirium are also similar in terms of their assessment and treatment approaches, both requiring a thorough multidisciplinary assessment and multifaceted treatment plans, mostly non-pharmacologic in nature. The value of a comprehensive geriatric assessment to improve outcomes has been established for the two syndromes[138,139].

6.6.7 Bidirectional association. More importantly, frailty and delirium may act as risk factors for one another, in a downward spiral. If frailty was first considered a purely physical syndrome, and delirium a purely cognitive one, this interpretation is being increasingly challenged. Depending on the model, impaired cognition may be a contributor to frailty and delirium may be associated with functional and physical performance decline[140].

The role of frailty as an independent risk factor for incident delirium has been suggested by many studies in general surgery[141] and cardiovascular procedures[102-104,142-145] and further reinforced in a recent meta-analysis of risk factors for delirium in patients undergoing elective surgery, where the pooled odds of developing delirium were 4.1 times higher (95% CI 1.4-11.7) in frail versus non-frail patients[146]. In patients admitted to medical wards, this association was also reported[147-149], although not consistently[150], possibly owing to the variety of tools used to measure frailty. Interestingly, in medical patients, frailty has also been associated to persistent delirium at discharge[145]. On the reverse of the above findings, in patients undergoing cardiac surgery, the experience of postoperative delirium was independently associated with the new onset of frailty[151], again pointing to the possible existence of a bidirectional association between the two syndromes.

In conclusion, frailty and delirium, although different, share many common features pertaining to their physiopathology and risk factors, their treatment and their prognosis. Their association may be bidirectional, although more studies would be required to confirm this.

6.7 FRAILTY AND DELIRIUM IN CARDIAC SURGERY

As was previously mentioned, preoperative frailty is highly prevalent in the older population undergoing open-heart surgery. To date, only a few studies have looked at its association with the onset of postoperative delirium in this context. In a prospective cohort study by Brown et al.[102], frailty, as defined by a score of three or more out of five on Fried's frailty scale, was present in 31% of patients to undergo coronary artery bypass graft (CABG) surgery and was associated with a two-fold increased risk of developing postoperative delirium. In this study, delirium developed in almost 50% of frail patients. In a similar study by Jung et al.[103] in which three different frailty scales were used and compared, about half of the enrolled patients were considered frail. Again, frailty was found to be associated with significantly increased odds of postoperative delirium, with odds for developing the syndrome between 3 and 8 times higher in frail versus non-frail individuals, depending on the scale used. In the same study, the addition of frailty measures to a standard preoperative risk score (EuroSCORE 2) was found to significantly increase the latter's ability to predict postoperative delirium. Finally, a prospective cohort study of patients undergoing elective open-heart surgery by Ogawa et al.[151] showed that preoperative frailty, defined as low handgrip strength and/or a slow walking speed was associated with a higher incidence of delirium. It also pointed to significantly higher odds of postoperative frailty, measured at discharge from hospital, in patients who had a diagnosis of postoperative delirium, with an adjusted odds ratio of 2.98 (95% CI 1.46-6.20). Therefore, although limited, the current evidence suggests a potentially bi-directional association between frailty and delirium in patients undergoing elective cardiac surgical procedures. More work in this field is required, notably to assess whether alleviating preoperative frailty has the potential to decrease the incidence of postoperative delirium and improve patient-centered outcomes in this patient population.

6.8 CONCLUSIONS

In this section, we were able to define delirium, an acute confusional state, and present its importance in medical and surgical patients. We also went over the hypothesized physiopathology and the effective prevention and treatment methods for this geriatric syndrome. This new knowledge allowed us to discuss the many parallels between delirium and frailty, which had been the main subject of this work so far, as well as their potentially bi-directional relation, suggested by work in cardiac surgical patients. The end of this chapter marks a shift in the orientation of our work, from frailty in transcatheter aortic valve replacement, to delirium in patients undergoing cardiac surgery, which will be the main subject of the following sections.

SECTION 7: DELIRIUM IN CARDIAC SURGERY

7.1 INTRODUCTION

This section is an introduction to the remainder of this thesis. Its goal is to provide the reader with information regarding the importance of delirium in patients undergoing cardiac surgery. We will review the prevalence, predisposing and precipitating factors for delirium in this patient population, as well as the influence of delirium on their post-surgical outcomes. We will also review current evidence regarding delirium prevention and treatment in this setting.

7.2 PREVALENCE, PREDISPOSING AND PRECIPITATING FACTORS OF DELIRIUM IN CARDIAC SURGERY

Delirium incidence in patients undergoing cardiac surgery varies greatly between studies, from 3% to 70%, with more rigorous estimates reporting incidence rates between 26% and 52%[152]. Of note, a significant proportion of patients developing delirium in this context (up to 92%)[153] present with its hypoactive form, associated with worse prognosis as seen in our previous section. An ongoing Canadian prospective study aiming at more precisely quantifying the burden of delirium in a contemporary cardiac surgical population, will likely help in in getting a better estimate of the current incidence of delirium in this patient population[154].

As explained in our previous section, delirium is almost invariably multifactorial in nature and tends to occur more frequently in vulnerable patients. In the following lines, we will discuss conditions predisposing to the development of this syndrome that are particularly relevant to the cardiac surgical population.

First, due to their age and the nature of their underlying disease, it is not uncommon for patients undergoing cardiac surgery to have some degree of cerebrovascular disease at baseline. It has been shown, that high grades of white matter hyperdensities on magnetic resonance imaging, consistent with a high burden of cerebral ischemia, increase the odds of developing delirium after cardiac surgery by almost four times[155]. Furthermore, during cardiac surgical procedures, especially on-pump surgeries, there is generation of cerebral microemboli, further affecting cognitive reserve in these patients[156]. Other cardiovascular diseases and risk factors,

such as a history of myocardial infarction, a previous stroke and diabetes have also been associated with post-sternotomy delirium[157].

Mood disorders, including anxiety and depression, were also identified as important risk factors for delirium in cardiac surgical patients[157]. Both entities are prevalent in this population, with 15-20% of patients undergoing open-heart procedures suffering from depression preoperatively[158], and high levels of pre-operative anxiety being present in up to 7%[159]. Furthermore, depression is intimately linked to cardiovascular disease[160]. Interestingly, in 2009, Rudolf and al developed and validated a preoperative risk prediction tool for delirium in cardiac surgical patients including the following four variables, with good predictive value: prior stroke/transient ischemic attack, Geriatric Depression Scale (GDS)[161] score greater than 4, abnormal albumin levels, and abnormal score on the Mini Mental State Examination (MMSE)[162], further emphasizing the importance of cerebrovascular disease and mood disorders as risk factors for postoperative delirium in this patient population.

Polypharmacy, especially the preoperative use of sedatives such as benzodiazepines[153], has been associated with increased delirium incidence in patients undergoing cardiac surgery. Preoperative use of anticholinergic medications was also associated with and increased risk of postoperative delirium[163].

Several common perioperative factors may act as precipitants for delirium in patients undergoing open-heart surgery, including the use of sedative/hypnotics and low systemic perfusion pressures. Indeed, many medications used postoperatively such as opiate analgesics as well as antiemetics have also been associated with the development of delirium in cardiac surgical patients[157].The use of physical restraints to prevent patients from removing important care devices such as endotracheal tubes or intravenous lines, has also been associated with an almost three times increase in the odds of developing delirium[153].

Finally, cardiac surgical patients visit various treatment settings in their postoperative course. Both being in an intensive care unit (ICU) setting as well as multiple room changes have been associated with an increased risk of delirium[157,164]. The ICU environment itself has been hypothesized to be a risk factor for delirium development through minimum natural light,

important noise, and poor sleep quality. However, a dedicated study in a cardiac surgical ICU setting was not able to demonstrate the benefit of private rooms and natural light over windowless non-private rooms on delirium incidence[165]. Still, it did show longer duration of delirium in patients in the windowless non-private rooms.

7.3 OUTCOMES OF DELIRIUM IN CARDIAC SURGERY

Similar to what is reported in other clinical settings, delirium has been found to be associated with worse cognitive, functional and survival outcomes in patients undergoing cardiac surgical procedures.

Cognitive recovery after cardiac surgery has been studied by Saczynski et al. in a cohort study published in 2012[166]. They found that patients who experienced delirium had a significantly greater decline in their scores on cognitive testing one month post procedure, and remained with lower scores than their delirium-free counterparts at one year. Furthermore, six months post procedure, patients with postoperative delirium were significantly less likely to have regained their preoperative cognitive baseline (40% of patients with delirium were not at their baseline versus 24% of the delirium-free patients). This observation was close to, but did not reach, statistical significance at 12 months. Koster and al. also reported on worsened cognitive function in patients with postoperative delirium 6 months after discharge[167]. Attention, memory as well as perceptual-motor tasking were the most affected domains in this patient cohort.

In 2010, Rudolf and al. reported on the functional trajectory of 190 patients undergoing cardiac surgery, and found that delirium was independently associated with loss of function at one month, defined as the loss of ability to perform at least two instrumental activities of daily living, but not at twelve months[168]. Post cardiac surgery delirium was also reported to be associated with worse quality of life scores at 6 months[167].

From a system perspective, post cardiac surgery delirium has also been associated with close to twofold 6-month rehospitalization rates[167], as well as with longer hospital lengths of stay[169].

Finally, mortality was found to be significantly increased in post cardiac surgical patients with delirium for up to 10 years after surgery (HR 1.65, 95% CI 1.38-1.97), compared to their delirium-free counterparts[169,170]. This association was even stronger in younger patients, and in those without a history of prior stroke.

7.4 DELIRIUM PREVENTION AND TREATMENT IN CARDIAC SURGERY

Delirium treatment is similar across clinical settings and involves the prompt identification and reversal of all potential risk factors and precipitants. Although antipsychotics are often used in treating severe agitation and psychosis symptoms related to delirium, their efficacy and safety has never been proven in the cardiac surgical or event in the ICU context[132].

Given the important consequences associated with postoperative delirium in cardiac surgery and no clear effective treatment for the syndrome, many efforts have already been deployed in order to see if simple preventive measures could be effective in reducing its incidence.

Most studied in the post cardiac surgical context, are pharmacological interventions. One study showed promising results after the administration of a single dose of risperidone, an antipsychotic, postoperatively, [171] but concerns regarding the safety profile of this medication remain. Statins were studied in at least two small observational studies with conflicting results[172,173]. Intraoperative administration of dexamethasone, because of its anti-inflammatory properties, has also been studied in a few studies without convincing results[174]. Cholinesterase inhibitors were also studied and found ineffective[175]. Furthermore, in a treatment study of non-cardiac ICU patients with delirium, rivastigmine in association with Haldol was associated with an increased risk of death[176].

Sedation agents used perioperatively in cardiac surgery, especially dexmedetomidine, an alpha-2 adrenergic agonist, have received a lot of attention in the recent years with regards to delirium prevention. A recent meta-analysis points to the superiority of dexmedetomidine over propofol for delirium prevention in post-cardiac surgery patients, at the expense of a higher risk of bradycardia[177]. In older surgical patients, dexmedetomidine could also favorably impact in-

hospital and operative mortality[178]. This recent discovery has not yet been reflected in new delirium prevention guidelines for patients in intensive care which predate it[132,179].

In 2014, Ettema et al. performed a systematic review of randomized controlled trials (RCTs) and cohort studies of preadmission interventions to prevent postoperative complications in cardiac surgery and found no effective intervention for delirium prevention. They were however able to produce a list of multifactorial interventions effective in preventing postoperative depression, infection, pulmonary infections, atrial fibrillation, as well as prolonged ICU and hospital length of stays[180].

In terms of non-pharmacologic prevention of postoperative delirium in patients undergoing cardiac procedures, the literature is sparse. To date, the only firm recommendations from guidelines regarding delirium prevention in an ICU population at large, are to implement strategies for early mobilization[132]. It is however mentioned that further studies on the subject are needed, especially given the important success of such interventions in regular medical and surgical populations[117,181].

7.5 CONCLUSIONS

Prevalence of postoperative delirium is high in patients undergoing open-heart procedures. This is in part due to the inherent vulnerability of these individuals, but also to the severity of the insults caused by such invasive procedures. In terms of delirium prevention in this setting, there seems to be promise in the optimal perioperative use of sedative agents, such as dexmedetomidine. Although the literature seems sparse on non-pharmacologic measures to prevent delirium in this patient population, major societies still recommend their implementation, especially that of early mobilization.

SECTION 8: MANUSCRIPT 2 - A SYSTEMATIC REVIEW OF NON-PHARMACOLOGIC INTERVENTIONS FOR DELIRIUM PREVENTION/TREATMENT IN PATIENTS UNDERGOING CARDIAC SURGERY

8.1 INTRODUCTION

Given the paucity of information regarding the effectiveness of multicomponent non-pharmacologic interventions for delirium prevention in patients undergoing cardiac surgery discussed in Section 7, we sought to determine what non-pharmacologic interventions should be included in a delirium prevention bundle to be tested in this patient population. Prior to trying to answer this question, we designed and conducted the following systematic review in order to identify what, if any, non-pharmacologic interventions had already been studied in the context of cardiac surgery, as well as in patients with similar profiles undergoing other cardiac procedures, such as angioplasties and transcatheter valve replacements.

This article has not yet been submitted to a journal for publication. The protocol for this systematic review may be found in Appendix B.

8.2MANUSCRIPT COVER PAGE

Non-Pharmacologic Interventions for the Prevention or Treatment of Post-Operative Delirium in Older Patients Undergoing Cardiac Surgery and Procedures: A Systematic Review of the Literature

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ABSTRACT

Background: Delirium is an acute confusional state complicating up to half of cardiac procedures performed on older patients and is associated with poor outcomes. Multicomponent non-pharmacologic interventions are considered the current gold standard to prevent this entity in a variety of clinical settings, but the evidence regarding their effectiveness in the context of cardiac procedures is limited.

Objectives: To identify all non-pharmacologic interventions for delirium prevention or treatment studied in older patient populations undergoing cardiac procedures.

Data Sources: MEDLINE, EMBASE Classic + EMBASE, the Cochrane Library, PsychInfo, CINAHL Plus and the Nursing and Allied Health Database.

Methods: Abstract screening, full text screening and data abstraction were run independently and in duplicate by two researchers. Randomized controlled trials and cluster randomized controlled trials enrolling patients with a minimum average age of 50 years and studying non-pharmacologic methods for delirium prevention or treatment compared to usual care were included if delirium incidence or delirium-related outcomes were reported.

Results: Three (3) studies were identified and are discussed in a narrative review, totalizing 382 patients. All pertained to delirium prevention or treatment in patients undergoing cardiac surgery and were set in intensive care units (ICUs). Only preoperative patient education showed a trend towards decreased delirium incidence that did not reach statistical significance. Caregiver education and empowerment and increased sensory feedback using a structured mirrors intervention showed shortened delirium duration and ICU stays that did not reach statistical significance.

Limitations: Most included studies had limited sample sizes and were at high risk of bias. The younger mean age of one of the samples also limits generalization of these results to the contemporary older cardiac surgical population.

Conclusions: Limited evidence of the effectiveness of non-pharmacologic interventions to prevent or treat delirium exists in patients undergoing cardiac surgery. Preoperative education and anxiety management seem particularly promising. More research is needed in this field.

INTRODUCTION

Delirium is an acute disorder of cognition and attention affecting 26-52% of patients after cardiac surgery. [1] Over the years, delirium has drawn increasing attention due to its association with poor outcomes, including increased hospital length of stay, functional decline, institutionalization, permanent cognitive impairment, loss of quality of life and mortality.[2] To date, the evidence is weak for pharmacologic interventions in the prevention or treatment of delirium.[3] On the other hand, many studies, the vast majority of which were described in a previous systematic review and meta-analysis[4], have demonstrated the effectiveness of multicomponent non-pharmacologic interventions on delirium prevention in different populations of medical and surgical inpatients. Available guidelines recommend the implementation of multicomponent non-pharmacologic interventions to prevent and treat delirium in the postoperative setting in general[5]. However, the evidence is scarce for the effectiveness of such interventions in patients undergoing cardiac surgeries or procedures.

If the exact reasons for this knowledge gap have not been formally explored, some have been hypothesized. First, it is well known that patients undergoing open-heart surgeries and other cardiac procedures are at high risk of developing delirium, due to high intrinsic vulnerability to the syndrome conferred by their important burden of cerebrovascular disease and other comorbid diseases[1] causing them to have decreased cognitive and physiological reserves. Second, the severity of the physiological stress imposed during cardiac surgery is so important that it alone could cause delirium in less vulnerable individuals. Given that patient vulnerability and surgical and anesthetic techniques are considered minimally modifiable, many have forfeited on preventing delirium in this patient population. Furthermore, it is believed that a significant portion of cardiac surgical patients become delirious during their procedure, making most attempts at delirium prevention starting in the cardiac intensive care unit seem futile[6]. Finally, as

delirium is often considered a marker of illness severity, it appears uncertain to practitioners in the field whether preventing it alone, rather than attempting to improve overall intensive care unit (ICU) care, would improve patient-centered outcomes. Literature on ICU delirium tends to be more optimistic on these points. Without ignoring patient vulnerability and illness severity as major drivers of the development of delirium in the ICU population, it also acknowledges the presence of many potentially modifiable delirium risk factors, related to patient, illness, treatment and environment, on which it is possible to intervene to prevent delirium[7].

Prior to designing and implementing a novel multicomponent non-pharmacologic delirium prevention intervention for cardiac surgical patients, it would be essential to know which interventions have previously been successful in this patient population. It would also be of relevance to compare the scope of these interventions to those studied on other surgical patients, to see if (and how) they differ. Therefore, the present systematic review was designed to assess the effectiveness of non-pharmacologic interventions for the prevention or treatment of delirium in older patients undergoing non-emergent cardiac surgery or procedures compared to usual care.

METHODS

Full methods were specified in advance and detailed in our protocol, designed in accordance with the PRISMA-P principles[8], available on demand.

Eligibility criteria

We considered randomized control trials (RCTs) and cluster randomized controlled trials pertaining to our subject. We excluded controlled before and after studies as we considered them at high risk of bias but kept them for our discussion. We included studies if they enrolled older (mean sample age 50 years of above) patients undergoing non-emergent cardiac surgeries or procedures, including coronary artery bypass grafting, surgical valve replacement or repair, combinations thereof, transcatheter aortic valve replacement, coronary artery angiography with or without angioplasty. We included studies of both cardiac and non-cardiac surgeries or

procedures as long as the number of cardiac patients was specified so as to be able to extract this specific subset of data. Furthermore, we broadened our search to studies of delirium prevention or treatment in intensive care units, as these often include cardiac surgical patients, in an attempt to render our search as sensitive as possible, conditional to these studies mentioning the number of cardiac surgical patients included, as previously mentioned. We included trials of uni- and multi-faceted non-pharmacologic interventions delivered at any time preoperatively or postoperatively by any member of a multidisciplinary care team (physiotherapist, occupational therapist, nurse, physician, psychologist, etc.) aiming at delirium prevention or treatment with the control group receiving usual pre- or post-operative care. The outcomes of interest were delirium incidence, ascertained by objective validated tools or criteria, delirium severity and delirium duration. In hospital complications, mortality and hospital length of stay were also considered of interest, as was patients' discharge destination. We excluded studies failing to report delirium prevalence prior to the seventh postoperative day as we considered that they unlikely were capturing the true postoperative delirium incidence and studies in non-English or French languages.

Data Sources

We first searched MEDLINE (Ovid interface, 1946-present), EMBASE classic + EMBASE (Ovid interface, 1947-present), the Cochrane Library (1992-present), PsychInfo (Ovid Interface, 1887-present), CINAHL Plus (EBSCOhost, 1985-present) and the Nursing and Allied Health Database (ProQuest interface, 1980s to present) up to April 18, 2017 for literature relevant to delirium in patients undergoing cardiac surgical and interventional procedures. We ran an updated search using the same databases and strategy on May 28, 2018, to ensure more recent work would be included if pertinent. A sample search strategy, designed using available evidence and with initial guidance from a trained librairian is presented in Appendix 1. References of retrieved articles were also searched manually as well as references of pertinent articles uncovered during our search.

Study selection

We removed duplicates prior to abstract screening using EndNote-X8™. Two independent reviewers (CTH, LB) performed abstract screening in parallel using the Rayyan web-based platform[9]. We resolved discrepancies by consensus, with arbitration by a third reviewer (JA) when necessary. Full text screening was performed by the same two reviewers, again with the input of a third reviewer (JA) when necessary. When needed, missing information was asked from study authors (first and last) was requested.

Data Extraction

One reviewer (CTH) performed data abstraction which was then revised by a second reviewer (LB) for accuracy. The study-level variables to be extracted were determined prior to initiating the review and captured: study design and methods, participant characteristics, nature of the intervention, nature of the control group, measured outcomes and timeframe. Missing data was requested from corresponding authors of the concerned studies. Two reviewers (CTH, LB) assessed study quality and risk of bias in duplicate using the "Cochrane Collaboration's tool for assessing risk of bias"[10].

Statistical analysis

We did not plan any specific statistical analysis prior to starting this review as too much heterogeneity in the study interventions and outcomes was expected. Otherwise, appropriate statistical tests for meta-analysis would be applied[11].

RESULTS

Study selection

Search results are summarized in figure 1. The initial database search identified 1099 unique records from which 45 full text articles were selected for full-text review after thorough abstract screening. The updated search allowed to identify 211 additional articles published after

the original search, from which 9 were selected for full-text review. The most frequent reason for exclusion was the absence of enrolment of older patients undergoing cardiac procedures. The second most frequent reason for exclusion was failure to systematically report delirium or delirium-related outcomes. Following full-text screen and manual search of reference lists of retrieved articles, ten studies potentially met our inclusion criteria and were considered for full data abstraction. Missing data were obtained from three out of nine corresponding authors upon request. A total of three studies were finally included, for a total population of 382 patients. Of note, our search also allowed us to identify eight (8) study protocols of interest for our current question, for which results had not yet been published or were not available to be shared with us, possibly showing increased interest for the field of delirium prevention in cardiac surgical patients.

Study characteristics

Included studies (table 1) had variable sample sizes, with Chevillon et al.[12] including 129 patients, Giraud et al.[13] including 223, and Mailhot and al.[14] studying only 30 patients. All were randomized-controlled trials, with Giraud et al. being a time-cluster RCT. All studies included only cardiac surgical patients, with one (Chevillon et al.), focusing of patients undergoing pulmonary artery thrombectomy. All studies were conducted in ICUs in North America, with one study (Mailhot et al) settled in a dedicated Heart Institute. Patients' mean age ranged from 54 years in Chevillon et al., to 77 and 75 years in Giraud et al., and Mailhot et al., respectively.

Chevillon and al. studied the effects of an ICU nurse-led preoperative education program on anxiety and postoperative delirium incidence, compared to a usual, unstructured preoperative information sessiondelivered by multiple members of the multidisciplinary team at preoperative visits. This individualized 45 minute education program designed for patients undergoing surgeries requiring a sternotomy combined visual, tactile, kinesthetic and auditory methods of teaching. Giraud and al. studied the benefits of increased sensory feedback through the addition of structured mirror use in the postoperative period and delirium incidence. In this study, nurses and physiotherapists used mirrors to support self-awareness, to promote multisensory feedback during care and procedures, and to support mobilization during

physiotherapy sessions and personal care routines. Finally, Mailhot et al. studied the benefit, in terms of delirium severity, hospital complications and length of stay as well as in terms of psychosocial recovery, of caregiver education and involvement in care for patients with an established diagnosis of delirium. This intervention consisted in six one-hour encounters between a nurse-mentor and a patient's caregiver over the first three days following delirium diagnosis, as well as a 30 minute pre-discharge encounter, during which the nurse-mentor shared knowledge around delirium, demonstrated appropriate behaviors to adopt with the delirious patient for the caregiver to reproduce and provided feedback on the observed behaviors. All proposed interventions were compared to the accepted standard of care.

In Chevillon et al. and Giraud et al., the Confusion Assessment Method – Intensive Care Unit (CAM-ICU) was used as the screening method for delirium. Mailhot et al. used the Intensive Care Delirium Screening Checklist (ICDSC) to identify patients with delirium for enrollment. Both tools have been validated for delirium screening in the ICU[15]. Mailhot et al. used the also validated Delirium Index, to measure delirium severity in their patients[16]. Both Chevillon et al. and Giraud et al. followed patients until ICU discharge, while Mailhot et al. followed study subjects for the complete duration of their hospital stay. Chevillon et al. reported non-delirium related outcomes, such as quality of life scores, at 12 weeks post discharge.

Risk of bias within studies

Overall, the quality of the included studies was poor to average, as all had multiple potentially important biases reported in table 2. The most frequently observed potential sources of bias related to the chosen method of sequence generation and to suboptimal blinding of the participants or outcome assessors. We must consider the high risk of publication bias for this review. With non-pharmacologic delirium prevention methods being advocated for in multiple guidelines, it is possible that the paucity of trials published reflects the small amount of positive trials studying these methods in the cardiac surgical population, or the preponderance of studies of pharmacologic (as opposed to non-pharmacologic) measures for delirium prevention in this population.

Results of individual studies

Study results are summarized in Table 3. Chevillon et al.[12], in their study of standardized preoperative education reported an almost 10% lower delirium prevalence in the intervention group (22.2% vs 31.8%, *P*=0.24), which did not reach statistical significance. Their intervention also produced a non-significant trend towards shorter delirium duration and ICU length of stay. Preoperative education also improved participants' knowledge of postoperative care (*P*<0.001), without a statistically significant improvement in anxiety scores measured with the State-Trait Anxiety Scale[17], patients in both the intervention and control groups having lower anxiety scores at the second testing point.

Giraud et al., who studied the impact of a structured mirror intervention, failed to demonstrate positive repercussions on delirium incidence in their patients (17% vs 16%, *P* = 0.705). Delirium tended to be shorter in the intervention group versus the control group (1 versus 2 days), although this result did not reach statistical significance. At twelve weeks post discharge, patients who had received the intervention had significantly more factual (as opposed to delusional) memories of their ICU stay compared to controls. Previous studies have linked poor factual recall to post-traumatic stress syndrome, another important outcome in ICU survivors[18]. Furthermore, studies on a more general ICU population found factual memories, as opposed to delusional memories, less likely to occur in delirious patients[19].

Mailhot et al. studied delirium treatment through caregiver education on delirium severity and did not find any significant differences between their intervention and control groups on this metric (*P*=0.27). Furthermore, no differences were observed with regards to the incidence of postoperative complications between the two groups. On the other hand, important between group differences were detected for total hospital length of stay (6.30 vs 12.10 days, *P*=0.34) and patient's psychosocial recovery at 30 days, measured with the Sickness Impact Profile[20] scale (4.80 vs 9.50, *P*=0.01) favoring the intervention group.

DISCUSSION

In this systematic review of the literature we have successfully identified only three randomized controlled trials of non-pharmacologic interventions aiming at delirium prevention or treatment in an older population undergoing non-emergent cardiac surgery. All identified studies were of poor to average quality and measured the effects of single component interventions, rather than the now standard-of care multicomponent interventions studied in other acute medical and surgical settings[21]. The most promising intervention in terms of delirium prevention was a standardized preoperative nurse-led education intervention by Chevillon et al., which decreased delirium incidence by 10% in a population of patients undergoing pulmonary artery thrombectomy. Despite non-statistically significant impacts on most delirium-related outcomes, all included studies, also comprising a structured mirrors intervention (Giraud et al.) and a delirium treatment intervention through caregiver education (Mailhot et al.), were able to demonstrate some benefit on other important outcomes such as ICU and overall lengths of stay and psycho-functional recovery.

Interestingly, all three studies feature interventions with the potential for alleviating anxiety. Chevillon and al. made anxiety reduction an explicit desirable outcome of their educational intervention. Giraud et al., through their structured mirror intervention, aimed to improve “mental status” through increased sensory feedback. Mailhot and al., through caregiver education and involvement, aimed at providing delirium care that was sensitive to the patient’s personality and prior experience, as well as to encourage the reassuring presence of a familiar individual. The focus on measures with the potential of alleviating anxiety related to the post-operative state and the ICU environment is interesting as it is not specifically found in the most studied non-pharmacologic delirium prevention bundles[3].

High levels of anxiety are present in almost 10% of patients who undergo open heart surgery[22]. Studies of patients undergoing cardiac surgery have linked preoperative anxiety with poor postoperative outcomes such as atrial fibrillation, myocardial infarction, increased risk of readmission and increased mortality[22,23]. No study has yet assessed the possible association between preoperative anxiety and postoperative delirium in cardiac surgical patients.

Interestingly, in this patient population, anxiety often seems to be triggered by perceived lack of information[23], which could possibly be alleviated though educational sessions or other non-pharmacological means, to be delivered ideally to patient and caregiver in the immediate pre-operative period.

During our review process, we were able to identify a few interesting controlled before-after studies demonstrating the value of anxiety reduction for delirium prevention in cardiac surgical patients. As mentioned in our methods, these were not included due to their design at higher risk of bias. A first study by Lee et al.[24], looked at the impact of a psycho-educational intervention during which a surgical resident, educated by a psychiatric consultant met with the patient and family members for one hour pre- and post-operatively to discuss the procedure and treatment plans, as well as to address any arising concern. They found their intervention to significantly reduce the incidence of delirium from 35% to 12%. (*P*=0.009) Another controlled before and after trial, by Rosa and al.[25], looked at the effect of extended visitation hours in the ICU on delirium cumulative incidence and found it to be significantly superior (adjusted relative risk 0.50, 95% CI(0.26-0.95)). One of the hypothesized mechanisms to explain the benefits of this intervention is through anxiety reduction. Family and caregivers may also benefit in delirium prevention and treatment through active participation to care-planning, assistance with early diagnosis, cognitive stimulation/reorientation, etc.[26] Family involvement has also been associated to better outcomes for the caregivers of patients with acute illness themselves[27].

Early mobilization is a core component in delirium prevention interventions studied in surgical patients[28]. Through our review process, we were able to identify one controlled before and after study pertaining to our patient population. This trial by Fraser et al. studied the impact of an early mobility intervention, starting in the intensive care unit, on delirium incidence in a mixed patient population, including patients undergoing cardiac surgery[29]. In this study, the number of days without delirium was significantly higher in the experimental group than in the control group receiving usual care. Patients receiving the intervention also had significantly less in-hospital complications, a lower readmission rate as well as a higher functional status at

discharge, pointing to potential for benefit far beyond delirium prevention from such an intervention. Unfortunately, no randomized controlled trial was found studying the same.

Limitations of this review, aside from the low number of included studies, comprise the relatively low mean age of patients, especially in the Chevillon et al. study, as well as the explicit exclusion of patients with prior diagnoses of major neurocognitive disorder in two out of three studies, therefore failing to reflect the current cohort of patients undergoing cardiac surgery. Furthermore, the absence of trials on delirium prevention outside of the ICU setting is problematic since delirium often occurs latently in step-down units and cardiovascular wards, and the absence of trials on delirium prevention in non-coronary non-valvular cardiac surgeries limits the generalizability to other types of cardiac procedures such as transcatheter aortic valve replacement and aortic surgery. General concerns regarding underdiagnosis of delirium also need to be mentioned, as it is well known that delirium recognition in the ICU, especially that of hypoactive delirium, is difficult to achieve. None of the included studies in this review discussed this issue. Finally, the existence of an important publication bias cannot be excluded.

CONCLUSION

Little is still known about the effectiveness of non-pharmacologic interventions for delirium prevention and treatment in patients undergoing cardiac procedures. Through our systematic review, we were only able to identify three low to average quality trials of single-component interventions studied in this patient population. Nevertheless, included studies showed benefits for preoperative patient education, for a structured mirrors intervention and for caregiver education on both delirium-related and non-related outcomes, possibly through anxiety alleviation. There is an urgent need for further high quality randomized controlled trials on the topic, particularly trials of multicomponent delirium prevention and treatment interventions.

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REFERENCES

1. Brown CH. Delirium in the cardiac surgical ICU. Current opinion in anaesthesiology 2014;27:117-22.
2. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Consequences of delirium after cardiac operations. The Annals of thoracic surgery 2012;93:705-11.
3. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. Jama 2017;318:1161-74.
4. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. The Cochrane database of systematic reviews 2016;3:Cd005563.
5. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. Journal of the American College of Surgeons 2015;220:136-48.e1.
6. Weiner MM. Finally Getting the "Attention" It Deserves. Journal of cardiothoracic and vascular anesthesia 2017;31:1974-6.
7. Hsieh SJ, Ely EW, Gong MN. Can intensive care unit delirium be prevented and reduced? Lessons learned and future directions. Annals of the American Thoracic Society 2013;10:648-56.
8. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews 2015;4:1.
9. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
10. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed) 2011;343:d5928.
11. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. (Accessed December 10, 2018, at www.handbook.cochrane.org.)
12. Chevillon C, Hellyar M, Madani C, Kerr K, Kim SC. Preoperative education on postoperative delirium, anxiety, and knowledge in pulmonary thromboendarterectomy patients. American journal of critical care : an official publication, American Association of Critical-Care Nurses 2015;24:164-71.
13. Giraud K, Pontin M, Sharples LD, et al. Use of a Structured Mirrors Intervention Does Not Reduce Delirium Incidence But May Improve Factual Memory Encoding in Cardiac Surgical ICU Patients Aged Over 70 Years: A Pilot Time-Cluster Randomized Controlled Trial. Frontiers in aging neuroscience 2016;8:228.
14. Mailhot T, Cossette S, Cote J, et al. A post cardiac surgery intervention to manage delirium involving families: a randomized pilot study. Nursing in critical care 2017;22:221-8.
15. Gusmao-Flores D, Salluh JI, Chalhub RA, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Critical care (London, England) 2012;16:R115.
16. McCusker J, Cole MG, Dendukuri N, Belzile E. The delirium index, a measure of the severity of delirium: new findings on reliability, validity, and responsiveness. Journal of the American Geriatrics Society 2004;52:1744-9.
17. Spielberger CD GR, Lushene R, Vagg PR, Jacobs GA. Manual of the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.

18. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Critical care medicine 2001;29:573-80.
19. Roberts BL, Rickard CM, Rajbhandari D, Reynolds P. CRITICAL CARE: Factual memories of ICU: recall at two years post-discharge and comparison with delirium status during ICU admission - a multicentre cohort study. Journal of Clinical Nursing 2007;16:1669-77.
20. Chwalow AJ, Lurie A, Bean K, et al. A French version of the Sickness Impact Profile (SIP): stages in the cross cultural validation of a generic quality of life scale. Fundamental & clinical pharmacology 1992;6:319-26.
21. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet (London, England) 2014;383:911-22.
22. Williams JB, Alexander KP, Morin JF, et al. Preoperative anxiety as a predictor of mortality and major morbidity in patients aged >70 years undergoing cardiac surgery. The American journal of cardiology 2013;111:137-42.
23. Joseph HK, Whitcomb J, Taylor W. Effect of Anxiety on Individuals and Caregivers After Coronary Artery Bypass Grafting Surgery: A Review of the Literature. Dimensions of Critical Care Nursing 2015;34:285-8.
24. Lee J, Jung J, Noh JS, Yoo S, Hong YS. Perioperative psycho-educational intervention can reduce postoperative delirium in patients after cardiac surgery: a pilot study. International journal of psychiatry in medicine 2013;45:143-58.
25. Rosa RG, Tonietto TF, da Silva DB, et al. Effectiveness and Safety of an Extended ICU Visitation Model for Delirium Prevention: A Before and After Study. Critical care medicine 2017;45:1660-7.
26. Halloway S. A family approach to delirium: a review of the literature. Aging & mental health 2014;18:129-39.
27. Pochard F, Azoulay E, Chevret S, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. Critical care medicine 2001;29:1893-7.
28. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. Journal of the American Geriatrics Society 2015;63:142-50.
29. Fraser D, Spiva L, Forman W, Hallen C. Original Research: Implementation of an Early Mobility Program in an ICU. The American journal of nursing 2015;115:49-58.

Table 1: Characteristics of included studies

First author, Year	Design	Setting	# partici-pants (% female)	Participant mean age in years (SD)	Intervention	Control	Length of follow-up (d)	Delirium screening tool	Delirium-related outcomes
Chevillon, 2015[12]	RCT	12-bed medical-surgical ICU, California, USA	129 (45)	54 (NA)	Preoperative patient education provided by experienced ICU nurses	Standard preoperative education by multidisciplinary team	7 days or ICU discharge	CAM-ICU	Delirium incidence Delirium duration (days)
Giraud, 2016[13]	Time-cluster RCT	32-bed ICU, USA	223 (24)	77.2(4.9)	Structured mirrors intervention	Standard of care without mirrors	For ICU LOS (mean 2 days)	CAM-ICU	Delirium incidence Delirium duration (days, % of ICU stay)
Mailhot, 2017[14]	RCT	Intensive care unit and surgical unit of a heart institute, CAN	30 (mostly males)	75(N/A)	Nursing intervention involving caregiver education	Usual Care	Hospital stay (mean 6.3 days in intervention group vs 12.1 in control group)	ICDSC and CAM-ICU	Same delirium severity scored in both groups Delirium severity (delirium index)

RCT: Randomized Controlled Trial, ICU: Intensive Care Unit, USA: United States of America, CAN: Canada, LOS: Length of Stay, CAM-ICU: Confusion Assessment Method – Intensive Care Unit, ICDSC: Intensive Care Delirium Screening Checklist, N/A: Not available

Table 2: Risk of bias in included studies using the Modified Cochrane Collaboration tool to assess risk of bias for randomized controlled trials

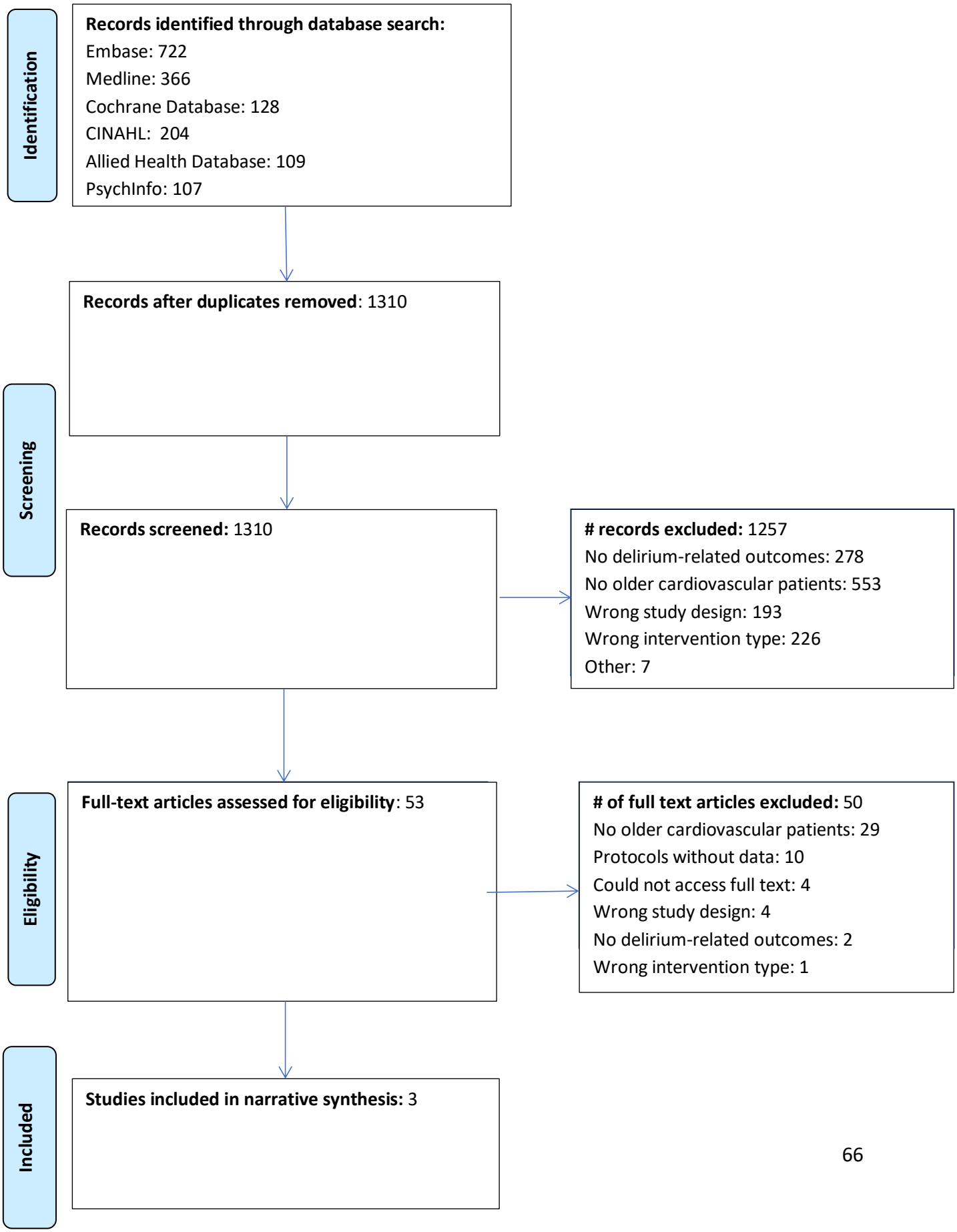
Study first author	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	In complete outcome data	Selective outcome reporting	Other source of bias
Chevillon, 2015[12]	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Giraud, 2016[13]	High	High	High	Low	Unclear	Unclear	Unclear
Mailhot, 2017[14]	High	Low	High	Unclear	Unclear	Low	Unclear

Table 3 : Selected study outcomes

	Delirium prevalence (%)	Delirium duration (days)	ICU length of stay (days)	Other
Chevillon, 2015[12]	22.2 vs 31.8	0.4 vs 0.7	4.2 vs 5.9	Lower state and trait anxiety scores (NS) in intervention group
Giraud, 2016[13]	17.4 vs 15.7	1 vs 2	2 vs 2	Factual memory improved in intervention group*
Mailhot, 2017[14]	100 vs 100	1.94 vs 4.14	6.3 vs 12.1‡	Psycho-functional recovery better in intervention group (SIP 4.80 vs 9.50)*

* statistically significant difference
†days without delirium
‡mean total hospital stay (days)
ICU: Intensive Care Unit
NS: not statistically significant
SIP: Sickness Impact Profile

Figure 1: Search results



APPENDIX 1: SAMPLE SEARCH STRATEGY FOR EMBASE CLASSIC + EMBASE

1. Delirium/
2. (acute adj2 (confusion$ or “brain syndrome” or “brain failure” or “psycho-organic syndrome” or “organic psychosyndrome”)).mp.
3. Deliri$.ti,ab.
4. (terminal$ adj restless$).mp.
5. Toxic confus$.mp.
6. Post-operative cognitive dysfunction.mp.
7. Postoperative cognitive dysfunction.mp.
8. Or/1-7
9. *alcohol psychosis/
10. *delirium tremens/
11. *withdrawal syndrome/
12. 0r/9-11
13. 8 not 12
14. (random$ or placebo$ or single blind$ or double blind$ or triple blind$)ti,ab.
15. RETRACTED ARTICLE/
16. OR/14-15
17. (animal$ not human$).sh,hw.
18. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
19. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. Not exp randomized controlled trial/
20. 16 not (17 or 18 or 19)
21. Exp cardiovascular surgery/
22. Cardiac.mp.
23. Coronary.mp.
24. Surgery.mp.
25. Surgical.mp.
26. Percutaneous aortic.mp..
27. Transcatheter aortic.mp.
28. Coronary artery bypass.mp.
29. Revascularization.mp.
30. Aorto-coronary.mp.
31. Aortocoronary.mp.
32. Valve replacement.mp.
33. Valve repair.mp.
34. Annuloplasty.mp.
35. Percutaneous coronary.mp.
36. Coronary intervention.mp.

37. Angioplasty.mp.
38. Stren*.mp.
39. Or/21-38
40. Exp intensive care unit/
41. Intensive*.mp.
42. Critical*.mp.
43. 0r/40-42
44. Exp postoperative period/
45. Post-operative.mp.
46. Post-surg*.mp.
47. Or/44-46
48. Limit 13 to (adult <18 to 64 years> or aged <65+ years>)
49. 13 and 20 and 48
50. 39 or 43 or 47
51. 49 and 50

METHODS AND RESULTS

MANUSCRIPT 3 - DELIRIUM PREVENTION IN CARDIAC SURGERY: A DELPHI CONSENSUS SURVEY

INTRODUCTION

Completing the systematic review presented in the previous section allowed us to confirm the paucity of available information regarding the effectiveness of single and multicomponent non-pharmacologic interventions for the prevention and/or treatment of delirium in the older cardiac surgical population. It also raised many questions. First, why was the effectiveness of non-pharmacologic interventions so infrequently tested in this clinical setting, where care delivery is otherwise very protocolized? We already gave some possible reasons for this knowledge gap in our previous manuscript. Also, if we were to go on to implement and measure the impact of a multicomponent non-pharmacologic intervention for delirium in this setting, could we simply use care bundles already designed for other surgical populations, or should we consider integrating other types of components to account for the important burden of frailty and comorbidities in this patient population, as discussed in Section 7? Would any intervention of the sort even be feasible in the post-cardiac surgical setting, where resources seem already stretched to provide the best possible care? Could implementing such interventions even be dangerous, given the inherent post-surgical instability of patients?

It is to answer these last three questions that we designed the following Delphi Consensus Survey. We are currently trying to identify journals to submit to for publication.

A few methodological details regarding the following study are worth discussion. To best answer our research questions, we have agreed that we should seek the opinion of experts in all specialties involved in the postoperative care of cardiac patients, to ensure optimal stakeholder involvement and increase the chances of future buy-in of a proposed intervention bundle inspired by our results. We have identified Canadian experts, through publication screening, in all our fields of interest: cardiac surgery, intensive care medicine and nursing, physiotherapy, occupational therapy and geriatric medicine.

We then sought to determine how to best collect and share each experts' opinion in order to reach consensus as to what components should be included into a future delirium prevention intervention in cardiac surgical patients. A formal survey in which we would propose intervention categories to participants seemed too directive to use, especially since we were interested in having participants generate a list of components that they later could comment on. We contemplated the idea of conducting group interviews, during which our experts could exchange their ideas and achieve consensus, but wanted to be cautious not to allow a single or very few stronger individuals to impose their views to the group. Furthermore, given the geographical dispersion of the identified experts, an in-person meeting would have been extremely difficult to organize.

For these reasons, we opted to design a Delphi Consensus Survey. The Delphi method was originally used to obtain consensus from a group of experts by a series of questionnaires separated by controlled feedback[182]. It is of special interest in areas where hard data is unavailable or costly to obtain[183]. In fact, the method was initially used by the military to predict the probability of enemy attack during the Cold War[184]. Since then, the Delphi Method has found applications in economic and financial settings as well as in health care research where it has, for example, assisted in the production of clinical guidelines.

A typical Delphi survey consists of a series of rounds in which participants are asked to rate proposed items, typically using ordinal scales. The first iteration may be used to identify broad issues to be addressed and can contain open-ended questions. After qualitative analysis of the collected answers and generation of categories or themes, a second questionnaire is designed where participants rate or rank the generated items. In final rounds, participants' answers as well as mean group ratings are fed back to contributors who are asked to revise their answers, if desired, until convergence of opinions or consensus are reached[185].

Most of the criticism around the Delphi Method is the absence of a widely accepted definition of consensus. Diamond et al.[184] conducted a systematic review in a random sample of 100 Delphi Studies and found highly variable consensus definitions across studies as well as poor reporting of these definitions in manuscripts. To improve the consistency and quality of Delphi consensus definitions as well as the overall quality of Delphi studies, the same authors have

proposed four quality criteria to guide researchers in their work. These criteria pertain to the reproducibility of the participants' selection criteria, to the clear statement of the number of rounds to be performed, to the disclosure of the criteria used to drop items as well as to the mention of predefined study termination criteria, other than the number of rounds. We have used these criteria in the design of our own study. Our complete protocol may be obtained on demand.

MANUSCRIPT COVER PAGE

Identifying Core Components of a Multifaceted Non-Pharmacologic Intervention for Delirium Prevention in Patients Undergoing Cardiac Surgery: A Delphi Consensus Survey

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ABSTRACT

Background: Despite multicomponent non-pharmacologic interventions being recognized as the gold standard for delirium prevention and treatment in a multitude of care settings, the evidence regarding their effectiveness in older patients undergoing cardiac surgery is lacking. Moreover, there is no guidance regarding the most important components to be included in such interventions.

Objectives: (1) To determine what multidisciplinary experts in the field of cardiac surgery see as important components to include in a delirium prevention and treatment bundle destined to this specific population. (2) To reach expert consensus on suggested components with regards to their importance, feasibility, as well as risk for adverse events. (3) To explore if proposed components differ in any aspect from those usually seen in multicomponent delirium prevention and treatment bundles used in other clinical settings.

Methods: Multidisciplinary experts in the field of cardiac surgery were approached to participate to a Delphi Consensus Survey. In a first iteration, they were asked to provide five components they thought most important to include in a delirium prevention and treatment bundle for this patient population. These propositions were coded into themes by two independent reviewers, then organized into ten categories agreed upon by all authors. In a second iteration, participants were asked to rate the importance, feasibility and potential for adverse events of all ten categories on seven-point Likert scales, as well as to provide feedback on the theme merging process. A third iteration was planned to achieve consensus but was not necessary.

Results: Thirteen (65%) and eleven (55%) out of twenty invited experts participated to the first and second iterations, respectively. Out of the ten generated categories of interventions, three were mentioned by all participants: promotion of early and frequent mobilization, normal sleep/wake cycle promotion and pain and anxiety management. Consensual ratings were obtained on close to all measures of importance and potential for adverse events, with participants rating all categories of intervention as important and safe to implement. Consensus could not be reached on feasibility of the different categories of components, with many participants commenting on the latter being highly dependent of unit and institutional cultures.

Conclusions: Experts identified ten categories of important and safe components to potentially include in a multicomponent non-pharmacologic delirium prevention and treatment intervention specific to older cardiac surgical patients. The mention of anxiety management by our expert panel as an important component to consider in this patient population is of interest as it has not been specifically addressed in delirium prevention bundles studied in other patient populations.

INTRODUCTION

Delirium is a confusional state characterized by the acute onset of inattention, fluctuating alertness, altered level of consciousness, and disorganized thinking[2]. It is an important complication in patients undergoing cardiac surgery, with studies reporting prevalence rates ranging from 26-52%[3]. The occurrence of postoperative delirium is associated with persistent impairments in cognition and function[4], as well as with an increased rate of in-hospital complications, with longer hospital stays, and with important health care costs[5]. Studies evaluating pharmacologic prevention or treatment of delirium have failed to demonstrate clear efficacy of any class of agents[4]. On the other hand, studies evaluating multicomponent non-pharmacologic interventions for delirium prevention have shown these measures to decrease delirium incidence by up to 40%[6]. When used to treat delirium, multicomponent non-pharmacologic interventions have also shown promise in reducing delirium duration, improving cognitive recovery, decreasing hospital length of stay, and decreasing delirium-associated health-care costs[7]. These non-pharmacologic interventions are frequently a combination of components targeting sensory optimization, normal sleep-wake cycle promotion, early mobilization, nutrition and hydration optimization, orientation and cognitive stimulation[8].

Whereas multicomponent non-pharmacologic delirium prevention interventions have proven benefits in general surgical and medical populations[9], they have not been adequately studied in cardiac surgical patients. We previously conducted a systematic review of randomized controlled trials evaluating the impact of non-pharmacologic delirium prevention and treatment measures in cardiac surgery and identified only three pertinent studies of low to average quality,

each relating modest and non-significant benefits of a single-faceted intervention on delirium incidence or treatment [10-12].

Thus, there is an important knowledge gap regarding the efficacy of multicomponent non-pharmacologic interventions for the prevention/treatment of delirium in older patients undergoing cardiac surgery. There is also uncertainty as to what components should be included in such interventions. Older cardiac surgical patients are considered at high risk of developing delirium. This is due to their high intrinsic vulnerability to the syndrome, caused by the high prevalence of comorbid diseases and frailty in this patient population[13,14], but also to the extreme nature of the physiological stressor that is open-heart surgery. Because of their increased vulnerability to the syndrome, patients undergoing cardiac surgical procedures may require more or different intervention components than those trialed and implemented in other clinical contexts.

OBJECTIVES

To inform the development of a multicomponent non-pharmacologic delirium prevention and treatment interventions for cardiac surgical patients, we designed and performed a Delphi Consensus Survey to synthesize experts' opinions on the desirable components of a delirium prevention bundle specific to cardiac surgical patients. We also sought their consensual opinion regarding the proposed components' importance, feasibility, and perceived potential for adverse events. Finally, we sought to compare the components identified by our panel to those included in existing delirium prevention and treatment bundles targeting other patient populations to see if and how they differed.

METHODS

The Delphi Method is well recognized as a valid means to seek consensus among a panel of selected experts using a series of questionnaires[15]. It involves multiple iterations or rounds

during which participants are fed results of previous rounds and asked to rank the earlier generated items on a Likert scale. The process is repeated until a consensus on the importance of the different items is reached. We chose this technique to conduct our study due to its many advantages. First, it allows participants to revise their own judgment over a certain time-period. Also, it provides anonymity to respondents and allows for a controlled feedback process, offsetting the potential drawbacks from a standard group opinion where there is risk for undue influence from a dominant individual and the possibility for participants to feel pressure for group conformity[15]. The issue of confidentiality is also ensured by geographic dispersion of the respondents and by the use of electronic communication to exchange information[16].

We selected individuals with high-levels of knowledge and experience in treating patients undergoing cardiac surgical procedures. All were Canadian. Most were identified through their published work or clinical leadership in the care of cardiac surgical patients while others were referred by identified experts. We used purposive sampling to invite representative participants from each specialty of a multidisciplinary heart team (cardiac surgeons, intensivists, cardiologists, geriatricians, nurses, occupational therapists and physiotherapists). During the first iteration of the survey, we asked participants to self-rate their knowledge and experience in the field on a 100 point Likert scale to confirm their degree of expertise. We sent out a total of 20 invitations for the first iteration. We anticipated a response rate of 50% to suffice to reach data saturation at this phase. We used the same potential participants for the subsequent rounds of the Delphi process. We carried all rounds using an online survey tool (www.surveymonkey.com)[17].

The first iteration of the Delphi Consensus Survey contained a short introduction explaining the aims of the study as well as the results from our previous systematic review on non-pharmacologic delirium prevention and treatment in older cardiac surgical patients. We asked each participant to anonymously list the five most important components they thought ought be included in a multicomponent non-pharmacologic delirium prevention and treatment intervention. We also asked them to specify which member(s) of a multidisciplinary team should be involved in the delivery of each of the proposed components. We compiled all answers in a single document. Two reviewers (CTH and LB) independently reviewed the proposed

components and coded them into themes. They then grouped these themes into ten (10) categories. The final grouping was approved by all investigators.

The second iteration consisted of a short narrative explaining how the final categories were obtained from the participant's previous suggestions. We invited participants were to comment on the results of the categorization process. We then asked participating experts to rate each proposed category in terms of (1) importance for delirium prevention and treatment, (2) feasibility, and (3) potential for adverse events, using seven-point Likert scales for each rating. We invited participants to leave comments to clarify their ratings when necessary. Prior to analyzing results, we decided that categories for which the median rating of importance would be 4 and below would not be carried forward to a third iteration, as consensus on a high importance rating was unlikely to be reached for these items. We also agreed that consensus on a specific item rating would be reached if 80% of participants had attributed it a rating comprised within the interval formed by the median rating, plus or minus one rating point.

A third iteration was planned, in which all items from the second iteration with median ratings of five and above for which consensual rating had not yet been reached, would be re-presented to remaining participants along with their statistical summary and comments from the previous iteration. Participant's individual ratings would be fed back to them and they would be asked whether they wished to change or maintain them, based on the presented statistics representing the group's opinion. As consensus on most items had been reached after iteration number two, we did not distribute this third iteration to participants, as we all agreed it was unlikely to yield any more important information with regards to our objectives.

Our protocol was approved by the McGill Institutional Review Board.

RESULTS

A total of 13 participants out of the 20 invited (65%) answered the first iteration of the survey, allowing for data saturation to be reached. Respondents' self-rated characteristics are presented in table 1. As two participants suggested four instead of five components, we collected a total of 63 component suggestions. Many of these suggestions contained more than one theme

and we coded them to reflect this. We extracted a total of 77 different themes that we organized into 10 categories of proposed components, agreed upon by all authors. These categories are presented in table 2.

Three categories of interventions were evoked by all participants: promotion of early and frequent mobilization, normal sleep-wake cycle promotion, as well as pain and anxiety management. Participants suggested that nurses should be responsible for the coordination and delivery of most proposed interventions, and that caregivers and other members of the multidisciplinary team should be involved within limits of their own expertise. Two participants suggested involvement of volunteers to deliver certain care components.

Nine out of twenty potential respondents answered iteration number two, initially, with a recall email allowing reaching another two respondents, for a participation rate of 55%. Seven participants agreed with the proposed intervention categories with only minor adjustments suggested. One respondent did not agree and suggested that components be regrouped under four broader categories, and one did not comment. One participant questioned whether encouraging normal elimination should not be part of a nutritional intervention, rather than a mobility intervention as we had classified. One participant suggested that another category be added to represent the diagnostic evaluation process of searching for and correcting the underlying cause for delirium.

All second iteration participants participated in rating proposed intervention categories according to their importance, but two participants omitted to rate their feasibility and risk for adverse effects. Median ratings with interquartile ranges, as well as percent agreement on each category are presented in table 3.

Our expert panel considered most of the proposed intervention categories to be important, with median ratings reaching 6 and above, on the provided 7-point Likert scale, for nine out of the ten proposed categories. Cognitive stimulation was the only category with a lower median rating. The four categories with the highest median rating of importance were: pain and anxiety management, medication review and polypharmacy avoidance, healthcare professionals training, and delirium risk/presence screening and treatment planning interventions. Consensus

on rating was reached on six out of the ten proposed category ratings of importance, as per our pre-set consensus definition, and was close to being reached on the four remaining categories, as shown by the relatively low interquartile range on ratings provided for these specific categories.

Median ratings for feasibility of the proposed intervention categories was moderate to high, but individual ratings varied greatly, precluding consensus on all but one category of intervention (medication review and polypharmacy avoidance). Four respondents commented specifically on the difficulty to predict and generalize the feasibility of the proposed intervention categories in different settings, owing to variations across sites with regards to the availability and expertise of personnel, and to the overall culture on units. For this reason, all authors agreed that consensus on feasibility items would not be sought.

Adverse event risk of the proposed intervention categories was rated as low by all expert respondents, with attributed median ratings for all categories of one to two on a seven point Likert scale. Consensus was reached on nine out of ten categories, and almost reached for the category of cognitive stimulation, as shown by a narrow interquartile range.

DISCUSSION

We have successfully conducted a Delphi Consensus Survey, allowing us to generate, from the input of multidisciplinary experts in the field of cardiac surgery, a list of ten categories of non-pharmacologic interventions aiming at delirium prevention in older patients undergoing cardiac surgical procedures. We demonstrated that, according the same group of experts, the proposed intervention categories were all important to include in a non-pharmacologic delirium prevention and treatment bundle in this patient population. The intervention categories were judged to be safe to implement. Nevertheless, important uncertainties regarding the feasibility of different categories of interventions, either on their own or as part of an intervention bundle, were raised, as ease of implementation may greatly vary depending on the resources of post-surgical care units and institutional culture.

To our knowledge, no evidence-based non-pharmacologic care bundle addressing delirium prevention and treatment in older patients undergoing cardiac surgery exists, and only limited evidence regarding single component interventions in the same patient population has been published. Studied interventions have focused on preoperative patient education, caregiver education regarding treatment of delirium, and sensory feedback for patients, most of which are thought to be effective through alleviating anxiety for patients. It is interesting that the panel selected for this study also suggested that interventions targeting pain and anxiety management were important targets for delirium prevention in patients undergoing cardiac surgery. Such interventions are also likely to improve other patient-centered outcomes, as high levels of anxiety in cardiac surgical patients have been associated with increased mortality and morbidity rates[18]. Our panel echoed the importance of active family/caregiver engagement in delirium prevention, as was suggested by a more recent study including mixed medical-surgical intensive care unit patients[19]. Early and frequent mobilization as well as promotion of a normal sleep/wake cycle were also mentioned by almost all experts as important components for delirium management in this patient population. This relates to the particularities of the ICU environment where mobilization can be difficult and where the busy and noisy environment and frequent procedures prevent normal sleep. Finally, particularly relevant to the context of cardiac surgical patients, our panel emphasized the importance of enhanced communication between care teams during care transitions.

Many of the interventions proposed by our panel were similar to those already imbedded in non-pharmacologic delirium prevention and treatment bundles, such as the Hospital Elder Life Program. Initially designed for medical inpatients, it has since been adapted to surgical populations and aims to prevent delirium and functional decline in older patients through interventions targeted at patient-specific risks such as baseline cognitive impairment, sleep deprivation, immobility, visual or hearing impairment, and dehydration.[8] The ABCDEF bundle, more specific to the critical care patient population, aims at optimizing patient recovery and outcomes in the intensive care unit through pain control, minimal sedation, delirium identification, prevention and treatment, as well as through early mobilization and family

engagement and empowerment. The importance of these two care bundles is also reflected in delirium prevention guidelines covering various care delivery settings[7,20-22].

Our work is novel in that it is a first attempt at defining what should be incorporated into a non-pharmacologic delirium prevention and treatment bundle specific to older patients undergoing open-heart procedures, while incorporating views and knowledge from experts with multidisciplinary backgrounds. This study aligns with the work of other experts in the field, who are aiming at developing delirium prevention and treatment strategies for cardiac surgical patients in a large Canadian-wide initiative[5], as well as with intensive care delirium research priorities set by an international network[23]. More work will be needed, in collaboration with experts in the field, patients, caregivers, and other stakeholders to transform this knowledge into acceptable, culturally sensitive, patient-centered care pathways, adaptable to the many different settings where care is provided to post-cardiac surgical patients.

Several limitations of this study are worth discussing. First, although our sample of respondents was diversified in terms of health care professions, it remains modest. We tried to overcome this limitation by ensuring data saturation was reached during our first iteration, but uncertainty as to whether we were able to capture all available experts' opinions remains. Furthermore, while maintaining respondent's anonymity, we were not able to ascertain whether experts from all desired disciplines were equally represented in our panel, in which overwhelming physician representation may have diluted important suggestions by allied health professionals. Another limitation to consider lies within the consensus definition used. As most answers from our panel were situated in the extremes of the Likert scale, attaining consensus using a definition pertaining to data distribution around the median was harder. We had chosen this definition of consensus, as it is one of the most frequently used in Delphi studies[24], but should consider, in future work, using other measures taking into account the difficulties related to extreme rankings[25]. As mentioned by our expert panel itself, another potential limit to our results pertains to their questionable applicability in various types of units with different cultures. Our hope with regards to this is that from the ten proposed intervention categories of importance identified through this process, at least a few will be judged feasible by each individual care unit

to initiate at first, with the possibility of incorporating other categories of intervention depending on individual units' performances. Finally, we realize that important stakeholders, namely patients and caregivers, were not involved in the design and conduct of this study, which may affect the acceptability of our results. We suggest that consultations with patient representatives take place prior to the design of future multicomponent non-pharmacologic interventions targeting delirium prevention and treatment in cardiac surgical patients.

CONCLUSION

Using a Delphi Consensus Survey of multidisciplinary experts in the field of cardiac surgical care, we were able to identify ten different categories of non-pharmacologic interventions aiming at delirium prevention and treatment, pertinent to this patient population. Our panel consensually rated nine out of the ten categories as being of high clinical importance for the problem at stake, and all agreed that their implementation could be done safely. However, the feasibility of implementing certain proposed intervention categories was uncertain, and mostly thought to be dependent on individual unit culture and resources. Suggested categories differ from existing work done on other patient populations, by the importance attributed by our panel to anxiety management, a known negative outcome predictor in our studied patient population. Our work provides guidance for the future elaboration of a delirium care pathways for cardiac surgical patients, which should be designed in concert with cardiac surgical multidisciplinary teams, patients and caregivers.

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Conflicts of interest: none

Authors' contributions: All authors contributed to the production of and approved the final version of this manuscript.

Sponsor's role: none

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:e28-e292.
2. Arora RC, Djaiani G, Rudolph JL. Detection, Prevention, and Management of Delirium in the Critically Ill Cardiac Patient and Patients Who Undergo Cardiac Procedures. Can J Cardiol 2017;33:80-7.
3. Brown CH. Delirium in the cardiac surgical ICU. Current opinion in anaesthesiology 2014;27:117-22.
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet (London, England) 2014;383:911-22.
5. Incidence of delirium after cardiac surgery: protocol for the DELIRIUM-CS Canada cross-sectional cohort study. CMAJ open 2017;5:E565-e9.
6. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. JAMA Intern Med 2015;175:512-20.
7. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. Journal of the American Geriatrics Society 2015;63:142-50.
8. Hshieh TT, Yang T, Gartaganis SL, Yue J, Inouye SK. Hospital Elder Life Program: Systematic Review and Meta-analysis of Effectiveness. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2018;26:1015-33.
9. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. Jama 2017;318:1161-74.
10. Chevillon C, Hellyar M, Madani C, Kerr K, Kim SC. Preoperative education on postoperative delirium, anxiety, and knowledge in pulmonary thromboendarterectomy patients. American journal of critical care : an official publication, American Association of Critical-Care Nurses 2015;24:164-71.
11. Giraud K, Pontin M, Sharples LD, et al. Use of a Structured Mirrors Intervention Does Not Reduce Delirium Incidence But May Improve Factual Memory Encoding in Cardiac Surgical ICU Patients Aged Over 70 Years: A Pilot Time-Cluster Randomized Controlled Trial. Frontiers in aging neuroscience 2016;8:228.
12. Mailhot T, Cossette S, Cote J, et al. A post cardiac surgery intervention to manage delirium involving families: a randomized pilot study. Nursing in critical care 2017;22:221-8.
13. Brown CHt, Max L, LaFlam A, et al. The Association Between Preoperative Frailty and Postoperative Delirium After Cardiac Surgery. Anesthesia and analgesia 2016;123:430-5.
14. Jung P, Pereira MA, Hiebert B, et al. The impact of frailty on postoperative delirium in cardiac surgery patients. The Journal of thoracic and cardiovascular surgery 2015;149:869-75.e1-2.
15. Hsu C-C, A. Sandford B. The Delphi Technique: Making Sense Of Consensus2007.
16. Adams S. Projecting the next decade in safety management: A Delphi technique study. Professional Safety 2001;46:26-9.
17. SurveyMonkey Inc. San Mateo, California, USA2018.
18. Williams JB, Alexander KP, Morin J-F, et al. Preoperative Anxiety as a Predictor of Mortality and Major Morbidity in Patients >70 Years of Age Undergoing Cardiac Surgery. The American journal of cardiology 2013;111:137-42.

19. Rosa RG, Tonietto TF, da Silva DB, et al. Effectiveness and Safety of an Extended ICU Visitation Model for Delirium Prevention: A Before and After Study. Critical care medicine 2017;45:1660-7.
20. Delirium: Prevention, Diagnosis and Management. 2010. (Accessed October 1st, 2018, at https://www.nice.org.uk/guidance/cg103.)
21. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical care medicine 2013;41:263-306.
22. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. Journal of the American College of Surgeons 2015;220:136-48.e1.
23. Pandharipande PP, Ely EW, Arora RC, et al. The intensive care delirium research agenda: a multinational, interprofessional perspective. Intensive care medicine 2017;43:1329-39.
24. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. Journal of clinical epidemiology 2014;67:401-9.
25. Akiyama Y, Nolan J, Darrah M, Abdal Rahem M, Wang L. A method for measuring consensus within groups: An index of disagreement via conditional probability. Information Sciences 2016;345:116-28.

Table 1: Self-rated characteristics of participants – First Iteration

Characteristic	Mean	Median	Range
Personal knowledge of delirium in cardiac surgical patients (%)	86.3	90	62-100
Clinical expertise in prevention and management of delirium in cardiac surgical patients (%)	76.5	80	49-100
Percentage of usual workload dedicated to taking care of or performing research on patients undergoing cardiac surgery	58.2	52	5-99

Table 2: Final intervention categories presented in iteration 2

Category name and description	Frequency of related themes
Promotion of early and frequent mobilization *All measures aiming at promoting mobility, including early extubation, restraints avoidance, and promotion of normal elimination.*	**19**
Normal sleep-wake cycle promotion *Environmental (noise, light) and patient-oriented measures to maintain a normal sleep-wake cycle.*	**22**
Sensory optimization *Optimization of vision and hearing through use of corrective aids, as needed.*	**6**
Cognitive stimulation *Interventions aiming at promoting orientation to time, place and self as well as overall cognitive stimulation through mental activity.*	**14**
Pain and anxiety management *Non-pharmacologic prevention, early screening and monitoring, as well as judicious use of pharmacologic agents for treatment of pain and anxiety.*	**21**
Medication review and polypharmacy avoidance *Interventions encouraging thorough medication assessment and careful use of psychotropic medications.*	**3**
Caregiver/family-centered interventions *Caregiver education and involvement in delirium prevention, detection and treatment*.	**10**
Healthcare professionals training *Education on delirium screening, prevention and treatment, mostly for nurses.*	**4**
Nutrition/hydration *Interventions for systematic nutritional assessments, and promotion of adequate nutritional intake and hydration.*	**6**
Delirium screening and treatment planning interventions *Interventions suggesting systematic preoperative delirium risk assessment, postoperative routine screening, monitoring and management protocols, as well as the use of delirium risk and/or presence communication tools.*	**13**

Table 3: Respondents ratings of importance, feasibility, and risk for adverse events

	Importance		Feasibility		Risk for adverse events	
	Median (IQR)	% agreement*	Median (IQR)	% agreement*	Median (IQR)	% agreement*
Promotion of early mobilization	6(2)	0.82	5.5 (2)	0.5	2(0.5)	0.89
Normal sleep-wake cycle promotion	6(1)	0.91	6[1]	0.75	1(1)	1
Sensory optimization	6(1)	0.82	5[1]	0.57	1.5(1)1	1
Cognitive stimulation	5(2)	0.73	5(3.5)	0.38	1(1)	0.78
Pain and anxiety management	7(2)	0.73	6(2)	0.75	2(2)	1
Medication review and polypharmacy avoidance	7(1)	0.91	6(2)	0.875	2(1)	0.89
Caregiver/family-centered interventions	6(2)	0.73	5(1.5)	0.75	1(1)	1
Healthcare professionals training	(7)1	0.82	5.5(2)	0.5	1(1)	1
Nutrition/Hydration	6(1)	0.91	5.5(1.5)	0.625	2(1.5)	0.89
Delirium risk/presence screening and treatment planning interventions	7(2)	0.73	6(2.5)	0.75	1(1)	1

*Percent agreement representing percentage of respondents with rating comprised in the interval formed by the median plus or minus one ordinal rating point. IQR: Interquartile range

DISCUSSION

INTRODUCTION

In this section we will discuss certain methodological matters pertaining to our modified Delphi Survey, as well as its results. This will allow us to elaborate on future steps to this project.

ON METHODOLOGY AND RESULTS

Our primary objective was to identify important and feasible non-pharmacologic interventions to incorporate into a multicomponent non-pharmacologic delirium prevention and treatment intervention that could eventually be implemented and studied in patients undergoing non-emergent cardiac surgeries. Our secondary objective was to discover whether these interventions should differ from those already incorporated into existing multicomponent interventions for delirium prevention and treatment in other patient populations. To do so, we first conducted a systematic review of the literature, allowing us to conclude on the paucity of quality clinical evidence from randomized controlled trials in this population, as well as to identify perioperative anxiety management as a potentially novel and effective measure to prevent and treat delirium in patients undergoing cardiac surgery.

We then conducted a Delphi Consensus Survey to collect expert opinions on our primary query. Chosen experts were stakeholders of various professional backgrounds who provided views presumably based on available evidence from the medical and surgical literature as well as on their personal knowledge of best practices in cardiac surgery. We thought the Delphi Consensus Survey superior to plain opinion surveys as it allowed participants to revise their opinion during an iterative process with controlled feedback. We also thought it to be better than traditional focus groups, where the predominant input from one individual could have affected our results.

Our respondents were chosen for their expertise, as well as for their respective professional backgrounds, to ensure good representation from all members of a multidisciplinary team. It is known that successful knowledge translation and program implementation should seek early stakeholder engagement[186]. In this regard, however, one may criticize our work in that it did not

include certain groups of professionals, for example patient attendants, pharmacists and nutritionists. We opted to seek their opinion later in the knowledge translation process. Other important stakeholders not included in our work were patients and their caregivers. It will be critical in the near future to seek their opinion on the desirability and acceptability of the different categories of components generated, to ensure that multicomponent interventions to be developed are truly in alignment with patients' values and priorities.

As one of our questions pertained to the possible differences between non-pharmacologic interventions to prevent delirium in cardiac surgery patients from interventions targeting other patient populations, we decided to design our first iteration to allow participants to suggest components they would like to see in a multicomponent delirium prevention intervention, rather than asking them to rate components we would have generated ourselves. We thought it was critical to collect experts' opinions without undue influence from our own knowledge and perceptions. On the other hand, it is possible that, in coding their suggestions, we relayed more than we intended on our own knowledge of delirium prevention and treatment strategies to regroup the suggested themes into intervention categories. In fact, many of our proposed categories are similar to those from landmark study by Inouye et al[122], which served as the premise for the development of the Hospital Elder Life Program (HELP), the most widely disseminated multicomponent intervention for delirium prevention in older patients[126]. The "promotion of early and frequent mobilization", "normal sleep-wake cycle promotion", "sensory optimization", "cognitive stimulation" as well as "nutrition/hydration" categories overlap with the original protocols from this publication. Pain management and medication reviews are also well known delirium prevention strategies present in the National Institute for Health and Care Excellence guidelines[187]. As we have coded the provided suggestions from participants in duplicate and independently and have asked participants' feedback on our work categorizing them, we perceive these similitudes to be due to our experts' knowledge of best practices in the field of delirium prevention, rather than to our own ideas being suggested.

We were positively surprised to see our panel generating new propositions of interventions, notably with regards to anxiety management, caregiver involvement, healthcare

professionals training as well as delirium screening and treatment planning interventions. We had already noted through our systematic review (Section 8) a signal to suggest that perioperative anxiety management was important in delirium prevention in cardiac surgery. Seeing it again suggested by experts in the field further reinforced the importance of studying this component in future clinical trials.

Caregiver education and training in delirium prevention, recognition and treatment is also novel and interesting, especially in the intensive care unit where visitation times are often limited. Accumulating evidence suggests that both patients and caregivers benefit such interventions, through reduced delirium incidence, as well as through reduced caregiver distress and increased caregiver empowerment[188,189]. Liberalizing visit hours has already been found to have a positive influence on delirium incidence in medical ICUs[190] and could potentially have a similar impact in patients undergoing cardiac surgery. Furthermore, caregivers are particularly likely to notice subtle changes in the mental status of their loved ones[191], and the use of caregiver-centered delirium screening tools could also be interesting to incorporate in future interventions.

Finally, in the highly protocolized ICU environment, experts called for routine and standardization of the management of delirium, starting with preoperative delirium risk assessment, either through published scales[192], frailty assessments[102,103], or through a comprehensive geriatric assessment (whose effectiveness in improving patient outcomes in this context remains to be studied). They also advocated for systematic screening for delirium during the patient's hospital stay and for individualized delirium treatment planning using a multidisciplinary team. Our panel also suggested protocolized communication of the information on the risk, presence and treatment plan for delirium between treating teams, as cardiac surgical patients tend to be treated on multiple different units during their stay, as the intensity of care they require decreases. These recommendations fit particularly well in the current, highly protocolized ICU culture, and could potentially be integrated to other care bundles, such as the ABCDEF bundle (**A**ssess, Prevent, and Manage Pain, **B**oth Spontaneous Awakening Trials and Spontaneous Breathing Trials, **C**hoice of analgesia and sedation**, D**elirium: Assess, Prevent, and

Manage, **E**arly mobility and Exercise, and **F**amily engagement and empowerment)[193], already considered by many to be standard of care.

Our Delphi Consensus Survey did not allow us to formulate recommendations regarding the design of a parsimonious bundle. Instead, our participants endorsed almost all proposed categories as important and safe to implement. This lack of ability to differentiate between important and vital components may be due to our choice of a 7-point Likert scale instead of a larger one. It may however also have occurred because participants really believed in the high importance of each of the proposed components, which is also likely in our case. Given this and the impossibility of getting consensus on individual categories' feasibility, we will likely need to discuss further with stakeholders prior to choosing the final components to be included in an intervention to be formally studied on cardiac surgical patients.

The reader will also have noticed that we were not able to reach consensus on the importance of certain proposed components. This may have been due to the consensus definition we have used (a two-sided dispersion value around the median) when we expected participants' answers to be in the extremes of the Likert scale. Our current consensus definition was inspired by a review asking for better consensus definition in Delphi studies[184]. Methods more adapted to measure consensus when skewed distribution of results is expected have been published[194]. These could be used if similar surveys were to be carried on our subject. On the other hand, all authors agreed that redistributing the survey for a third iteration as was initially planned, would only have led to respondent burnout and not necessarily to increased precision of our observations which already pointed to the high importance of all identified categories of components.

ON FUTURE STEPS

With new information generated by our work, we feel better equipped to continue the design of a non-pharmacologic multicomponent intervention for delirium prevention in patients undergoing non-emergent cardiac surgical procedures. Because uncertainty still lies around the feasibility of the proposed components, stakeholder input, including that of patients and caregivers, will be sought prior to identifying a subset of five or six more easily feasible

components to include in a first intervention bundle. This will allow us to be confident in that we are delivering high quality patient-centered care. If possible, we will try to incorporate our intervention to already existing care protocols to increase clinical uptake. This journey will likely involve multiple challenges but given the importance of delirium and its consequences in this patient population, it is likely to be a rewarding one for all involved.

In the meantime, we encourage all involved in cardiac surgical care delivery to consider implementing the delirium prevention components highlighted in our research, as we believe that they represent the highest standard of care we should strive to achieve for our patients.

CONCLUSION

Through this work, we were able to discuss parallels and differences between the aging process and the frailty syndrome. We went over the importance of frailty in predicting outcomes in a variety of settings, including cardiac procedures such as transcatheter aortic valve replacement (TAVR) as well as cardiac surgery. From then, we went on to discuss delirium, as well as its association to frailty in medical, surgical and cardiac surgical patients.

The rest of our work concerned non-pharmacologic delirium prevention in patients undergoing non-emergent cardiac surgical procedures. Through a systematic review of the literature we were able to demonstrate the paucity of available good quality randomized clinical trials of their efficacy in this setting. We were also able to highlight a possible signal regarding the importance of anxiety management with regards to delirium prevention and treatment in this patient population.

Finally, through a modified Delphi Survey, we were able to generate ten categories of components to possibly include in multicomponent non-pharmacologic delirium prevention bundles to be tested in patients undergoing cardiac surgery. Our expert panel rated all proposed components as very important and safe, but no consensus could be reached on any individual component's feasibility. Interestingly, anxiety management was again proposed as an important component to explore as a mean to prevent and treat delirium, specific to this patient population.

More work lies ahead as we continue move towards the design, implementation and study of a patient-centered, acceptable, feasible and effective non-pharmacologic treatment bundle for delirium prevention and treatment in patients undergoing cardiac surgery.

REFERENCES

1. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. Journal of the American Geriatrics Society 2007;55:780-91.
2. Age. Merriam-Webster. (Accessed July 8, 2018, at www.merriam-webster.com/dictionary/age.)
3. Butler RN. Age-ism: another form of bigotry. The Gerontologist 1969;9:243-6.
4. Lowsky DJ, Olshansky SJ, Bhattacharya J, Goldman DP. Heterogeneity in healthy aging. The journals of gerontology Series A, Biological sciences and medical sciences 2014;69:640-9.
5. Cefalu CA. Theories and mechanisms of aging. Clinics in geriatric medicine 2011;27:491-506.
6. Pacala JT SG. Geriatric review syllabus: a core curriculum in geriatric medicine. 7th edition ed. New York2010.
7. Cannon W. The Wisdom of the Body. New York: W.W. Norton & Company; 1932.
8. Cassel C. Geriatric Medicine: An Evidence-Based Approach. 4th ed. New-York: Springer; 2003.
9. Organization WH. Global Health and Aging2011.
10. Projections of mortality and causes of death, 2015 and 2030. 2015. (Accessed July 16, 2018, at http://www.who.int/healthinfo/global_burden_disease/projections/en/.)
11. Canada Year Book: Seniors. 2012. (Accessed July 16, 2018, at https://www150.statcan.gc.ca/n1/pub/11-402-x/2012000/chap/seniors-aines/seniors-aines-eng.htm.)
12. Age and sex, and type of dwelling data: Key results from the 2016 Census. 2016. (Accessed July 16, 2018, at https://www150.statcan.gc.ca/n1/daily-quotidien/170503/dq170503a-eng.htm.)
13. A portrait of the population aged 85 and older in 2016 in Canada. 2017. (Accessed July 16, 2018, at http://www12.statcan.gc.ca/census-recensement/2016/as-sa/98-200-x/2016004/98-200-x2016004-eng.cfm.)
14. Research Highlights on Health and Aging. 2016. (Accessed July 16, 2018, at https://www150.statcan.gc.ca/n1/pub/11-631-x/11-631-x2016001-eng.htm.)
15. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circulation research 1991;68:1560-8.
16. Gerstenblith G, Frederiksen J, Yin FC, Fortuin NJ, Lakatta EG, Weisfeldt ML. Echocardiographic assessment of a normal adult aging population. Circulation 1977;56:273-8.
17. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. Journal of the American College of Cardiology 1997;29:630-4.
18. Aronow WS, Ahn C, Shirani J, Kronzon I. Comparison of frequency of new coronary events in older subjects with and without valvular aortic sclerosis. The American journal of cardiology 1999;83:599-600, a8.
19. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). The American journal of cardiology 1999;83:897-902.
20. Nassimiha D, Aronow WS, Ahn C, Goldman ME. Association of coronary risk factors with progression of valvular aortic stenosis in older persons. The American journal of cardiology 2001;87:1313-4.
21. Jones SA. Ageing to arrhythmias: conundrums of connections in the ageing heart. The Journal of pharmacy and pharmacology 2006;58:1571-6.
22. Virmani R, Avolio AP, Mergner WJ, et al. Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities. The American journal of pathology 1991;139:1119-29.
23. Kass DA, Bronzwaer JG, Paulus WJ. What mechanisms underlie diastolic dysfunction in heart failure? Circulation research 2004;94:1533-42.
24. Karavidas A, Lazaros G, Tsiachris D, Pyrgakis V. Aging and the cardiovascular system. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2010;51:421-7.

25. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. Circulation 2003;107:490-7.
26. Parati G, Di Rienzo M. Determinants of heart rate and heart rate variability. Journal of hypertension 2003;21:477-80.
27. Nussbacher A, Gerstenblith G, O'Connor FC, et al. Hemodynamic effects of unloading the old heart. The American journal of physiology 1999;277:H1863-71.
28. Docherty JR. Cardiovascular responses in ageing: a review. Pharmacological reviews 1990;42:103-25.
29. Vlachopoulos C, Aznaouridis K, Stefanadis C. Clinical appraisal of arterial stiffness: the Argonauts in front of the Golden Fleece. Heart (British Cardiac Society) 2006;92:1544-50.
30. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European heart journal 2006;27:2588-605.
31. What is Cardiovascular Disease? 2017. (Accessed August 6, 2018, at https://www.heart.org/en/health-topics/consumer-healthcare/what-is-cardiovascular-disease.)
32. Global Health Observatory (GHO) data: NCD mortality and morbidity. 2018. (Accessed October 3, 2018, at http://www.who.int/gho/ncd/mortality_morbidity/en/.)
33. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:e28-e292.
34. Swinne CJ, Shapiro EP, Lima SD, Fleg JL. Age-associated changes in left ventricular diastolic performance during isometric exercise in normal subjects. The American journal of cardiology 1992;69:823-6.
35. Andersson C, Vasan RS. Epidemiology of heart failure with preserved ejection fraction. Heart failure clinics 2014;10:377-88.
36. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. the Tromso study. Heart (British Cardiac Society) 2013;99:396-400.
37. Veerasamy M, Ford GA, Neely D, et al. Association of aging, arterial stiffness, and cardiovascular disease: a review. Cardiology in review 2014;22:223-32.
38. Rojas JI, Zurru MC, Romano M, Patrucco L, Cristiano E. Acute ischemic stroke and transient ischemic attack in the very old--risk factor profile and stroke subtype between patients older than 80 years and patients aged less than 80 years. European journal of neurology 2007;14:895-9.
39. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. The Lancet Neurology 2003;2:43-53.
40. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Jama 2001;285:2370-5.
41. Jensen PN, Gronroos NN, Chen LY, et al. Incidence of and Risk Factors for Sick Sinus Syndrome in the General Population. Journal of the American College of Cardiology 2014;64:531-8.
42. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences 2001;56:M146-56.
43. Rockwood K. What would make a definition of frailty successful? Age and ageing 2005;34:432-4.
44. Arora RC, Brown CHt, Sanjanwala RM, McKelvie R. "NEW" Prehabilitation: A 3-Way Approach to Improve Postoperative Survival and Health-Related Quality of Life in Cardiac Surgery Patients. The Canadian journal of cardiology 2018;34:839-49.
45. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC geriatrics 2002;2:1.

46. De Lepeleire J, Iliffe S, Mann E, Degryse JM. Frailty: an emerging concept for general practice. The British journal of general practice : the journal of the Royal College of General Practitioners 2009;59:e177-82.
47. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Archives of internal medicine 2006;166:418-23.
48. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing research reviews 2016;31:1-8.
49. Calvani R, Marini F, Cesari M, et al. Biomarkers for physical frailty and sarcopenia: state of the science and future developments. Journal of cachexia, sarcopenia and muscle 2015;6:278-86.
50. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. Journal of the American Geriatrics Society 2006;54:991-1001.
51. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. Frailty in NHANES: Comparing the frailty index and phenotype. Archives of gerontology and geriatrics 2015;60:464-70.
52. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. TheScientificWorldJournal 2001;1:323-36.
53. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. Journal of the American Geriatrics Society 2012;60:1478-86.
54. Mitnitski A, Fallah N, Rockwood MR, Rockwood K. Transitions in cognitive status in relation to frailty in older adults: a comparison of three frailty measures. The journal of nutrition, health & aging 2011;15:863-7.
55. Malmstrom TK, Miller DK, Morley JE. A comparison of four frailty models. Journal of the American Geriatrics Society 2014;62:721-6.
56. Hubbard RE, O'Mahony MS, Woodhouse KW. Characterising frailty in the clinical setting--a comparison of different approaches. Age and ageing 2009;38:115-9.
57. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. The journals of gerontology Series A, Biological sciences and medical sciences 2007;62:722-7.
58. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age and ageing 2014;43:10-2.
59. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. Journal of the American Geriatrics Society 2012;60:1487-92.
60. Xue QL. The frailty syndrome: definition and natural history. Clinics in geriatric medicine 2011;27:1-15.
61. Poli S, Cella A, Puntoni M, et al. Frailty is associated with socioeconomic and lifestyle factors in community-dwelling older subjects. Aging clinical and experimental research 2017;29:721-8.
62. McNallan SM, Singh M, Chamberlain AM, et al. Frailty and healthcare utilization among patients with heart failure in the community. JACC Heart failure 2013;1:135-41.
63. Park SK, Richardson CR, Holleman RG, Larson JL. Frailty in people with COPD, using the National Health and Nutrition Evaluation Survey dataset (2003-2006). Heart & lung : the journal of critical care 2013;42:163-70.
64. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment--a review of the evidence and causal mechanisms. Ageing research reviews 2013;12:840-51.
65. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. Journal of the American Medical Directors Association 2015;16:940-5.

66. Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. The journals of gerontology Series A, Biological sciences and medical sciences 2006;61:262-6.
67. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. Journal of the American Geriatrics Society 2005;53:1321-30.
68. Pugh JA, Wang CP, Espinoza SE, et al. Influence of frailty-related diagnoses, high-risk prescribing in elderly adults, and primary care use on readmissions in fewer than 30 days for veterans aged 65 and older. Journal of the American Geriatrics Society 2014;62:291-8.
69. Bagshaw SM, Stelfox HT, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2014;186:E95-102.
70. Watt J, Tricco AC, Talbot-Hamon C, et al. Identifying older adults at risk of harm following elective surgery: a systematic review and meta-analysis. BMC medicine 2018;16:2.
71. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation 2010;121:973-8.
72. Afilalo J, Eisenberg MJ, Morin JF, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. Journal of the American College of Cardiology 2010;56:1668-76.
73. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. Journal of the American College of Surgeons 2010;210:901-8.
74. Landi F, Cesari M, Onder G, Lattanzio F, Gravina EM, Bernabei R. Physical activity and mortality in frail, community-living elderly patients. The journals of gerontology Series A, Biological sciences and medical sciences 2004;59:833-7.
75. Abbasi M, Rolfson D, Khera AS, Dabravolskaj J, Dent E, Xia L. Identification and management of frailty in the primary care setting. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2018;190:E1134-e40.
76. Rodriguez-Manas L, Fried LP. Frailty in the clinical scenario. Lancet (London, England) 2015;385:e7-e9.
77. Theou O, Stathokostas L, Roland KP, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. Journal of aging research 2011;2011:569194.
78. Bibas L, Levi M, Bendayan M, Mullie L, Forman DE, Afilalo J. Therapeutic interventions for frail elderly patients: part I. Published randomized trials. Progress in cardiovascular diseases 2014;57:134-43.
79. Saad F, Rohrig G, von Haehling S, Traish A. Testosterone Deficiency and Testosterone Treatment in Older Men. Gerontology 2017;63:144-56.
80. Turner G, Clegg A. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age and ageing 2014;43:744-7.
81. Golia E, Limongelli G, Natale F, et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Current atherosclerosis reports 2014;16:435.
82. Cote N, Mahmut A, Bosse Y, et al. Inflammation is associated with the remodeling of calcific aortic valve disease. Inflammation 2013;36:573-81.
83. Bouras G, Giannopoulos G, Hatzis G, Alexopoulos D, Leventopoulos G, Deftereos S. Inflammation and chronic heart failure: from biomarkers to novel anti-inflammatory therapeutic strategies. Medicinal chemistry (Shariqah (United Arab Emirates)) 2014;10:682-99.
84. Ricci NA, Pessoa GS, Ferriolli E, Dias RC, Perracini MR. Frailty and cardiovascular risk in community-dwelling elderly: a population-based study. Clinical interventions in aging 2014;9:1677-85.

85. Veronese N, Sigeirsdottir K, Eiriksdottir G, et al. Frailty and Risk of Cardiovascular Diseases in Older Persons: The Age, Gene/Environment Susceptibility-Reykjavik Study. Rejuvenation Research 2017;20:517-24.
86. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. The American journal of cardiology 2009;103:1616-21.
87. Khan H, Kalogeropoulos AP, Georgiopoulou VV, et al. Frailty and risk for heart failure in older adults: the health, aging, and body composition study. American heart journal 2013;166:887-94.
88. Bellumkonda L, Tyrrell D, Hummel SL, Goldstein DR. Pathophysiology of heart failure and frailty: a common inflammatory origin? Aging cell 2017;16:444-50.
89. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. Journal of the American College of Cardiology 2014;63:747-62.
90. Goldfarb M, Bendayan M, Rudski LG, et al. Cost of Cardiac Surgery in Frail Compared With Nonfrail Older Adults. The Canadian journal of cardiology 2017;33:1020-6.
91. Wang W, Bagshaw SM, Norris CM, Zibdawi R, Zibdawi M, MacArthur R. Association between older age and outcome after cardiac surgery: a population-based cohort study. Journal of Cardiothoracic Surgery 2014;9:177.
92. Wang C, Tang YF, Zhang JJ, et al. Comparison of four risk scores for in-hospital mortality in patients undergoing heart valve surgery: A multicenter study in a Chinese population. Heart & lung : the journal of critical care 2016;45:423-8.
93. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2012;41:734-44; discussion 44-5.
94. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. The Annals of thoracic surgery 2009;88:S2-22.
95. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. The Annals of thoracic surgery 2009;88:S23-42.
96. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 3--valve plus coronary artery bypass grafting surgery. The Annals of thoracic surgery 2009;88:S43-62.
97. Afilalo J, Kim S, O'Brien S, et al. Gait Speed and Operative Mortality in Older Adults Following Cardiac Surgery. JAMA cardiology 2016;1:314-21.
98. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. Circulation Cardiovascular quality and outcomes 2012;5:222-8.
99. Sundermann S, Dademasch A, Praetorius J, et al. Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2011;39:33-7.
100. Sundermann S, Dademasch A, Rastan A, et al. One-year follow-up of patients undergoing elective cardiac surgery assessed with the Comprehensive Assessment of Frailty test and its simplified form. Interactive cardiovascular and thoracic surgery 2011;13:119-23; discussion 23.
101. Sepehri A, Beggs T, Hassan A, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. The Journal of thoracic and cardiovascular surgery 2014;148:3110-7.
102. Brown CHt, Max L, LaFlam A, et al. The Association Between Preoperative Frailty and Postoperative Delirium After Cardiac Surgery. Anesthesia and analgesia 2016;123:430-5.
103. Jung P, Pereira MA, Hiebert B, et al. The impact of frailty on postoperative delirium in cardiac surgery patients. The Journal of thoracic and cardiovascular surgery 2015;149:869-75.e1-2.
104. Assmann P, Kievit P, van der Wulp K, et al. Frailty is associated with delirium and mortality after transcatheter aortic valve implantation. Open heart 2016;3:e000478.

105. Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. Journal of the American College of Cardiology 2017;69:1313-46.
106. Inouye SK. Delirium in older persons. The New England journal of medicine 2006;354:1157-65.
107. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet (London, England) 2014;383:911-22.
108. Brummel NE, Girard TD. Preventing delirium in the intensive care unit. Critical care clinics 2013;29:51-65.
109. Kales HC, Kamholz BA, Visnic SG, Blow FC. Recorded delirium in a national sample of elderly inpatients: potential implications for recognition. Journal of geriatric psychiatry and neurology 2003;16:32-8.
110. Marcantonio ER. In the clinic. Delirium. Annals of internal medicine 2011;154:ITC6-1, ITC6-2, ITC6-3, ITC6-4, ITC6-5, ITC6-, ITC-7, ITC6-8, ITC6-9, ITC6-10, ITC6-1, ITC6-2, ITC6-3, ITC6-4, ITC6-5; quiz ITC6-6.
111. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. Jama 2010;304:443-51.
112. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ (Clinical research ed) 2015;350:h2538.
113. Akunne A, Murthy L, Young J. Cost-effectiveness of multi-component interventions to prevent delirium in older people admitted to medical wards. Age and ageing 2012;41:285-91.
114. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age and ageing 2009;38:19-26.
115. Marcantonio ER. Delirium in Hospitalized Older Adults. The New England journal of medicine 2017;377:1456-66.
116. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. Jama 1996;275:852-7.
117. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. The Cochrane database of systematic reviews 2016;3:Cd005563.
118. Association AP. Diagnostic ans statistical manual of mental disorders. 5th edition ed. Washington, DC: American Psychiatric association; 2013.
119. International Statistical Classification of Diseases and Related Health Problems (11th Revision). 2018. (Accessed December 14, 2018, at https://icd.who.int/browse11/l-m/en.)
120. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Annals of internal medicine 1990;113:941-8.
121. O'Keeffe ST. Clinical subtypes of delirium in the elderly. Dementia and geriatric cognitive disorders 1999;10:380-5.
122. Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. The New England journal of medicine 1999;340:669-76.
123. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. Jama 2010;304:779-86.
124. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). Jama 2001;286:2703-10.
125. Han JH, Zimmerman EE, Cutler N, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 2009;16:193-200.

126. Hospital Elder Life Program (HELP) for Prevention of Delirium. 2018. (Accessed August 12, 2018, at https://www.hospitalelderlifeprogram.org/.)
127. Hshieh TT, Yang T, Gartaganis SL, Yue J, Inouye SK. Hospital Elder Life Program: Systematic Review and Meta-analysis of Effectiveness. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2018.
128. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. Journal of the American Geriatrics Society 2001;49:516-22.
129. Larsen KA, Kelly SE, Stern TA, et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. Psychosomatics 2010;51:409-18.
130. Excellence NIfHaC. Delirium in adults: Quality standard. UK: National Institute for Health and Clinical Excellence; 2014.
131. Serafim RB, Bozza FA, Soares M, et al. Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review. Journal of Critical Care 2015;30:799-807.
132. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical care medicine 2013;41:263-306.
133. Chesnokova V, Pechnick RN, Wawrowsky K. Chronic peripheral inflammation, hippocampal neurogenesis, and behavior. Brain, behavior, and immunity 2016;58:1-8.
134. Bonnefoy M, Berrut G, Lesourd B, et al. Frailty and nutrition: searching for evidence. The journal of nutrition, health & aging 2015;19:250-7.
135. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. Age and ageing 2014;43:326-33.
136. Quinlan N, Marcantonio ER, Inouye SK, Gill TM, Kamholz B, Rudolph JL. Vulnerability: the crossroads of frailty and delirium. Journal of the American Geriatrics Society 2011;59 Suppl 2:S262-8.
137. Dani M, Owen LH, Jackson TA, Rockwood K, Sampson EL, Davis D. Delirium, frailty and mortality: interactions in a prospective study of hospitalized older people. The journals of gerontology Series A, Biological sciences and medical sciences 2017.
138. Shields L, Henderson V, Caslake R. Comprehensive Geriatric Assessment for Prevention of Delirium After Hip Fracture: A Systematic Review of Randomized Controlled Trials. Journal of the American Geriatrics Society 2017;65:1559-65.
139. Puts MTE, Toubasi S, Andrew MK, et al. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies. Age and ageing 2017;46:383-92.
140. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. Journal of the American Geriatrics Society 2007;55:780-91.
141. Leung JM, Tsai TL, Sands LP. Brief report: preoperative frailty in older surgical patients is associated with early postoperative delirium. Anesthesia and analgesia 2011;112:1199-201.
142. Bagienski M, Kleczynski P, Dziewierz A, et al. Incidence of Postoperative Delirium and Its Impact on Outcomes After Transcatheter Aortic Valve Implantation. The American journal of cardiology 2017;120:1187-92.
143. McRae PJ, Walker PJ, Peel NM, et al. Frailty and Geriatric Syndromes in Vascular Surgical Ward Patients. Annals of vascular surgery 2016;35:9-18.
144. Pol RA, van Leeuwen BL, Visser L, et al. Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: a prospective cohort study. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2011;42:824-30.
145. Verloo H, Goulet C, Morin D, von Gunten A. Association between frailty and delirium in older adult patients discharged from hospital. Clinical interventions in aging 2016;11:55-63.
146. Watt J, Tricco AC, Talbot-Hamon C, et al. Identifying Older Adults at Risk of Delirium Following Elective Surgery: A Systematic Review and Meta-Analysis. Journal of general internal medicine 2018.

147. Hubbard RE, Peel NM, Samanta M, Gray LC, Mitnitski A, Rockwood K. Frailty status at admission to hospital predicts multiple adverse outcomes. Age and ageing 2017;46:801-6.
148. Jarrett PG, Rockwood K, Carver D, Stolee P, Cosway S. Illness presentation in elderly patients. Archives of internal medicine 1995;155:1060-4.
149. Eeles EM, White SV, O'Mahony SM, Bayer AJ, Hubbard RE. The impact of frailty and delirium on mortality in older inpatients. Age and ageing 2012;41:412-6.
150. Joosten E, Demuynck M, Detroyer E, Milisen K. Prevalence of frailty and its ability to predict in hospital delirium, falls, and 6-month mortality in hospitalized older patients. BMC geriatrics 2014;14:1.
151. Ogawa M, Izawa KP, Satomi-Kobayashi S, et al. Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery. PloS one 2017;12:e0190359.
152. Brown CH. Delirium in the cardiac surgical ICU. Current opinion in anaesthesiology 2014;27:117-22.
153. McPherson JA, Wagner CE, Boehm LM, et al. Delirium in the cardiovascular ICU: exploring modifiable risk factors. Critical care medicine 2013;41:405-13.
154. Incidence of delirium after cardiac surgery: protocol for the DELIRIUM-CS Canada cross-sectional cohort study. CMAJ open 2017;5:E565-e9.
155. Hatano Y, Narumoto J, Shibata K, et al. White-matter hyperintensities predict delirium after cardiac surgery. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2013;21:938-45.
156. Abu-Omar Y, Balacumaraswami L, Pigott DW, Matthews PM, Taggart DP. Solid and gaseous cerebral microembolization during off-pump, on-pump, and open cardiac surgery procedures. The Journal of thoracic and cardiovascular surgery 2004;127:1759-65.
157. Sockalingam S, Parekh N, Bogoch, II, et al. Delirium in the postoperative cardiac patient: a review. Journal of cardiac surgery 2005;20:560-7.
158. Tully PJ, Baker RA. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: a contemporary and practical review. Journal of geriatric cardiology : JGC 2012;9:197-208.
159. Williams JB, Alexander KP, Morin JF, et al. Preoperative anxiety as a predictor of mortality and major morbidity in patients aged >70 years undergoing cardiac surgery. The American journal of cardiology 2013;111:137-42.
160. Seligman F, Nemeroff CB. The interface of depression and cardiovascular disease: therapeutic implications. Annals of the New York Academy of Sciences 2015;1345:25-35.
161. Yesavage JA. Geriatric Depression Scale. Psychopharmacology bulletin 1988;24:709-11.
162. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 1975;12:189-98.
163. Farrimond P. Intensive care. Two. Post-cardiotomy delirium. Nursing times 1984;80:39-41.
164. Merwin S AH. Psychologic response to coronary artery bypass. Southern Medical Journal 1977;70:153-5.
165. Arenson BG, MacDonald LA, Grocott HP, Hiebert BM, Arora RC. Effect of intensive care unit environment on in-hospital delirium after cardiac surgery. The Journal of thoracic and cardiovascular surgery 2013;146:172-8.
166. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. The New England journal of medicine 2012;367:30-9.
167. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Consequences of delirium after cardiac operations. The Annals of thoracic surgery 2012;93:705-11.
168. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. Journal of the American Geriatrics Society 2010;58:643-9.
169. Martin BJ, Buth KJ, Arora RC, Baskett RJ. Delirium: a cause for concern beyond the immediate postoperative period. The Annals of thoracic surgery 2012;93:1114-20.

170. Gottesman RF, Grega MA, Bailey MM, et al. Delirium after coronary artery bypass graft surgery and late mortality. Annals of neurology 2010;67:338-44.
171. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesthesia and intensive care 2007;35:714-9.
172. Mariscalco G, Cottini M, Zanobini M, et al. Preoperative statin therapy is not associated with a decrease in the incidence of delirium after cardiac operations. The Annals of thoracic surgery 2012;93:1439-47.
173. Katznelson R, Djaiani GN, Borger MA, et al. Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. Anesthesiology 2009;110:67-73.
174. Dieleman JM, Nierich AP, Rosseel PM, et al. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. Jama 2012;308:1761-7.
175. Gamberini M, Bolliger D, Lurati Buse GA, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. Critical care medicine 2009;37:1762-8.
176. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet (London, England) 2010;376:1829-37.
177. Liu X, Xie G, Zhang K, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: A meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care 2017;38:190-6.
178. Cheng H, Li Z, Young N, et al. The Effect of Dexmedetomidine on Outcomes of Cardiac Surgery in Elderly Patients. Journal of cardiothoracic and vascular anesthesia 2016;30:1502-8.
179. Baron R, Binder A, Biniek R, et al. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) - short version. German medical science : GMS e-journal 2015;13:Doc19.
180. Ettema RG, Van Koeven H, Peelen LM, Kalkman CJ, Schuurmans MJ. Preadmission interventions to prevent postoperative complications in older cardiac surgery patients: a systematic review. International journal of nursing studies 2014;51:251-60.
181. Abraha I, Trotta F, Rimland JM, et al. Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series. PloS one 2015;10:e0123090.
182. Dalkey NC HO. An Experimental Application of the Delphi Method to the Use of Experts. Management Science 1963;9:458-67.
183. Helmer O LH, Turroff M. Delphi Method:Techniques and Application. Massachussets: Addison-Wesley; 1975.
184. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. Journal of clinical epidemiology 2014;67:401-9.
185. Thangaratinam S, Redman CW. The Delphi technique. The Obstetrician & Gynaecologist 2005;7:120-5.
186. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. Implementation science : IS 2012;7:50.
187. Young J, Murthy L, Westby M, Akunne A, O'Mahony R. Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ (Clinical research ed) 2010;341:c3704.
188. Bull MJ, Boaz L, Jerme M. Educating Family Caregivers for Older Adults About Delirium: A Systematic Review. Worldviews on evidence-based nursing 2016;13:232-40.
189. Finucane AM, Lugton J, Kennedy C, Spiller JA. The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. Psycho-oncology 2017;26:291-300.

190. Rosa RG, Tonietto TF, da Silva DB, et al. Effectiveness and Safety of an Extended ICU Visitation Model for Delirium Prevention: A Before and After Study. Critical care medicine 2017;45:1660-7.
191. Rosgen B, Krewulak K, Demiantschuk D, et al. Validation of Caregiver-Centered Delirium Detection Tools: A Systematic Review. Journal of the American Geriatrics Society 2018;66:1218-25.
192. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009;119:229-36.
193. Marra A, Ely EW, Pandharipande PP, Patel MB. The ABCDEF Bundle in Critical Care. Critical care clinics 2017;33:225-43.
194. Birko S, Dove ES, Ozdemir V. Evaluation of Nine Consensus Indices in Delphi Foresight Research and Their Dependency on Delphi Survey Characteristics: A Simulation Study and Debate on Delphi Design and Interpretation. PloS one 2015;10:e0135162.

APPENDIX A: MCGILL IRB APPROVAL CERTFICATE

McGill

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CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board (IRB) is a registered University IRB working under the published guidelines of the Tri-Council Policy Statement, in compliance with the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique (MSSS, 1998), and the Food and Drugs Act (17 June 2001); and acts in accordance with the U.S. Code of Federal Regulations that govern research on human subjects. The IRB working procedures are consistent with internationally accepted principles of Good Clinical Practices.

At a Board meeting on 15 January 2018, the Faculty of Medicine Institutional Review Board, consisting of:

Frances Aboud, PhD	Kelly Davison, MD
Patricia Dobkin, PhD	Frank Elgar, PhD
Carolyn Ells, PhD	Catherine Lecompte
Daniel Saumier, PhD	Blossom Shaffer, MBA

Examined the research project **A01-B06-18A** titled: *Identifying core components of a multifaceted non-pharmacologic intervention for delirium prevention in patients undergoing cardiac surgery: a Delphi consensus survey*

As proposed by: Dr. Jonathan Afilalo (Applicant) to _____ (Granting Agency, if any)

And consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

15 January 2018
Date

Carolyn Ells
Chair, IRB

Dean of Faculty /
Assoc. Dean, Research

Institutional Review Board Assurance Number: FWA 00004545

APPENDIX B: PROTOCOL FOR THE SYSTEMATIC REVIEW OF THE LITERATURE

Non-Pharmacologic Interventions for the Prevention and/or Treatment of Post-Operative Delirium in Older Patients Undergoing Cardiac Surgery and Procedures: A Protocol for a Systematic Review of the Literature

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ABSTRACT

Background: Delirium, a state of acute confusion, is commonly seen in older patients undergoing cardiac surgical procedures and is associated with poorer prognosis. Current recommendations for delirium management favor its prevention through multi-faceted non-pharmacologic interventions. However, to date, the effectiveness of such interventions in older cardiac surgical patients has not been rigorously and extensively studied. Through a systematic review of the literature, we aim to determine the effectiveness of non-pharmacologic interventions for the prevention and/or treatment of delirium in older patients undergoing non-emergent cardiac surgery or procedures compared to usual care.

Methods: We will search MEDLINE, EMBASE Classic+EMBASE, the Cochrane Library, PsychInfo, CINAHL Plus as well as the Nursing and Allied Health Database for randomized controlled trials, cluster randomized controlled trials, controlled clinical trials and cluster trials of single- or multi-faceted non-pharmacologic interventions pertaining to the prevention or treatment of delirium in older patients undergoing non-emergent cardiac surgery or procedures. We will supplement our search by scanning the references of pertinent systematic reviews. Title and abstract screening will be conducted in parallel by two authors. Disagreements on inclusion of studies will be resolved by discussion, with the assistance of a third reviewer if required. Similarly, full text screening will be conducted by the same two reviewers, with the assistance of a third reviewer as needed to achieve consensus. Data extraction will be done sequentially by two authors using a standardized data extraction form. The primary outcome of interest will be delirium incidence, with secondary outcomes of importance including delirium severity and duration, ICU and hospital length of stay, duration of mechanical ventilation, patient functional outcomes, in-hospital falls, long term cognitive function, postoperative complications, in-hospital mortality and costs of hospitalization. Quality appraisal will be done in duplicate by two authors using the Cochrane Collaboration tool for assessing the risk of bias. Due to an anticipated low number of included studies, we plan on performing a narrative review.

Results: This systematic review will allow us to summarize and present the quantity and the quality of the available evidence regarding the use of non-pharmacologic interventions for delirium prevention or treatment in older patients undergoing non-emergent cardiac surgery or procedures. It will also allow us to appreciate the effectiveness of such interventions in this clinical context. Furthermore, it will inform further research and will lay the groundwork for future empirical studies on non-pharmacologic delirium prevention in this vulnerable population. The results may also be of importance to clinicians and allied health professionals caring for these patients, to patients themselves as well as to their caregivers. Finally,

policy-makers and administrators may find the findings of this review of use for future program-development.

Systematic Review registration: none.

INTRODUCTION

Rationale

Delirium is an acute disorder of cognition and attention affecting 26-52% of patients after cardiac surgery. [1] Over the years, delirium has drawn increasing attention due to its association with poor outcomes, including increased hospital length of stay, functional decline and discharge to alternate living situations, permanent cognitive impairment, loss of quality of life and mortality.[2] To date, no strong epidemiologic evidence favors pharmacologic interventions in the prevention and/or treatment of delirium.[3] On the other hand, many studies, the vast majority of which were described in a previous systematic review and meta-analysis[4], have demonstrated the effectiveness of multicomponent non-pharmacologic interventions on delirium prevention in medical inpatients and in some surgical patients. Available guidelines recommend the implementation of multicomponent non-pharmacologic interventions to prevent and treat delirium in the postoperative setting[5]. However, evidence on the effectiveness of such interventions in patients undergoing cardiac surgery or procedures seems scarce.

Multiple factors are hypothesized as potential explanations for the paucity of research in this field. First, the trajectory of patients following open-heart surgery is often complex, with short stays on multiple units under different treating teams such as the intensive care unit, the coronary care unit, the intermediate (step-down) care units and the post-surgical ward, making any intervention even more complex to implement on many levels. Second, with such a high prevalence in the post-cardiac surgery setting, there may be a circulating belief that delirium is almost inevitable in a frail population undergoing invasive procedures, discouraging any efforts to study its prevention. Finally, the majority of delirium prevention studies in this population were looking at the effectiveness of pharmacologic treatments administered both intraoperatively and postoperatively and may have unintentionally derived the researchers' attention away from perhaps more labor-intensive and time-consuming non-pharmacologic interventions.

In the process of designing our own multicomponent non-pharmacologic intervention to prevent delirium in older cardiac surgery patients, we first want to outline which other interventions have already been studied in this patient population. This protocol is written in accordance with the "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)", 2015 statement.[6]

Objectives

The goal of this systematic review is to study the effectiveness of non-pharmacologic interventions, compared to usual postoperative care, for the prevention and/or treatment of delirium in older patients undergoing non-emergent cardiac surgery or procedures (valvular replacement/repair, coronary artery bypass, transcatheter aortic valve replacement (TAVR), angiography/angioplasty).

METHODS

Eligibility Criteria

Studies will be selected according to the following criteria:

Study designs

We will include randomized controlled trials (RCTs) and cluster RCTs pertaining to our subject. We will exclude all controlled before and after studies, observational studies, case studies and case reports due to their higher risk of bias. Controlled before and after studies will however be kept aside for potential inclusion into the results discussion. Pertinent systematic reviews and/or meta-analyses will be identified and used for reference screening.

Participants

We will include studies including older patients, insisting on a mean age of chosen samples to be above 50 years. Additionally, we will look for studies including patients undergoing either non-emergent cardiac surgery or procedures, including coronary artery bypass graft surgeries with and without valve replacement/repair surgery, isolated valve replacement/repair surgeries (open), transcatheter aortic valve replacements or coronary artery angiography with or without angioplasty. We chose to include studies looking at patients undergoing less invasive procedures than open-heart surgeries, to increase the probability of finding data on patients cared for on regular hospital wards and coronary care units, by

opposition to intensive care units. Studies including patients with other characteristics will be included if the exact number of patients undergoing cardiac procedures can be extracted.

Interventions

We will include any non-pharmacologic intervention delivered at any time preoperatively or postoperatively by any member of a multidisciplinary care team (physiotherapist, occupational therapist, nurse, physician, psychologist, etc.) aiming at delirium prevention or treatment. Intraoperative interventions, because of their unique and limited and time nature, will be excluded. Multicomponent and single component interventions will be included. Multicomponent interventions including a pharmacologic intervention will be excluded, unless the effects of each individual component of the bundle on the outcome of interest are reported separately.

Comparators

Studies using any comparator considered to be usual pre- and post-operative care in patients undergoing non-emergent cardiac procedures will be included.

Outcomes

We will include studies with delirium incidence as primary outcome. Studies including outcomes related to delirium treatment such as delirium severity and duration, ICU and hospital length of stay, duration of mechanical ventilation, patient functional outcomes, in-hospital falls, long term cognitive function, postoperative complications, in-hospital mortality and costs of hospitalization will be included as well.

Timing

We will include any article published from 1980 onwards. We will exclude studies without documentation of delirium before the 7^{th} postoperative day, as these have likely failed to capture all incident delirium cases. We will not apply restrictions in terms of length of patient follow-up.

Setting

We will include studies of patients in the intensive care unit, intermediate (step-down) care unit, coronary acute care unit and regular postoperative ward. Studies conducted in multiple settings will be included.

Language

All articles in English and French will be included.

Information Sources

Literature search strategies will be developed using medical subject headings (MeSH) and text words related to delirium and cardiovascular procedures. We will search MEDLINE (Ovid interface, 1946-present), EMBASE classic + EMBASE (Ovid interface, 1947-present), the Cochrane Library and PsychInfo (Ovid Interface, 1887-present). To ensure that all relevant articles coming from allied health literature are included, we will search CINAHL Plus with Full Text (EBSCOhost, 1985-present) and the Nursing and Allied Health Database (ProQuest, 1980s-present). To ensure literature saturation, we will scan the references of included articles as well as that of pertinent reviews identified by our search for potential missed studies of interest.

Search Strategy

The search strategy was developed by CTH with the assistance of JA, and under the guidance of a trained librarian. When available, search terms previously studied and retained for their high sensitivity in each database were used. The developed Medline Search strategy is included in Appendix 1.

Study Records

after duplicate search and removal using EndNote-X8™, identified titles and abstracts will be uploaded to Rayyan a web and mobile application for systematic reviews, designed to facilitate communication and collaboration between reviewers.[7] Because this tool may not be very accurate in its ability to detect duplicates, this task will be done in parallel using EndNote X8 citation manager.

Two reviewers (CTH and LB) will screen each title and abstract independently and induplicate using the preselected inclusion criteria (i.e. duplicate screening). At the end of the screening process, discrepancies will be resolved by discussion between the two reviewers. If consensus on inclusion or exclusion cannot be reached, a third reviewer (JA) will be asked to decide on the classification of the study. Potentially relevant articles identified through screening will have their full text reviewed by the same 2 independent reviewers (CTH and LB) using the same inclusion criteria. Once again discrepancies will be resolved by discussion, with the input of a third reviewer (JA) if necessary, to reach consensus. We will seek additional information from study authors (first and last author for each study) of articles if they do not contain

enough information to decide on their classification. We will record reasons for exclusion for each article. Inter-rater agreement will not be calculated.

Data from eligible studies will be extracted unto a predefined Excel sheet by one reviewer (CTH) and reviewed by a second (LB). Types of abstracted data will include patient demographics, study methods, details of interventions and all relevant outcomes. Discrepancies will be reviewed by discussion. If needed, a third reviewer (JA) will be asked to resolve conflicts. Missing data will be sought from individual study authors. Should we encounter multiple reports of a single study, only the earliest report with the outcomes of interest will be kept. This decision will require consensus from all 3 authors.

Data Items

For each included study, we will extract the study type and setting, inclusion and exclusion criteria, the randomization technique and the blinding technique. We will record the specific number of patients undergoing cardiac surgery or procedures and the total number of patients. Patient demographics such as mean age, sex, ethnicity and major comorbidities will be extracted. Details regarding the surgery will also be extracted when available (time on bypass, clamp time, intubation time). We will record details regarding the intervention as well as the treatment received by the controls. The number of patients included in each group will be extracted. We will also record the timing of the intervention with regards to the surgery/procedure. We will also report the duration of follow-up in each individual study. When available and applicable, measures of dispersion will also be extracted.

Outcomes

Primary Outcome

The primary outcome of interest will be delirium incidence in the intervention versus in the control groups. We will extract the scale used to measure delirium and the frequency of testing. When available, intention to treat analyses results will be reported. If not available, incidence will be calculated based on the number of randomized patients. If reported, we will also extract the time elapsed between surgery and delirium onset. We will also extract the absolute difference in delirium incidence between groups as well as the relative risk of delirium incidence in the treatment group, compared to the control group (with dispersion measures if available). P. values for all outcomes will be extracted if reported.

Secondary Outcomes

a) Delirium severity

The type of scale used, and score will be extracted for each group. Only validated scaled recognized by the Network for Investigation of Delirium: Unifying Scientists (NIDUS) will be considered[8]. Means will be reported with their associated measure of dispersion, when available.

b) Delirium duration

Delirium duration will be reported in days. Means for each group will be reported with measures of dispersion if available.

c) Mortality

In-hospital mortality and 30-day mortality will be reported when available.

d) Length of stay in the intensive care unit

We will report the mean for both groups in days, with measures of dispersion if available.

e) Duration of mechanical ventilation

We will report the mean for both groups in days, with measures of dispersion if available.

f) Hospital length of stay

We will report the mean for both groups in days, with measures of dispersion if available.

g) Surgical Complications

The nature and frequency of complications for each group will be extracted using percentages.

h) In-hospital falls

The frequency of falls will be extracted, along with the frequency of severe or traumatic falls, if available, in falls per patient-days.

i) Functional status at discharge and at follow-up

Measures of functional status and their measuring scales will be extracted if reported using validated scales, for example the Functional Independence Measure[9]. Mean values for each group will be extracted with dispersion measures when available.

j) Discharge destination

The proportion of patients discharged to an alternate living situation from hospital will be recorded. Alternate discharge destinations may be rehabilitation facilities, assisted living facilities or long-term care facilities, as long as the patient did not come to hospital from the same setting.

k) Quality of life

Objective measures of quality of life will be extracted if available as well as the time they were collected. Some more frequently used and validated measures of quality of live include the SF-36[10] and the EQ-5D[11].

l) Cognitive outcomes

Cognitive changes from baseline, if measured with a validated scale such as the Mini Mental State Exam (MMSE)[12], the Montreal Cognitive Assessment (MoCA)[13], the MiniCog[14] and others, will be extracted for each group. Time of testing with regards to the surgery will be recorded.

m) Time administering intervention

The mean required time in minutes per day required to administer the intervention will be reported. Measures of dispersion will be reported if available. Furthermore, the mean time to deliver the control intervention will also be extracted.

n) Unintended harm from intervention

If reported in individual studies, unintended harm from the implementation of the intervention will be recorded as free text.

o) Others

All other pertinent outcomes judged relevant by the authors and not specified above will be extracted and reported as free text.

Risk of bias in individual studies

Risk of bias for each included study will be assessed using the Cochrane Collaboration tool for assessing the risk of bias[15]. This tool considers the risk of bias from the following potential sources: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources. Each potential bias category will be rated as high or low risk of bias by two independent reviewers (CTH and LB). When studies will not provide enough information to decide on the risk of bias for certain categories, the label uncertain will be used and authors will be contacted for precisions. Discrepancies will be resolved by discussion. When necessary, a third reviewer (JA), will assist in reaching consensus on ratings.

Data synthesis

Because of the anticipated diversity in the interventions expected to be found in the studies we are to include, we do not anticipate finding enough homogeneity between studies to allow a meta-analysis and subsequently plan to perform a narrative review, with important information for readers being presented in tables and in text. Study characteristics and patient characteristics will be included in a first table. Study outcomes will be reported in a second table. The last table will report on the quality of each of the included studies. We will keep all studies regardless of their quality, to be able to better describe the advancement

of the literature on our specific subject. The narrative synthesis will be done in accordance with the recommendations from the Centre for Reviews and Dissemination.[16]

Meta-biases

We plan to assess for publication bias using a funnel plot, if feasible. We will assess for selective reporting by looking for published protocols for each of the included studies and screening to see if any pre-specified outcomes were not reported on.

Confidence in cumulative evidence

If possible, the quality of the evidence for all outcomes will be reported using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[17]

DISCUSSION

This systematic review will allow us to summarize and present the quantity and the quality of the available evidence regarding the use of non-pharmacologic interventions for delirium prevention or treatment in older patients undergoing non-emergent cardiac surgery or procedures. It will also allow us to appreciate the effectiveness of such interventions in this clinical context. Furthermore, it will inform further research and will lay the groundwork for future empirical studies on non-pharmacologic delirium prevention in this vulnerable population. In fact, our group plans on building on the results from this study to design a Delphi consensus survey aiming at identifying important non-pharmacologic interventions to include in a multi-faceted non-pharmacologic delirium prevention intervention specific to the older population undergoing cardiac surgical procedures which could eventually be implemented and studied in our institution. The results may also be of importance to clinicians and allied health professionals caring for these patients, to patients themselves as well as to their caregivers, looking for ways to improved outcomes for frail older cardiac patients. Finally, policy-makers and administrators may find the findings of this review of use for future program-development, especially now that delirium is recognized as a quality of hospital care indicator[18].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

DISSEMINATION

This systematic review will be published as part of CTH's Masters' thesis' manuscript. Should we consensually judge the findings worthy of dissemination, we will identify pertinent journals to submit our manuscript to for publication.

FOOTNOTES

Contributors: CTH, LB and JA formulated the idea for the study. CTH wrote the first draft of this protocol and the co-authors (LB and JA) revised it for important intellectual context. CTH will act as a guarantor for the work.

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REFERENCES

1. Brown CH. Delirium in the cardiac surgical ICU. Current opinion in anaesthesiology 2014;27:117-22.
2. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Consequences of delirium after cardiac operations. The Annals of thoracic surgery 2012;93:705-11.
3. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. Jama 2017;318:1161-74.
4. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. The Cochrane database of systematic reviews 2016;3:Cd005563.
5. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. Journal of the American College of Surgeons 2015;220:136-48.e1.
6. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews 2015;4:1.
7. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Systematic reviews 2016;5:210.
8. Delirium Severity Measures Summary Table. 2017. at https://deliriumnetwork.org/delirium-severity-measures-summary-table/.)
9. Keith RA, Granger CV, Hamilton BB, Sherwin FS. The functional independence measure: a new tool for rehabilitation. Advances in clinical rehabilitation 1987;1:6-18.
10. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ (Clinical research ed) 1992;305:160-4.
11. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:1727-36.
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 1975;12:189-98.
13. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005;53:695-9.
14. McCarten JR, Anderson P, Kuskowski MA, McPherson SE, Borson S. Screening for cognitive impairment in an elderly veteran population: acceptability and results using different versions of the Mini-Cog. Journal of the American Geriatrics Society 2011;59:309-13.
15. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed) 2011;343:d5928.
16. Popay J RH, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. a product from the ESRC methods programme. ESRC 2006.
17. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed) 2008;336:924-6.
18. Inouye SK. Delirium: A Barometer for Quality of Hospital Care. Hospital Practice 2001;36:15-8.

APPENDIX 1

Medline Search Strategy

1. Deliri$.ti.ab.
2. (acute adj2 (confusion$ or "brain syndrome" or "brain failure" or "psycho-organic syndrome" or "organic psychosyndrome")).mp.
3. (terminal$ adj restless$).mp.
4. Toxic confus$.mp
5. Delirium/
6. Confusion/
7. Or/1-6
8. *psychoses, alcoholic/ or *alcohol withdrawal delirium/
9. *substance withdrawal syndrome/
10. 8 or 9
11. 7 not 10
12. Post-operative cognitive dysfunction.mp.
13. Postoperative cognitive dysfunction.mp.
14. 11 or 12 or 13
15. Randomized control trial.pt.
16. Controlled clinical trial.pt.
17. Randomized.ab.
18. Placebo.ab.
19. Clinical trials as topic.sh.
20. Randomly.ab.
21. Trial.ti.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. Exp animals/ not humans.sh.
24. 22 not 23
25. Exp Cardiovascular Surgical Procedures/
26. Cardiac.mp.
27. Coronary.mp
28. Surgery.mp
29. Surgical.mp.
30. Percutaneous aortic.mp.
31. Transcatheter aortic.mp.
32. Coronary artery bypass.mp.
33. Revascularization.mp.
34. Aorto-coronary.mp.
35. Aortocoronary.mp.
36. Valve replacement.mp.
37. Valve repair.mp.

38. Annuloplasty.mp.
39. Percutaneous coronary.mp.
40. Coronary intervention.mp.
41. Angioplasty.mp.
42. Stent*.mp.
43. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. Exp Intensive Care Units/
45. Critical*.mp.
46. Intensive*.mp.
47. 44 or 45 or 46
48. Exp Postoperative period/
49. Post-operative.mp.
50. Post-surg*.mp.
51. 48 or 49 or 50
52. Limit 14 to “all adult (19 plus years)”
53. 43 or 47 or 51
54. 14 and 24 and 52 and 53