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A Retrospective Study of Cholinesterase Inhibitors for Alzheimer's Disease: The Effect of Cerebrovascular Disease on Patient Outcomes and the Impact of Biases on the Results

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A Retrospective Study of Cholinesterase Inhibitors for Alzheimer's Disease: The Effect of Cerebrovascular Disease on Patient Outcomes and the Impact of Biases on the Results

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ABSTRACT

Introduction: Dementia may be caused by Alzheimer's disease (AD), cerebrovascular disease (CVD), or a combination of both. When CVD is associated with dementia, survival is thought to be reduced. It is unclear whether treatment with cholinesterase inhibitors (ChEIs), which has been found to improve cognitive symptoms and global function in AD patients, has similar benefits in vascular forms of dementia.

Objectives: The present study was designed to determine whether co-existing CVD is associated with survival or time to nursing home placement (NHP) among AD patients treated with ChEIs. Findings of poorer outcomes in patients with versus without CVD might argue against the use of ChEIs for AD patients in whom CVD co-exists. The objective of a second analysis was to assess for the first time in patients with AD the potential impact of immortal time (and follow-up) bias on risk for these outcomes.

Methods: A retrospective cohort study was undertaken using the Régie de l'Assurance Maladie du Québec (RAMQ) databases to examine the time to NHP or death for AD patients aged 66+, with or without CVD, treated with ChEIs between July 1, 2000, and June 30, 2003. Because ChEIs are approved only for AD in Canada, a ChEI prescription was used as a surrogate for an AD diagnosis. Concomitant CVD was identified on the basis of a lifetime diagnosis of stroke or

endarterectomy, or a diagnosis of transient ischemic attack within the six months prior to the index date. Separate analyses were performed for patients with persistent ChEI use and those who discontinued ChEI therapy. Seven Cox proportional hazard regression models which varied in the definition of the index date (start of follow-up) and the duration of follow-up were used to evaluate the impact of immortal time bias.

Results: 4,428 patients met inclusion criteria for AD with CVD; 13,512 were classified as having AD alone. For the composite endpoint of NHP or death, 1,000-day survival rates were lower among AD patients with versus without CVD ($p<0.01$), but absolute differences were very small (84% vs. 86% with continuous ChEI use; 77% vs. 78% with discontinuous ChEI therapy). Of the secondary endpoints, time to death was shorter for patients with versus without CVD, but time to NHP did not differ between groups. In the primary, unbiased analysis, no association was found between ChEI treatment type and death or NHP. However, after introduction of immortal time bias, a strong differential effect was observed.

Limitations: Results may have been affected by selection (misclassification) bias, between-group differences in smoking and body mass index (information on which was not available in the RAMQ databases), and duration of ChEI therapy.

Conclusions: Associations between co-existing CVD and time to NHP or death appeared to be of little clinical relevance among AD patients treated with ChEIs.

The lack of difference between AD patients with and without CVD suggests that CVD should not be used as a reason to deny AD patients access to ChEI treatment. Properly accounting for unexposed person-time in the analysis eliminates biased estimates of drug efficacy.

Keywords: cholinesterase inhibitors; dementia; Alzheimer's disease; cerebrovascular disease; administrative database

RÉSUMÉ

Introduction: La démence peut être causée par la maladie d'Alzheimer (MA), la maladie cérébrovasculaire (MCEREV), ou une combinaison des deux. Lorsque la maladie cérébrovasculaire est associée à la démence, les chances de survie sont considérées réduites. Il reste à démontrer si le traitement avec des inhibiteurs de la cholinestérase (ChEIs), qui améliore les symptômes cognitifs et la fonction globale chez les patients atteints de la MA, agit aussi sur les formes vasculaires de démence.

Objectifs: La présente étude a été conçue pour déterminer si la coexistence d'une MCEREV était associée avec les chances de survie ou la durée de la période jusqu'au placement en hebergement chez les patients atteints de la MA et traités avec des ChEIs. Des études montrant de moins bons résultats chez les patients souffrant de MCEREV que chez ceux n'en souffrant pas pourrait militer contre l'utilisation des ChEIs chez les patients atteints à la fois de la MA et la MCEREV. L'objectif d'une seconde analyse était d'évaluer pour la première fois chez les patients atteints de la MA l'impact potentiel du biais de « temps-immortel » (et de suivi) sur ces résultats (mort ou placement en hebergement).

Méthodes: Une étude de cohorte rétrospective a été conduite en utilisant les bases de données de la Régie de l'Assurance Maladie du Québec (RAMQ) pour examiner la durée de la période jusqu'au placement en hebergement ou jusqu'au

décès des patients atteints de la MA, âgés de 66 ans et plus, avec ou sans MCEREV, et traités avec des ChEIs entre le 1er Juillet 2000 et le 30 Juin 2003. Puisque les ChEIs sont uniquement indiquées pour la MA au Canada, chaque prescription de ChEIs a été considérée comme un diagnostic de la MA. La MCEREV concomitante a été identifié sur la base d'un diagnostic à vie d'un accident vasculaire cérébral (AVC) ou d'une endartériectomie, ou d'un diagnostic d'un accident ischémique transitoire au cours des six mois précédant la date d'entrée. Des analyses séparées ont été conduites pour les patients utilisant les ChEIs de façon persistante et pour ceux ayant interrompu la thérapie. Sept modèles de régression à risque proportionnel de Cox qui ont varié par rapport à la définition de la date d'entrée (début du suivi) et à la durée du suivi ont été utilisés pour évaluer l'impact du biais de temps-immortel.

Résultats: 4,428 patients ont répondu aux critères d'inclusion pour la MA avec MCEREV; le groupe de patients souffrant seulement de la MA comptait 13,512 individus. Pour le critère d'évaluation composite considérant la durée de la période jusqu'au placement en hebergement ou jusqu'au décès, les taux de survie à 1,000 jours étaient plus faibles parmi les patients atteints de la MA avec MCEREV que parmi ceux atteints seulement de la MA ($p<0.01$), mais les différences absolues étaient très faibles (84% vs. 86% pour l'utilisation continue de ChEIs ; 77% vs. 78% pour la thérapie avec ChEIs interrompue). Pour les critères d'évaluation secondaires, la période jusqu'au décès était plus courte chez les patients avec la MCEREV que sans la MCEREV, mais la période jusqu'au

placement en hebergement n'était pas différente entre les deux groupes. Dans l'analyse primaire (non-biaisée), aucune association a été trouvée entre le type de ChEI et la mort ou le placement en maison d'hébergement. Cependant, après l'introduction du biais de temps-immortel, on a observé un fort effet différentiel.

Limitations: Les résultats peuvent avoir été affectés par le biais de sélection (classification impropre), par les différences entre les groupes en termes de consommation de tabac et d'indice de masse corporelle (ces informations n'étaient pas disponibles dans les bases de données de la RAMQ) et de durée de la thérapie avec les ChEIs.

Conclusions: Les associations entre la coexistence d'une MCEREV et la durée de la période jusqu'au placement en hebergement ou au décès apparaissent peu pertinentes cliniquement parmi les patients atteints de la MA traités avec des ChEIs. L'absence de différence entre les patients atteints de la MA souffrant ou non de la MCEREV suggère que la coexistence d'une MCEREV ne devrait pas être une raison de refuser aux patients atteints de la MA l'accès au traitement avec des ChEIs. Le calcul des « personne-temps » non exposés dans l'analyse élimine les estimations biaisées de l'efficacité des médicaments.

Mots-clés : inhibiteurs de la cholinestérase ; démence ; maladie d'Alzheimer ; banque de données administrative

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DISCLAIMER

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND ACRONYMS

3MS	Modified Mental Status Examination
Aβ	Beta-amyloid
ACCORD	Canadian Collaborative Cohort of Related Dementias
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADDTC	State of California Alzheimer's Disease Diagnostic and Treatment Centers
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADFACS	Alzheimer's Disease Functional Assessment and Change Scale
ADLs	Activities of daily living
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
BuChE	Butyrylcholinesterase
CAA	Cerebral amyloid angiopathy
CCCD	Canadian Consensus Conference on Dementia
CDR-SB	Clinical Dementia Rating-Sum of the Boxes
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
ChEIs	Cholinesterase inhibitors

CSHA	Canadian Study of Health and Aging
CIBIC-Plus	Clinician's Interview-Based Impression of Change-Plus caregiver input
CIND	Cognitive impairment, no dementia
CIVIC	Consortium to Investigate Vascular Impairment of Cognition
CSF	Cerebrospinal fluid
CSN	Canadian Stroke Network
CT	Computerized tomography
CVD	Cerebrovascular disease
DAD	Disability Assessment for Dementia
DSM-IV	Diagnostic and Statistics Manual – Fourth Edition
HIS	Hachinski Ischemic Scale
IALDs	Instrumental activities of daily living
ICD-10	International Statistical Classification of Diseases, 10th Revision
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN	National Institute of Neurological Disorders and Stroke, and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NFTs	Neurofibrillary tangles
NHP	Nursing home placement
NPI	Neuropsychiatric Inventory
NMDA	N-methyl-d-aspartate
NSAIDs	Non-steroidal anti-inflammatory drugs
PET	Positron emission tomography
RAMQ	Régie de l'assurance maladie du Québec
SALAs	Selective Aβ-lowering agents
VaD	Vascular dementia
VCI	Vascular cognitive impairment

1.0 INTRODUCTION

Dementia is a common, but complicated illness of aging that may currently affect over 24.3 million individuals worldwide [1], including more than 450,000 Canadian residents [2,3]. As the elderly population grows over the next several decades, the global prevalence of dementia is projected to increase by 4.6 million new cases each year, such that 81.1 million patients may be diagnosed with dementia by 2040 [1]. The anticipated surge in dementia cases is of particular concern, given that there is presently no cure for the illness and that the underlying causes of dementia are only beginning to be understood. Clearly, a more sophisticated understanding of dementia will be essential, given the increasing public health burden of this devastating disease.

Although often construed by the public as a single disease entity, dementia is actually an umbrella term, used to describe a heterogeneous group of diseases associated with cognitive changes and functional impairment. Of the various dementia subtypes, the most commonly recognized is Alzheimer's disease (AD), followed by vascular dementia (VaD). Historically, these subtypes have been construed as distinct entities, with AD attributed to the formation of plaques and tangles in the brain, and VaD related to various forms of cerebrovascular disease (CVD). However, researchers are now recognizing that AD and VaD frequently co-exist, and that "pure" forms of dementia (particularly VaD) may be relatively

rare. Such discoveries have led to a paradigm shift, which places more emphasis on mixed dementia [4].

While some researchers are appreciating the overlap between the dementia disorders, others are focusing on the etiological heterogeneity within each dementia subtype [4]. VaD, in particular, is being increasingly construed as a multi-factorial disease, arising not only from stroke, but also from subcortical vascular changes. Importantly, the different causes of VaD seem to be associated with different clinical phenotypes, suggesting: (1) that specific criteria could be developed to identify VaD subtypes, and (2) that specific therapies could be developed for the various subpopulations of dementia patients [4].

In Canada, the cholinesterase inhibitors (ChEIs) are the main class of medications approved by the health authorities (Santé Canada) to treat dementia associated with AD [5]. These medications—donepezil (Aricept), galantamine (Reminyl) and rivastigmine (Exelon)—which until recently have been approved only for mild-to-moderate AD, have not been shown to have disease-modifying effects, but may nevertheless exert cognitive benefits that prolong survival and delay admission to nursing home care [6].

Currently, no medications are approved in Canada for therapy of VaD. Given that AD and VaD share pathological mechanisms, it has been speculated that drugs with efficacy in AD may be beneficial for VaD as well [7]. Researchers have been

testing this hypothesis, with encouraging results, for a number of years. However, a recent meta-analysis of randomized, controlled trials of ChEIs in VaD concluded that while evidence suggests these agents produce small benefits in cognition in patients with mild-to-moderate VaD, insufficient data exist to support widespread use of ChEIs in this patient population [8].

Definitive demonstration of the efficacy of ChEIs for treating dementia symptoms requires randomized, placebo-controlled clinical trials that include appropriate measures of cognition, functional ability, and global change [9]. A more comprehensive assessment of clinical benefit would also include measures of behavioural alteration and caregiver burden [10]. Unfortunately, instruments developed to assess these endpoints in AD trials may not be optimal for VaD clinical trials because of the subtle but distinct differences in the disease course, cognitive and functional deficits, and pattern of caregiver burden seen in patients with AD compared to those with VaD [10]. Previous VaD clinical trials of ChEIs may have had limited ability to detect treatment effects since they used instruments developed for use in AD trials that may not have been sufficiently sensitive to the clinical changes associated with VaD [8]. The 6-month follow-up period of these trials may also have been too short to assess overall benefit.

Pending long-term, randomized, placebo-controlled trials of ChEIs in VaD and mixed dementia using disease-specific instruments, retrospective epidemiological analyses of administrative databases may provide valuable insight into the

effectiveness of dementia treatments and which populations may benefit most from them. Although such databases do not contain detailed clinical assessments of cognition, functional ability, and global change, they provide information on drug claims and medical services that can be used to construct other clinically relevant endpoints, such as time to survival and nursing home placement (NHP).

Accordingly, the first of the two original studies contained in this thesis (see Chapter 5) is a retrospective cohort study undertaken using data from two of the Régie de l'Assurance Maladie du Québec (RAMQ) administrative databases: the prescription claims database and the medical services database in the Province of Québec, Canada. The main objective of this study was to determine whether co-existing CVD is associated with survival or time to NHP among AD patients treated with ChEIs. A secondary objective was to identify predictors of death or NHP during and after ChEI treatment in AD patients with and without CVD.

Despite their potential, the retrospective nature of epidemiological analyses of administrative databases subjects them to a variety of limitations potentially leading to bias, which need to be carefully considered in study design and interpretation of results. Bias in epidemiologic research is any systematic error that distorts an estimate of the relationship between exposure and outcome. Biases are generally categorized into three types. Selection bias refers to errors that occur in identifying the study population. Information bias, also known as observation bias, consists of error in ascertaining data on exposure or outcome. Immortal time

bias is a form of information bias in which a time-dependent exposure is treated as a time-invariant factor, and is of particular concern in retrospective cohort analyses. Confounding occurs when the relationship between exposure and outcome is affected by another factor [11].

Minimization of bias is imperative for the design and interpretation of epidemiologic studies, given that its presence raises doubts about the quality and credibility of results. Key contributors to bias include the type of study design, which may be susceptible to particular forms of bias, and the conduct of investigators during study implementation. Whereas the effects of confounding may be controlled at the time study data are analyzed, it is critical to prevent selection bias and information bias at the design stage in order to avoid compromising study validity [12]. Although quantitative analysis of the magnitude of potential bias is not always possible, the likely effect of the error on study findings can often be deduced either at the design or at the analysis phase of the study [11].

Issues related to bias are addressed in the second of the two original studies contained in this thesis, reported in Chapter 6. This study is a methodological analysis of the RAMQ databases, conducted to demonstrate the importance of carefully considering study biases in retrospective cohort analyses. The primary objective of this study was to evaluate the impact of immortal time bias on the estimated risk of death or NHP among AD patients who took rivastigmine or

galantamine compared to those who were prescribed donepezil. A secondary objective was to examine whether immortal time bias would lead to erroneous conclusions about the effectiveness of treatment with the three ChEIs.

Chapters 1 and 2 provide a broad overview of AD and vascular cognitive impairment, and the issue of bias in epidemiological research, respectively. Neither of these is intended to be a systematic or comprehensive literature review. Instead, the purpose of Chapter 2 is to introduce the disease states and therapeutic agents examined in both original studies (Chapters 5 and 6), while Chapter 3 explains the issues related to bias in retrospective cohort analyses that are explored in the methodological analysis (Chapter 5). Chapter 4 provides the context for the objectives and hypotheses of the two original studies.

2.0 ALZHEIMER'S DISEASE AND VASCULAR COGNITIVE IMPAIRMENT: A REVIEW OF THE LITERATURE

2.1 HISTORY

Although the concept of dementia is centuries old, the history of AD can be directly traced to November 1901, when a German physician named Alois Alzheimer first described the case of Auguste D. to a group of his colleagues. Auguste D., according to reports, was a 51-year-old woman who exhibited a strange constellation of symptoms, including rapid memory loss, disorientation, aphasia, delusions, and disordered behavior. Because the patient's symptoms were inconsistent with any known diagnosis, Alzheimer set out to determine their cause, eventually performing an autopsy after her death. The results of Alzheimer's neuropathological studies suggested that Auguste's illness was related to diffuse shrinkage of the brain, as well as widespread cell death and two types of microscopic deposits (beta-amyloid plaques and neurofibrillary tangles) that had not previously been seen. The disorder was soon recognized as a distinct disease entity, and given the name "Alzheimer's disease" by Emil Kraeplin in the 1910 edition of his textbook on mental disorders [13].

Like AD, the concept of VaD also dates back approximately 100 years, when the neuropsychiatric community began to recognize that mental changes could occur when the blood supply to the brain was reduced. Over time, researchers such

Alzheimer, Otto Binswanger, and Pierre Marie determined that these cognitive changes could be caused either directly through arterial narrowing or indirectly via reactive inflammation in the brain. Formal subclasses of VaD were not recognized, however, until Binswanger provided a description of eight patients with subcortical arteriosclerotic encephalopathy, a phenomenon that would later be termed "Binswanger's disease." The term "multi-infarct dementia" was coined in 1970, when researchers found that dementia could be triggered by loss of brain tissue after stroke. Experts later identified a number of other VaD etiologies, including sustained hypoperfusion, incomplete white matter infarction, and single strategic infarcts [4,14].

Research into the causes and consequences of VaD has been increasing since 1991, when the International Workshop on Vascular Dementia convened to developed standardized diagnostic criteria [14]. Recent advances include the application of newer imaging modalities (e.g., diffusion-weighted imaging) in VaD research, and the discovery of pathophysiological interactions between cerebrovascular disease (CVD) and AD [15,16]. Interestingly, it has been speculated that the symptoms exhibited by Alzheimer's original patient, August D., were caused not by typical AD neurodegeneration, but rather by cerebrovascular causes [13].

The relevance of dementia as a public health concern is increasing at a rapid pace, fueling a growing number of studies aimed at developing treatments to alleviate the effects of this debilitating disorder. Since the early 1990s, Canadian

population-based studies such as the Canadian Study of Health and Aging (CSHA), the Canadian Collaborative Cohort of Related Dementias (ACCORD), and the Consortium to Investigate Vascular Impairment of Cognition (CIVIC) have contributed greatly to knowledge about the epidemiology and burden of dementing diseases. In addition, Canada has taken a leading role in developing clear consensus guidelines for the management, assessment, and treatment of dementia. The Canadian Consensus Conference on Dementia (CCCD), held in 1998, represented a major effort toward using solid evidence to inform research methodology and clinical practice [17,18].

2.2 DEFINITIONS

2.2.1 Dementia

The term dementia refers to a progressive loss of cognitive abilities that negatively impacts daily functioning. Most definitions of dementia specify that the condition must be associated with deficits in at least two of four essential cognitive domains, which include memory, language, executive performance (e.g., planning or organizing), and visual processing. In addition, dementia is defined by a marked interference in the ability to perform daily tasks, such as dressing, grooming, and preparing meals. These elements emphasize the breadth and magnitude of dementia's impact on everyday life [14,19-21].

As stated, dementia is not a unitary construct, but rather an umbrella term used to describe numerous manifestations of cognitive decline. Historically, the various types of dementia have been distinguished using a categorical approach, with the presence of certain symptoms and brain abnormalities viewed as surrogates for discrete pathological changes. As research into dementia has advanced, however, it has become increasingly apparent that the symptoms and pathologies of different dementias frequently overlap, rendering distinctions between subtypes somewhat artificial. According to the emerging paradigm, dementia lies on a continuum from "pure" AD to "pure" VaD, with the majority of cases lying somewhere in between [4]. Other, less common types of dementia include dementia with Lewy bodies, frontotemporal dementia, dementia from Parkinson's disease, and normal pressure hydrocephalus.

2.2.2 Alzheimer's Disease

Alzheimer's disease (AD) is a diagnostic label given to patients whose cognitive decline is attributed to the formation of beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) within the brain [21]. AD is the leading cause of dementia, with estimates of the proportion of dementia cases accounted for by AD ranging from 50% in a postmortem series [22] to 75% in the CSHA [23]. The "classic" symptom presentation includes an initial loss of recent memory, followed by a gradual decline in language, organization, judgment, and other cognitive domains [24]. The two primary subcategories of AD are the early-onset familial type, which

is rare and manifests at ages 40-65 years, and late-onset sporadic AD, which is far more common and develops spontaneously at age 65 years or older [25]. Early-onset familial AD has been associated with mutations in at least three genes: presenilin 1, presenilin 2, and amyloid precursor protein [26-28]. The type 4 allele of another gene, apolipoprotein E, has been identified as a risk factor for late-onset AD [29]. Research is ongoing to test other candidate genes for a role in AD [30].

2.2.3 Vascular Dementia

The concept of vascular dementia (VaD) refers to a clinical syndrome of cognitive and functional impairment that occurs when blood flow is reduced to parts of the brain, often as a result of cerebrovascular disease (CVD). Like dementia, VaD is also used as an umbrella term, used to describe a range of clinical presentations that vary according to the type, location, and severity of cerebrovascular injury. Frequently recognized subcategories of VaD include multi-infarct dementia, strategic infarct dementia, and small vessel disease with dementia [4,15].

Perhaps as a result of its heterogeneous nature, definitions of VaD are often frustratingly imprecise. For example, the terms multi-infarct dementia, post-stroke dementia, and atherosclerotic dementia are often used interchangeably with VaD, despite their failure to recognize small vessel disease and other vascular etiologies. In addition, VaD is sometimes referred to as VCI in the clinical literature, even though the general consensus is that VaD represents but one

subset of the larger VCI construct. Such imprecision in terminology is confusing, and may have hampered effective research in VaD populations [15].

2.2.4 Mixed Dementia

The term mixed dementia is usually used to describe a pattern of cognitive dysfunction that is characterized by both AD and VaD abnormalities, but may also refer to other combinations of dementia subtypes (e.g., AD plus vascular encephalopathy) [31]. Due to a lack of diagnostic criteria, mixed dementia is often difficult to diagnose, and thus may not be recognized until autopsy. Many epidemiological studies group cases of mixed dementia together with VaD, or use the category of VCI to include both VaD and mixed dementia cases [32]. Other experts dispense with the term mixed dementia entirely, advocating instead for the label "AD with CVD" to designate patients with possible AD accompanied by evidence of a vascular injury [14].

2.2.5 Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a term that has been coined to describe cognitive changes that do not meet criteria for dementia. It is generally considered to be a transitional state between the cognitive decline of normal aging and the development of "full-blown" dementia [33]. Its clinical significance derives from its ability to predict dementia in persons with subthreshold symptoms [34]. MCI has been referred to by many terms, including benign senescent forgetfulness and

aging-associated cognitive decline. Recently, the concept of cognitive impairment no dementia (CIND) has come into the nomenclature, and is often used interchangeably with MCI. It has been argued, however, that MCI and CIND are not synonymous, as CIND encompasses a broader range of individuals, only some of whom have MCI [33].

In most cases, MCI is associated with memory impairment, and thus assumed to be AD-related. The precise manifestations of MCI, however, can be quite heterogeneous, and may extend to non-memory domains. Subcategories of MCI have been proposed to differentiate between probable etiologies, with amnestic MCI used to describe memory-impaired cases and nonamnestic MCI reserved for cases with other cognitive deficits [33]. The term vascular CIND (VCIND) is a related construct, used to describe patients with mild dysfunction in predominantly executive cognitive domains.

2.2.6 Vascular Cognitive Impairment

The construct of vascular cognitive impairment (VCI) is a relatively new phenomenon, having emerged in reaction to advances in the understanding of cognitive decline and the importance of early detection. Representing yet another umbrella term, VCI is used to reflect a spectrum of cerebovascular lesions and associated cognitive impairment, ranging from VCIND to VaD and mixed dementia. Although clearly a non-specific diagnosis, VCI may be advantageous in

identifying all cases in which vascular injury has contributed to cognitive changes, even if AD has also played a role or if symptoms have not yet led to functional deficits [4,35]. Used in this way, the term VCI recognizes the difficulties inherent in differentiating VaD from mixed dementia, and also identifies patients with subthreshold symptoms who are nonetheless at increased risk of institutionalization and death [36].

2.3 PATHOPHYSIOLOGY

2.3.1 Dementia – pathophysiology

Dementia can arise due to a number of causes, many of which are reversible (see Figure A). For patients with non-reversible dementias, any of several pathological mechanisms may be at play, either in combination or isolation. At present, there is no definitive way to identify the underlying cause(s) with certainty until an autopsy is performed [21]. Thus, clinicians must speculate about a patient's pathology based on clinical, historical, and neuroimaging characteristics, and choose the most appropriate treatment accordingly. In cases attributed to reversible causes, such therapy will be targeted to the underlying etiology (e.g., depression or anemia), rather than the cognitive symptoms per se.

Figure A. Potentially reversible causes of dementia [37]

D	Drugs (any with anticholnergic activity)
E	Emotional (depression)
M	Metabolic (hypothyroidism
E	Eyes and ears declining
N	Normal pressure hydrocephalus
T	Tumor
I	Infection (AIDS or syphilis)
A	Anemia (deficiency in folate or vitamin B12)

2.3.2 Alzheimer's Disease – pathophysiology

As described by Alois Alzheimer in the early 1900s, the hallmark pathological features of AD are extracellular (senile) plaques composed of aggregated beta-amyloid (Aβ) peptide and neurofibrillary tangles (NFTs) that are made up largely of tau protein. These pathologies, which have been identified in both early- and late-onset AD, seem to preferentially attack the memory centers of the brain (i.e., the hippocampus and entorhinal cortex), triggering the death of cholinergic neurons and related memory impairment. Although experts do not know for certain whether cell death triggered by amyloid plaques (the "amyloid hypothesis") or NFTs represents the true underlying cause of AD or is merely a consequence of other processes, the general consensus is that neurodegeneration is caused by the combination of plaques and tangles, whereas cholinergic declines and other mechanisms (e.g., oxidative stress, inflammation, and apoptosis) lead to AD symptoms.

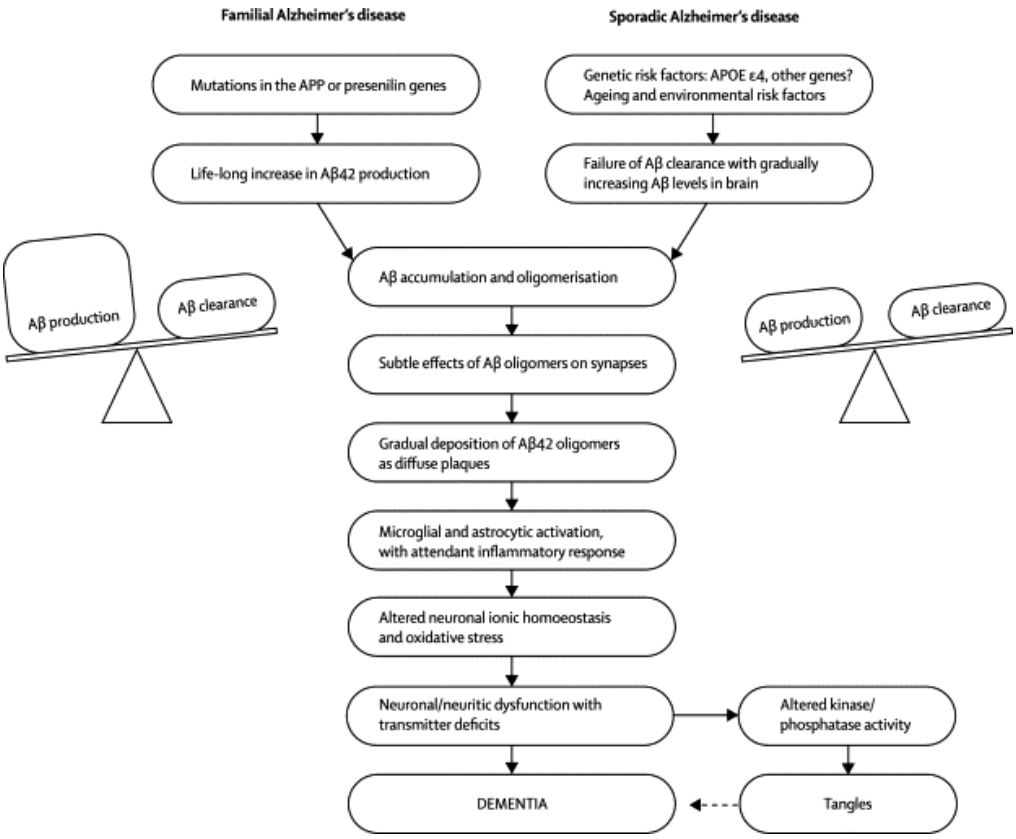
2.3.2.1 Amyloid plaques

The amyloid hypothesis of AD represents the reigning theory of AD development, and provides the foundation for nearly all current and emerging treatment strategies. According to the theory, AD is the consequence of an imbalance between Aβ clearance and production, which causes amyloid plaques to aggregate at the synapses between neurons, setting off a cascade of neurological and cognitive consequences (see Figure B) [34]. One of the primary events in this

"amyloid cascade" is the blockade of impulses across the synaptic cleft, which interferes with cognitive processing. Of the various types of neurons in the brain, those in the cholinergic system seem particularly vulnerable to the effects of amyloid plaques, and are thus among the first to die in the presence of this pathology [38].

As stated, the amyloid hypothesis of AD regards an imbalance between Aβ clearance and production as the central event in AD development. It is important to note, however, that there are two forms of the Aβ peptide (Aβ-40 and Aβ-42), both of which are produced from the amyloid precursor protein (APP), but only one of which (Aβ-42) is associated with plaque formation. In the case of familial AD, the production of Aβ-42 appears to be elevated, thereby increasing the likelihood of plaque development. With regard to late-onset AD, however, reduced clearance of Aβ-42 appears to be the primary contributor to plaque formation. Of note, there is also evidence that CVD inhibits Aβ clearance in the brain, which could explain how CVD exacerbates underlying AD pathology in patients with mixed dementia [34]. Regardless of which mechanism is at play, strategies that correct the imbalance of Aβ clearance and production may have the potential to modify AD progression [39].

Figure B. Amyloid cascade hypothesis [34]



2.3.2.2. Neurofibrillary tangles

Neurofibrillary tangles (NFTs) represent the second hallmark AD pathology, but are thought to play a predominant role only at the later stages of disease. Composed of aggregated tau proteins, NFTs are thought to disrupt intracellular transport, rendering neurons unable to transport trophic factors from their synapses back to the cell body. Because trophic factors are essential for survival,

the intracellular disruptions induced by NFTs may cause neurons to die, thereby impairing a patient's ability to process environmental stimuli and/or form or retrieve encoded memories. Experts are divided as to whether the NFTs represent a downstream event in the "amyloid cascade" or whether NFT formation is the initiator of AD pathogenesis [40,41].

2.3.2.3 Cholinergic deficits

A deficit in cholinergic neurons is a well-recognized consequence of AD pathology, as Aβ plaques appear to preferentially attack the cholinergic system. As a result of this cholinergic deficit, neurodegeneration may be triggered in the serotonergic and noradrenergic systems as well, thereby leading to depression, psychosis, and other behavioral sequelae [42]. The currently available AD drugs strive to compensate for the loss of cholinergic neurons by reducing levels of an enzyme that destroys acetylcholine (ACh), which is depleted in the brains of AD patients. Unfortunately, it becomes impossible to achieve sufficient ACh levels once a certain number of cholinergic neurons have died. In addition, because the degree of cholinergic decline varies widely across patients, the benefits of elevating ACh levels are also highly variable [43].

2.3.2.4 Genetics

Early-onset, familial AD, which accounts for only a small portion of all AD cases, has been linked to three genes, including the gene for APP and those for two presenilins (PS1 and PS2) that are involved in the cleavage of APP to produce the Aβ peptide. The finding that mutations in any of these genes can lead to an increase in Aβ-42 formation lends support to the amyloid hypothesis of AD. It also suggests that targeting the APP processing pathway and/or Aβ aggregation may have disease-modifying effects [34].

2.3.2.5 NMDA receptors, glutamate, and oxidative stress

Oxidative stress has been implicated in the pathogenesis of a number of diseases, including AD and other dementias. In AD, the increase in oxidative stress is attributed to an elevation in calcium concentrations between neurons, which is brought about by excessive glutamate release and an overactivation of N-methyl-d-aspartate (NMDA) receptors. Under normal conditions, glutamate is transferred from presynaptic neurons to postsynaptic neurons, where it binds to NMDA receptors and allows calcium to pass. When the amount of glutamate released from presynaptic neurons is excessive, however, the NMDA receptors become overly excited, and the intraneuronal calcium levels rise to toxic concentrations. It is this process that occurs in the brains of AD patients, triggering mitochondrial damage, oxidative damage, and cell death. The NMDA receptor antagonist memantine was developed to prevent calcium toxicity by blocking overly active

NMDA receptors. Antioxidants represent another potential therapeutic strategy based on the role of oxidative damage in AD and other dementia disorders [44].

2.3.3 Vascular Dementia – pathophysiology

Among patients with VaD, cognitive impairments can be initiated by a variety of cerebrovascular events, including multiple large infarcts, single strategic infarcts, small vessel disease, and hypoperfusion. In rare cases, the dementia may arise solely as a result of a cerebrovascular injury. More frequently, however, it is a combination of vascular and AD pathologies that give rise to the cognitive deficits. Thus, there is often a degree of uncertainty as to whether the cerebrovascular insult is the root cause of a patient's dementia, a contributor underlying degenerative decline, or an unrelated event. In addition, because several pathophysiological mechanisms may contribute to VaD, it can be difficult to tease out which is the primary etiology or whether the effects of various neuropathologic changes are additive [14,15].

2.3.3.1 Multiple large infarcts

The occurrence of multiple large-vessel occlusions, whether located in cortical or subcortical areas, almost inevitably triggers cognitive symptoms. While such symptoms are usually transitory, they may persist in a subset of patients, leading to constant or progressive cognitive decline. These cases, which are typically characterized by an abrupt onset, stepwise progression, and variable cognitive

deficits, are usually diagnosed as multi-infarct dementia, suggesting that the dementia is directly attributed to the index stroke [4]. Importantly, the cognitive deficits in multi-infarct dementia patients appear to become more widespread with stroke recurrence, which reinforces the value of secondary prevention strategies in this population [15].

The mechanism by which infarcts may lead to dementia is usually attributed to reduced blood flow (hypoperfusion) in the brain [45]. According to this theory, the infarcts generate hypoperfusion, which can then trigger dementia either directly, by initiating neuronal cell death, or indirectly, by increasing Aβ peptide production and contributing to amyloid plaques [46]. Related to these phenomena, it appears that stroke may cause significant changes in the cholinergic system, as cholinergic tracts are located in several brain regions (e.g., the hippocampus and subcortical white matter) that are particularly vulnerable to ischemic insult [47].

2.3.3.2 Single strategic infarcts

Like multiple large infarcts, small single infarcts may also lead to dementia, but only if the focal lesion is strategically localized in a functionally important brain region. The specific manifestations of VaD following strategic infarcts are highly variable, but may be predicted by the cognitive functions controlled at the site of ischemic damage (see Table 1). As with multi-infarct dementia, the onset of dementia following a strategic infarct is typically abrupt with a stepwise

progression. There is some evidence, however, that the cognitive deficits associated with strategic infarcts may be reversible, with less persistence over time [4,15].

Table 1. Manifestations of dementia according to location of strategic infarct [14]

Location of Infarct	**Clinical Manifestations**
Angular gyrus	• Acute onset of fluent aphasia • Alexia with agraphia • Memory deficit • Spatial disorientation • Constructional impairment
Posterior cerebral artery	• Amnesia • Psychomotor agitation • Visual hallucinations • Confusion • Visual impairment
Anterior cerebral artery	• Abulia • Transcortical motor aphasia • Memory deficit • Dyspraxia
Basal forebrain	• Severe amnesia • Behavioral changes

2.3.3.3 Small vessel disease

Small vessel disease may cause both cortical and subcortical lesions, including lacunes and white matter insults commonly associated with aging. Given that small vessel disease often occurs in otherwise healthy individuals, this form of CVD has historically been considered benign, and in isolation, seems unlikely to trigger pervasive, severe dementia. A growing body of research, however, suggests that white matter abnormalities on MRI may signal more significant CVD (e.g., focal and diffuse lesions in cortical and subcortical areas; lacunes and microinfarcts in the central gray matter), which could lead to more widespread cognitive dysfunction and a two-fold increase in dementia risk [4,15].

Because patients with small vessel disease do not often experience stroke, their cognitive decline is usually attributed to a disruption in the connections between subcortical structures and the frontal cortex. The resulting constellation of symptoms, which include deficits in memory and executive functioning, as well as psychomotor retardation, neurologic signs, speech problems, and mood/personality changes, is sometimes referred to as "subcortical dementia syndrome." This subtype of VaD is typically characterized by an insidious onset and slow progression, which stands in stark contrast to the abrupt onset and step-wise course associated with infarct-related VaD [4,14,15].

2.3.3.4 Lacunar strokes

VaD attributed to lacunar stroke represents a sub-category of VaD with small vessel disease. In these cases, blood flow becomes cut off from the brain because of a blockage in the tiny blood vessels located in the deep white matter. As with strategic infarcts, the site of lacunar stroke is a major determinant of clinical presentation, with frontal white matter lacunes frequently leading to executive dysfunction and lacunes of the basal ganglia and pons often triggering pseudobulbar palsy. Unique characteristics of lacunar VaD include multifocal motor, reflex, and sensory disturbances [14,15]

2.3.3.5 Leukoaraiosis

Leukoaraiosis is a cerebrovascular condition, recently identified as a cause of cognitive impairment. Based on research findings, the cognitive correlates of leukoaraiosis seem to resemble those of subcortical VaD, including frontal impairments and executive dysfunction. The speed at which leukoaraiosis progresses may be a major determinant of the rate of cognitive decline. Given that patients with more severe leukoaraiosis progress at faster speeds, researchers have suggested that the cognitive benefits of slowing leukoaraiosis progression may be greatest in the more severe subgroups [48].

2.3.3.6 CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited non-amyloid form of small-vessel disease that has been linked to cognitive impairment and dementia [49]. The clinical presentation of CADASIL, which has been identified as the first genetic form of VaD, is variable, but usually marked by recurrent subcortical strokes, which are accompanied by cognitive deficits and psychiatric symptoms [50]. The mean age of symptom onset of CADASIL in a pooled analysis of 105 published cases was 37 years [51]. Diagnoses are based on genetic testing and magnetic resonance imaging (MRI) findings [4].

2.3.3.7 Hypertension

Although the link between VaD and hypertension is somewhat controversial, some evidence suggests that cognitive impairment may be more frequent in hypertensive individuals. There are three mechanisms by which hypertension may contribute to cognitive decline. First, it has been suggested that hypertension induces a shift in the cerebral blood flow autoregulation curve, leading to tissue infarction and related cognitive deterioration. Second, hypertension has been shown to induce changes in the vessel wall, thereby triggering a cascade in which protein extravasion into brain parenchyma leads to brain edema and eventually, neuronal death and lacunae formation. Finally, myelin loss has been identified as potential mediator of the association between hypertension and cognitive decline [15].

2.3.3.8 Hemorrhagic lesions

VaD may also arise from hemorrhagic lesions, such as chronic subdural hematoma, subarachnoid hemorrhage, and cerebral hematoma [14].

2.3.3.9 Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a condition in which fibrillar amyloid replaces the normal wall of arterioles in the brain, thereby rendering the vessels vulnerable to rupture and subsequent cerebral hemorrhage. According to autopsy data, some degree of CAA is present in the vast majority of AD patients, suggesting that it has contributed to cognitive decline. Another, albeit rarer, consequence of CAA is vasculitis, which is often characterized by seizures and rapid cognitive deterioration. Given the association between CAA and cognitive decline, it has been speculated that severe CAA represents a subtype of VaD. Findings of severe CAA in 8-10% of persons at high risk for VaD have been used to support this hypothesis [4].

2.3.3.10 Cholinergic deficits

Loss of neurons in the cholinergic system has been reported in patients with VaD [52], and may be associated with VaD even in the absence of AD pathology [53]. Evidence for an independent link between VaD and deficits in the cholinergic system have been

found in experimental, clinical, and pathologic studies [7]. In addition, benefits of cholinesterase inhibitors have been found in VaD patients, providing even more support for a VaD-associated cholinergic deficit [15].

2.3.4 Mixed Dementia – pathophysiology

Mixed dementia reflects the co-occurrence of multiple dementia pathologies, but is most often used to describe patients in whom AD and VaD pathologies overlap (see Table 2) Because research into the mechanisms of mixed dementia is lacking, it is not currently known whether the condition stems from the additive effects of AD and VaD pathologies, or whether CVD interacts with AD pathology to exacerbate the underlying degenerative dementia [15].

What is known is that rates of CVD and AD both increase with age, and that the two conditions frequently co-occur in patients aged ≥85 years. Thus, while it is possible that AD causes CVD, or vice versa, it is equally likely that AD and CVD are simply simultaneous consequences of the aging process. Regardless of which is true, the combination of vascular and degenerative components appears to trigger a substantial increase in the rate of cognitive decline. Beyond the speed of progression, however, the course of mixed dementia may be highly variable, depending on the type of contributing vascular pathology [4,54].

Table 2. Prevalence of AD- and VaD-associated pathologies in patients with clinical diagnoses of AD and VaD [55]

Pathologic feature		**AD**	**VaD**
AD-associated pathologies	CAA	98%	30%
	Microvascular degeneration	100%	30%
	Loss of cholinergic markers	70%	40%
VaD-associated pathologies	CAA-related intracerebral hemorrhage	7%	15%
	Infarctions	36%	100%
	Microinfarcts	31%	65%
	White matter pathology	35%	70%

2.3.5 Vascular Cognitive Impairment – pathophysiology

Because vascular cognitive impairment (VCI) encompasses both vascular dementia (VaD) and mixed dementia, its pathological features are essentially the same as those discussed above. The inclusion of subthreshold dementia in the definition of VCI, however, raises the question of how much vascular pathology is sufficient to cause cognitive impairment. In particular, research has shown that infarcts occur in fewer than 50% of VCI cases, suggesting that the presence of infarcts is not essential for VCI development. By contrast, extensive leukoaraiosis

has been documented in 30-65% of VaD cases, which raises the possibility that even minor leukoariaosis could contribute to VCI of lesser severity [54].

2.3.6 Mild Cognitive Impairment – pathophysiology

Conceptually, mild cognitive impairment (MCI) may represent either a benign consequence of aging or the earliest manifestation of a dementia syndrome. If attributed to the normal aging process, no specific pathological features would be expected. As an early sign of dementia, however, the potential etiology could be degenerative, vascular, psychiatric, or medical in nature, and it is the clinician's responsibility to determine the most probable cause based on history or clinical features (see Table 3). If the features are consistent with a degenerative etiology, it is likely that AD pathology underlies the patient's cognitive decline. In cases with a presumed vascular etiology, VaD is the most likely outcome, and CVD is the most probable cause. Autopsy data seem to confirm these hypotheses, as patients with MCI have shown intermediate levels of both AD and VaD pathology, relative to normal controls and dementia patients [33,56].

Table 3. Features associated with potential etiologies of MCI [33]

Presumed Etiology	**Characteristic Features**
Degenerative (AD)	Gradual onset Insidious progression

Presumed Etiology	Characteristic Features
Vascular (VaD)	Abrupt onset Vascular risk factors History of strokes Transient ischemic attacks
Psychiatric	History of depression Depressed mood Anxiety
Medical	Congestive heart failure Diabetes Systemic cancer

2.4 PATIENT ASSESSMENT

2.4.1 Canadian Consensus Conference on Dementia (CCCD) guidelines

Given the complexity and heterogeneity of the dementia disorders, a thorough assessment is required for proper diagnosis. In Canada, the assessment and diagnosis of dementia is guided by recommendations established at the 1998 Canadian Consensus Conference on Dementia (CCCD), led by experts from the fields of family medicine, neurology, preventive healthcare, geriatric medicine, and psychiatry. The CCCD recommendations, which were based on research

evidence, specify that dementia diagnoses must be based on a detailed history and physical examination, combined with office-based tests (e.g., the Mini-Mental State Examination [MMSE]), measures of instrumental functioning (e.g., the Functional Assessment Questionnaire), and, in some cases, neuroimaging (see Table 4). In addition, the CCCD recommendations call for serial assessments to be conducted at intervals of three to six months, as these may be necessary to confirm progression and establish clinical prognosis [17].

Table 4. CCCD consensus recommendations for assessment of dementia [17]

Topic	**Recommendations**
Laboratory Tests	Basic laboratory work-up should be conducted, including: • complete blood count, • thyroid stimulating hormone • serum electrolytes • serum calcium • serum glucose Extensive laboratory testing not needed, except when presentation suggests delirium or a particular reversible cause.

Topic	**Recommendations**
Neuroimaging	CT has a role in detecting certain causes of dementia (e.g., VaD) and should be performed when any of the following criteria are met: • age <60 years • rapid cognitive or functional decline • duration of dementia <2 years • recent/significant head injury • neurological symptoms of unknown origin • history of cancer • anticoagulant use or history of bleeding disorder • presence of urinary incontinence and gait disorder in the early stage of dementia • any new localizing sign • atypical features (e.g., progressive aphasia) • gait disturbance MRI offers no benefits over CT in most cases.

Topic	Recommendations
Ancillary Tests	There is insufficient evidence to support routine use of ancillary tests such as: • PET, SPECT, or functional MRI • MRI hippocampal volumes • Reaction time measures • EEG with power spectral analysis • Sleep EEG • Cognitive evoked potentials • Genetic/neurochemical testing for ApoE genotype, CSF tau or beta-amyloid fragments

2.4.2 Assessment Tools

2.4.2.1 The Mini-Mental State Examination (MMSE)

Among the various tools used in dementia assessment, the Mini-Mental State Examination (MMSE) [57,58] stands out as one of the most frequently used and important, particularly in Canada, where reimbursement for anti-dementia drugs is based on MMSE scores. Developed as a simple and practical alternative to lengthy cognitive batteries, the MMSE includes only 11 questions and requires only five to 10 minutes to administer and score. Its focus is on the cognitive

aspects of mental functioning, such as memory, orientation, attention, and language, which the clinician assesses by asking the examinee to vocally answer questions (e.g., "what is today's date?") or complete various tasks (e.g., write a sentence, copy a design, or spell "WORLD" backwards). Items addressing mood and thought processes, which are typically included in lengthier cognitive measures, are specifically excluded from the MMSE assessment [57].

In clinical practice, the MMSE is typically used to assess dementia severity, as it provides a valid system for differentiating between different levels of impairment and tracking changes in cognition over time (see Table 5). In Quebec, clinicians must document an MMSE score of 10-26 on the 30-point scale, which corresponds to mild or moderate cognitive impairment, in order to obtain reimbursement for approved AD treatments. The rationale for categorizing dementia as mild, moderate, or severe stems from the observation that certain therapies may only be effective at certain disease stages. Once a patient has reached severe dementia, as evidenced by an MMSE score of <10, many drugs are considered to be ineffective, and thus not reimbursable under Quebec's healthcare system.

Table 5. Stages of dementia progression, by MMSE score and corresponding disability level [19,21,59]

Stage	MMSE Range	Level of Disability
Mild	18-26	Minimal impairment in work or social activities Relatively intact judgment Appropriate personal hygiene Capacity for independent living despite some cognitive problems Possible depression No psychotic symptoms
Moderate	10-17	Independent living is hazardous Need for assistance with self care Possible wandering Difficulty recognizing family and friends Apparent agitation and psychotic behavioral symptoms

Stage	MMSE Range	Level of Disability
Severe	0-9	Need for assistance with almost all daily activities Increased frequency and severity of behavioral symptoms Possibility of being bed-ridden, mute, and/or unaware of surroundings Frequently fatal accidents and infections

2.4.2.2 Alternatives to the MMSE

Although the MMSE has proven to be valid and reliable for testing general cognitive function [57], it has been criticized for being insensitive to executive dysfunction and failing to identify subclinical cognitive deficits [60,61]. The Canadian Study of Health and Aging (CSHA) attempted to address the limitations of the MMSE by using the Modified Mental Status (3MS) as a screen for dementia, but ultimately failed to establish the usefulness of either measure for identifying early cognitive decline [61]. Other researchers have proposed that the St. Louis University Mental Status Examination may be a better alternative for detecting dementia in its earliest stages [37]. In addition, the Montreal Cognitive Assessment (MoCA) tool was developed specifically to detect mild cognitive impairment that may progress to dementia, and has been shown to have greater sensitivity to detect mild cognitive impairment than the MMSE [62].

In addition to the MMSE and 3MS, a number of other measures are commonly used to assess the impact of dementia on various aspects of functioning, and to track changes over time (see Table 6). For detecting cognitive change, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [63,64] is frequently used in clinical trials, whereas the Clinician's Interview-Based Impression of Change-Plus caregiver input (CIBIC-Plus) [65] has become a popular tool for evaluating overall response to treatment. Another frequently used instrument is the Clinical Dementia Rating (CDR), which provides a global score and a summary rating (sum of box score: CDR-SB) for the domains of memory, orientation, judgment, community affairs, home/hobbies, and personal care [66,67]. More detailed neuropsychological evaluations may include specific tests for memory, abstract thinking, judgment, aphasia, apraxia, agnosia, and construction [2]. Finally, evaluations of behavioral changes and psychiatric symptoms may be indicated to identify related areas of impairment.

The assessment of activities of daily living (ADLs) usually relies on caregiver input regarding the patient's ability to perform basic tasks (e.g., dressing, washing, and personal grooming), as well as instrumental activities (e.g., shopping, preparing food, using the telephone, and housekeeping). Instruments such as the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) [68] and the Disability Assessment for Dementia (DAD) [69] provide valuable scoring systems for both basic and instrumental ADLs. Measures of

instrumental ADLs are often considered to be reliable surrogates for the assessment of executive function [16].

Table 6. Commonly used instruments in the assessment of dementia

Domain of Assessment	**Popular Instrument**	**Citation(s)**
Cognition	Mini-Mental State Examination (MMSE)	[57,58]
	Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)	[63,64]
	Modified Mental Status Examination (3MS)	[70]
Global functioning	Clinician's Interview-Based Impression of Change-Plus caregiver input (CIBIC-Plus)	[65]
	Functional Assessment Questionnaire (FAQ)	[71,72]
	Blessed Dementia Scale	[73]
	Clinical Dementia Rating – Sum of the Boxes (CDR-SB)	[66,67]
	Functional Rating Scale	[74]
	Global Deterioration Scale	[75]

Domain of Assessment	**Popular Instrument**	**Citation(s)**
Psychiatric symptoms	Hamilton Rating Scale for Depression (HAM-D)	[76]
	Neuropsychiatric Inventory (NPI)	[77]
	Cornell Scale for Depression	[78]
	Geriatric Depression Scale	[79]
	Present State Examination	[80]
Activities of Daily Living (ADLs)	Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)	[68]
	Disability Assessment for Dementia	[69]

2.4.3 Neuroimaging Tests

The role of neuroimaging in the assessment and diagnosis of dementia has been extensively debated, with the general consensus being that neuroimaging should play an ancillary role in the evaluation process. Magnetic resonance imaging (MRI) and computerized tomography (CT) represent two frequently used instruments for identifying infarcts and other brain abnormalities that may contribute to cognitive impairment. Other potentially useful strategies include positron emission tomography (PET), single-photon emission computer technology (SPECT), and magnetic resonance spectrometry, each of which has

demonstrated an ability to distinguish AD from VaD patients. Within the VaD population, diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) have exhibited promise in tracking longitudinal changes. With DWI in particular, researchers may be able to detect recent small infarcts associated with small vessel disease, even before patients begin to exhibit cognitive decline [15].

2.5 CLINICAL DIAGNOSIS

2.5.1 Dementia – diagnosis

The diagnosis of dementia is a complex process, beginning with the identification of cognitive decline and ending with a hypothesis about its probable cause. The first step is usually to determine that cognitive impairment exists, and to establish that the impairment represents a deterioration from previous functioning. Once cognitive impairment has been established, it is important to assess the severity of the dementia, to specify which cognitive domains and areas of functioning have been most affected, and to rule out potentially reversible causes (e.g., AIDS or hypothyroidism). The pattern of symptoms and course of decline must be assessed both retrospectively and prospectively over time, as features of disease progression may be helpful in differential diagnosis (e.g., AD vs. VaD vs. frontotemporal dementia). Ultimately, however, the accuracy of a clinical diagnosis cannot be confirmed while a patient is still alive, as the detection of pathological features (e.g., amyloid plaques and NFTs) requires autopsy examination. Because of this limitation, it is essential to collect as much

information as possible to support a specific diagnosis. Tools such as neuroimaging and laboratory tests may be useful in this process [34].

2.5.1.1 The problem of underdiagnosis

Given the clinical and pathophysiological heterogeneity of dementing diseases, it is perhaps not surprising that diagnoses are often missed in community settings. Family members rarely recognize memory impairments before the dementia reaches moderate severity, often dismissing subtle declines as part of the natural aging process and/or denying symptoms due to fear of an AD diagnosis. Compounding the problem, community physicians may fail to render a correct diagnosis in as many as 50% of patients who meet standard dementia criteria, which suggests that greater education is needed at both the public and professional levels regarding dementia and its proper diagnosis [37].

2.5.1.3 Potential biomarkers

Although diagnoses of dementia are currently behaviorally based, researchers are actively searching for biomarkers that may facilitate early detection. Among such potential surrogates, cerebrospinal fluid (CSF) levels of total tau, phosphorylated tau, and Aβ42 have all shown accuracy in differentiating AD from normal aging, but appear to be far less useful in distinguishing AD from other forms of dementia. A more promising alternative involves the use of Aβ plaque imaging techniques, such as Pittsburgh Compound B, which would allow researchers to

view AD pathology in the living human brain [34]. Experts are hopeful that this strategy may allow AD to be detected at earlier stages, thereby promoting more effective therapeutic intervention [81].

2.5.2 Alzheimer's Disease – diagnosis

As stated, the second step of dementia diagnosis involves reaching an informed conclusion about its most probable cause. In this process, all of the data collected during clinical, neurological, and psychiatric examinations are analyzed and compared with standard diagnostic criteria.

2.5.2.1 NINCDS-ADRDA Criteria for AD

The most commonly used system for diagnosing AD is that set forth in 1984 by the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), which provides guidelines for identifying possible, probable, and definite AD (see Table 7). Noteworthy features of this diagnostic system include the emphasis placed on course variables (e.g., insidious onset and progressive decline), as well as the importance given to ruling out other identifiable causes [21].

Table 7. NINCDS-ADRDA criteria for diagnosis of probable AD [21]

Criteria required for diagnosis	• Dementia, established by clinical examination and neuropsychological tests • Deficits in ≥2 cognitive domains • Progressive decline in memory and other cognitive functions • No disturbance of consciousness • Onset at age 40-90 years (usually at age >65 years) • No evidence of systemic disease or other brain disorders that could be sole cause of cognitive impairment
Criteria that support diagnosis	• Progressive decline in specific cognitive domains: language, motor skills, and perception • Impairments in behavior and daily functioning • Family history of cognitive impairment • Laboratory results: normal lumbar puncture, normal or nonspecific EEG findings, CT evidence of cerebral atrophy

Features consistent with diagnosis (after exclusion of other causes)	• Plateaus in disease progression • Associated behavioral and psychiatric symptoms (e.g., depression, delusions, insomnia) • Motor signs (e.g., increased muscle tone, myoclonus, gait disorder) in advanced disease • Seizures in advanced disease • Normal CT for age
Features that make diagnosis uncertain or improbable	• Sudden onset • Focal neurologic signs (e.g., hemiparesis, sensory loss, visual field deficits, incoordination) in early disease • Seizures or gait disturbance in early disease

Although the NINCDS-ADRDA criteria are widely used in clinical and research settings [82,83], they have been criticized for having a relatively low diagnostic accuracy, as well as imprecise specifications for evidence of mixed dementia. To some extent, the low accuracy rates may be inevitable, as there will always be some degree of uncertainty in diagnoses made prior to death. At the same time, however, the failure of the NINCDS-ADRDA to address the impact of concomitant CVD is a noteworthy weakness, as it may hamper accurate differential diagnosis. Because no thresholds for vascular pathology have been

set, there has been little consistency in how clinicians and researchers distinguish between AD and mixed dementia [34].

To address such shortcomings in the original NINCDS-ADRDA criteria, a working group at the Second Congress of the International Society for Vascular Behavioural and Cognitive Disorders (Vas-Cog) developed revised diagnostic criteria [81]. The revised criteria, published in 2007, no longer refer to a dementia threshold, and instead attempt to identify AD on the basis of clinical, biochemical, structural, and metabolic features (see Table 8). Using these criteria, AD can be diagnosed even in its early, predementia stages following objective evidence of significantly impaired memory, presence of hippocampal atrophy on MRI, an abnormal pattern of CSF biomarkers, or a specific pattern on PET neuroimaging.

Table 8. Revised Vas-Cog diagnostic criteria for AD [81]

Probable AD	A plus one or more supportive features B, C, D, or E
Core diagnostic criteria	A. Presence of an early and significant episodic memory impairment that includes the following features: 1. Gradual and progressive change in memory function reported by patients or informants over >6 months 2. Objective evidence of significantly impaired episodic memory on testing

	3. Episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances
Supportive features	B. Presence of medial temporal lobe atrophy • Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI
	C. Abnormal cerebrospinal fluid biomarker • Low amyloid β_{1-42} concentrations, increased total tau concentrations, increased phospho-tau concentrations, or combinations of the three • Other well validated markers to be discovered in the future
	D. Specific pattern on functional neuroimaging with PET • Reduced glucose metabolism in bilateral temporal parietal regions • Other well validated ligands, including those that foreseeably will emerge
	E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria	History • Sudden onset • Early occurrence of gait disturbances, seizures, behavioral changes
	Clinical features • Focal neurological features including hemiparesis, sensory loss, visual field deficits • Early extrapyramidal signs
	Other medical disorders severe enough to account for memory and related symptoms • Non-AD dementia • Major depression • Cerebrovascular disease • Toxic and metabolic abnormalities • MRI FLAIR or T2 signal abnormalities in the medial temporal lobe consistent with infectious or vascular insults
Definite AD	• Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD [84] • Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD

2.5.2.2 DSM-IV Criteria for AD

The Diagnostic and Statistics Manual-Fourth Edition (DSM-IV) provides an alternative approach to diagnosing AD, and was actually used in combination with the NINCDS-ADRDA in the second wave of the Canadian Study of Health and Aging (CSHA) [83]. Like the NINCDS-ADRDA, the DSM-IV requires evidence of memory impairment as well as progressive cognitive decline. The primary difference between the two systems seems to lie in the DSM-IV's failure to differentiate between criteria that are definitive vs. supportive of an AD diagnosis. For example, while the NINCDS-ADRDA considers functional impairment to be supportive of AD, the DSM-IV makes this an essential feature of the disease [19].

2.5.2.3 ICD-10 Criteria for AD

The International Statistical Classification of Diseases, 10th Revision (ICD-10) criteria for AD resemble those of the DSM-IV in that they do not outline levels of evidence supporting diagnosis. According to the ICD-10, a definite diagnosis of AD can made in all cases with an insidious onset and slow deterioration of dementia, provided that evidence of focal neurological signs and systemic causes (e.g., hypothyroidism) are absent. The ICD-10 definition of dementia includes deficits in both memory and "thinking," as well as functional impairment and a duration of illness of at least six months [20].

2.5.2.4 Neuropathologic criteria

Because the presence of AD can be validated only after death, criteria for establishing definitive neuropathologic diagnoses are of utmost importance. Among the most commonly used neuropathologic systems, the Consortium to Establish a Registry for AD (CERAD) recommends that diagnoses of possible, probable, and definite AD be based on semiquantitative estimates of amyloid plaques. By contrast, recommendations from the National Institute of Aging (NIA)-Reagan Institute Working Group suggest that estimates of plaques are not enough, and thus specify that the estimated NFT burden must also be considered to establish an AD diagnosis [84].

2.5.3 Vascular Dementia – diagnosis

Diagnostic criteria for VaD have been evolving over the past 20 years, and continue to generate controversy in the clinical and research communities. When first recognized, definitions of VaD resembled those of AD, and thus may have over-emphasized the importance of memory and learning deficits. In more recent years, experts have begun to recognize that VaD is often characterized by declines in non-memory cognitive domains, and that a lack of memory impairment may not preclude a VaD diagnosis. As a result of such discoveries, the methods conventionally used to identify VaD are being re-evaluated.

As with AD, strategies for VaD diagnosis have historically relied on a two-stage process of first identifying dementia and then differentiating between subtypes. Because the initial detection of dementia was based primarily on AD features, only VaD patients with AD characteristics (i.e., memory impairment) were considered for diagnosis. Use of this strategy in research settings may have artificially magnified the similarities between VaD and AD patients, while simultaneously creating VaD populations with a disproportionately high number of mixed dementia cases. Clinically, many VaD cases may have been missed because they did not resemble AD dementia, thereby precluding opportunities for optimal treatment. The newer methods for diagnosing VaD, including the popularization of the VCI concept, reflect an increased awareness of the co-occurrence of AD and VaD, as well as an attempt to identify VaD patients with non-AD presentations [4,54].

Clinically, patients with VaD and AD may have similar presentations, supporting an overlap between VaD and AD pathologies. The "classic" VaD syndrome, however, is marked by several differences from AD (see Table 9), including a relative preservation of memory function, a more abrupt onset of illness, and higher frequencies of mood changes and gait impairment early in the disease. In addition, the course of cognitive decline in VaD may be stepwise or fluctuating, in contrast to the characteristically progressive decline seen in AD patients. These features are often cited in diagnostic criteria as supporting a VaD diagnosis

Table 9. Distinguishing characteristics of VaD and AD [15]

Feature	**VaD**	**AD**
Onset	Sudden or gradual	Gradual
Progression	Slow, step-wise	Insidious, progressive
Focal neurological signs/symptoms	Present	Usually absent
Memory	Mild deficits	Early and severe impairment
Executive function	Early and severe impairment	Late deficits
Vascular risk factors	Strokes, transient ischemic attacks (TIAs)	Less common
Modified Hachinski score	>7	<4
Neuroimaging	Infarcts, white matter lesions	Normal, hippocampal atrophy

At present, several systems exist for diagnosing VaD patients, all of which are based on a presumed link between co-existing CVD and dementia. While the importance of this link is not debated, questions remain regarding how it should be established. For example, even though most systems require that the onset of dementia occur within a certain time period after cerebrovascuar injury, others regard this temporal association as too restrictive, particularly in cases arising from non-infarct-related injury. Related to this debate, controversy exists over neuroimaging criteria for CVD, as some experts worry that cases of non-infarct-related VaD will be overlooked if neuroimaging evidence is required. Proponents of VCI favor broadening the concept of VaD to include more types of vascular pathology. Others advocate the development of separate, more specific criteria

that may be tailored to either infarct-related VaD or VaD secondary to other vascular causes [4].

2.5.3.1 Hachinski Ischemic Scale

The Hachinski Ischemic Scale (HIS) represents one of the first attempts to distinguish VaD from AD. Geared toward the diagnosis of multi-infarct dementia, the original version of HIS asked clinicians to rate patients' conformity with 13 features thought to be associated with VaD. A newer, modified version retains 8 of the 13 original criteria (see Table 10), with the resulting score intended to reflect the likelihood that a patient's dementia has a vascular origin [15].

Table 10. Modified Hachinski Ischemic Scale* [15]

Feature	**Score**
Abrupt onset	0 or 1 or 2
Stepwise deterioration	0 or 1
Somatic complaints	0 or 1
Emotional lability	0 or 1
History of hypertension	0 or 1
History of stroke	0 or 1 or 2
Focal neurological symptoms	0 or 1 or 2
Focal neurological signs	0 or 1 or 2

*A score of ≥4 indicates that CVD is a likely contributor to dementia

Although the HIS has exhibited sensitivity and specificity values of 70-80% for distinguishing VaD from AD, it has been less reliable for identifying cases of mixed dementia, and provides no context for integrating neuroimaging data into the diagnostic process. These drawbacks, combined with its failure to recognize characteristics of non-infarct-related VaD, have limited the use of the HIS as a primary diagnostic tool [15].

2.5.3.2 DSM-IV Criteria for VaD

The DSM-IV approach to diagnosing VaD is noteworthy in several respects, particularly as it requires a memory deficit as evidence of cognitive impairment. According to the DSM-IV, the presence of a CVD component must be established either by focal neurological signs and symptoms (e.g., pseudobulbar palsy, gait abnormalities, and extensor plantar response) or laboratory evidence (e.g., multiple cortical or subcortical infarctions), but a temporal link between CVD and dementia is not required. No specifications are made regarding the onset or progression of VaD, which stands in contrast to the insidious onset and progressive course required for a DSM-IV diagnosis of AD [19]. Because of these features, the DSM-IV may be among the most inclusive but least specific methods for VaD diagnosis [85].

2.5.3.3 ICD-10 Criteria for VaD

The World Health Organization's ICD-10 offers an alternative approach to VaD diagnosis, and outlines the features of VaD subtypes such as multi-infarct dementia, subcortical VaD, and VaD with mixed cortical and subcortical components. Like the DSM-IV, the ICD-10 requires memory impairment for a VaD diagnosis, and considers an abrupt onset, stepwise deterioration, and focal neurological signs to be supportive of a vascular etiology. No specifications are made regarding the temporal relationship between CVD and dementia, but a number of associated features are listed, including hypertension, emotional lability, transient delirium, apathy, and other mood and personality changes [20].

2.5.3.4 NINDS-AIREN Criteria for VaD

In 1991, the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) organized an International Workshop of Vascular Dementia, which was held at the National Institutes of Health in Bethesda, Maryland. With the support of the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN), the Workshop aimed to develop a consensus definition of VaD to be used in research settings, as well as a set of specific diagnostic criteria for use in epidemiologic studies. The results of their efforts highlight the complexity of VaD, and offer a strategy for diagnosing probable, possible, and definite VaD (see Table 11). In addition, these criteria

specify that VaD can be sub-categorized into cortical VaD, subcortical VaD, Binswanger's disease, and thalamic dementia for research purposes [14].

Of the current diagnostic criteria for VaD, those developed by the NINDS-AIREN are considered to be the most specific, as they have very restrictive requirements for a temporal relationship and neuroimaging evidence of CVD [85]. The NINDS-AIREN system is very commonly used in epidemiological and clinical studies, including the CSHA, which based VaD diagnoses on both NINDS-AIREN and ICD-10 criteria [83].

Table 11. NINDS-AIREN Diagnostic Criteria for Probable, Possible, and Definite VaD [14]

Diagnostic Category	**Criteria**	**Comments**
Probable VaD	Dementia	• Decline in memory and ≥2 other cognitive domains • Preferably established by clinical exam and neuropsychological testing • Deficits must interfere with daily functioning

Diagnostic Category	**Criteria**	**Comments**
	CVD	• Presence of focal signs on neurologic exam* AND • Neuroimaging evidence of CVD**
	A relationship between dementia and CVD	• Onset of dementia at <3 months post-stroke, OR • Abrupt cognitive deterioration and fluctuating, stepwise progression of cognitive deficits
	Features consistent with diagnosis	• Early gait disturbance • History of unsteadiness and falls • Early urinary symptoms not explained by urologic disease • Pseudobulbar palsy • Mood and personality changes
Possible VaD	Dementia	• Defined as a decline in memory and ≥2 other cognitive domains • Preferably established by clinical exam and neuropsychological testing • Deficits must interfere with daily functioning

Diagnostic Category	**Criteria**	**Comments**
	Focal neurologic signs	• In patients with missing neuroimaging data, OR • In the absence of a clear temporal relationship, OR • In patients with an insidious onset and variable course of cognitive decline + evidence of cerebrovascular disease
Definite VaD	Clinical criteria for Probable VaD	• Dementia • CVD • Relationship between dementia and CVD
	Histopathic evidence of CVD	• Obtained from biopsy or autopsy
	Absence of other causes of cognitive decline	• No NFTs or senile plaques in excess of what is expected for age • No clinical or pathologic disorder associated with dementia

* Focal signs include hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke.

** Neuroimaging evidence includes multiple large-vessel infarcts, a single strategic infarct, multiple basal ganglia, white matter lacunes, and/or extensive periventricular white matter lesions.

2.5.3.5 ADDTC Criteria for VaD

As an alternative to the NINDS-AIREN criteria, the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) developed its own recommendations for diagnosing VaD in clinical and research settings. The structure of the ADDTC system is quite similar to that of the NINDS-AIREN, as both differentiate between probable, possible, and definite forms of the disease. The primary difference between two systems lies in the scope of pathology addressed by the criteria, as the ADDTC is limited to only ischemic forms of VaD, while the NINDS-AIREN includes both ischemic and non-ischemic VaD subtypes. In addition, the ADDTC is unique in its inclusion of specific criteria for mixed dementia and its recognition that mixed dementia may include the co-occurrence of CVD with dementias other than AD (e.g., dementia with Lewy bodies).

Beyond these obvious differences, the ADDTC system differs from the NINDS-AIREN in a number of subtler (but no less noteworthy) ways, including its

definition of dementia, criteria for functional impairment, and specifications for a temporal relationship between CVD and dementia. With regard to dementia definition, the ADDTC places more emphasis on clinical judgment, and rejects the NINDS-AIREN contention that dementia is defined by a certain type, number, or pattern of cognitive deficits. In terms of functional impairment, the ADDTC de-emphasizes the importance of deficits in social and occupational functioning, viewing these as relatively common consequences of normal aging. In line with these more inclusive criteria, the ADDTC does not cite any specific type of course or require disease progression for a VaD diagnosis. In addition, the ADDTC requires evidence of a temporal relationship between CVD and dementia only in cases of isolated infarcts. This stands in contrast to the NINDS-AIREN criteria, which call for a temporal relationship even among patients who have experienced multiple strokes [86].

Table 12. ADDTC diagnostic criteria for probable, possible, and definite ischemic VaD [86]

Diagnostic Category	**Criteria**	**Comments**
Probable VaD	Dementia	• Decline in more than one area of intellectual performance • Deficits must broadly interfere with daily living • Deficits must be independent of level of consciousness
	Stroke	• Historical, neurologic, or neuroimaging evidence of ≥2 ischemic strokes OR a single stroke with a temporal relationship to dementia onset • Neuroimaging evidence of ≥1 infarct outside of the cerebellum

	Features that support diagnosis	• Evidence of multiple infarcts in brain areas associated with cognition • History of multiple transient ischemic attacks • History of vascular risk factors (e.g., hypertension, diabetes, heart disease) • Elevated score on the Hachinski Ischemia Scale
	Features consistent with diagnosis, but await further research	• Early gait disturbance or urinary incontinence • Neuroimaging evidence of periventricular and deep white matter changes that are excessive for age • Focal changes on electrophysiologic or physiologic neuroimaging studies
	Features inconsistent with diagnosis	• Transcortical sensory aphasia without neuroimaging evidence of corresponding focal lesions • Absence of central neurological symptoms and signs other than cognitive impairment

Possible VaD	Dementia	• Decline in more than one area of intellectual performance • Supported by historical evidence • Documented by bedside mental status exam or ideally, by neuropsychological assessment • Deficits must broadly interfere with daily living • Deficits must be independent of level of consciousness
	Cerebrovascular Disease	• A history of a single stroke without a temporal relationship to dementia onset OR Binswanger's syndrome*

Definite VaD	Dementia	• Decline in more than one area of intellectual performance • Supported by historical evidence • Documented by bedside mental status exam or ideally, by neuropsychological assessment • Deficits must broadly interfere with daily living • Deficits must be independent of level of consciousness
	Histopathic evidence of cerebrovascular disease	• Confirmation of multiple infarcts, including some outside the cerebellum

* Binswanger's syndrome is diagnosed based on the presence of: (1) early-onset urinary incontinence or gait disturbance; (2) vascular risk factors; and (3) extensive white matter changes on neuroimaging.

2.5.4 Mixed Dementia – diagnosis

Although most diagnostic guidelines address the possibility that dementia subtypes may overlap, none provide specific, comprehensive guidance for making a mixed diagnosis. Perhaps because of this limitation, diagnoses of "pure" AD and VaD may often be assigned inappropriately in clinical practice, and cases of mixed dementia may frequently be lumped into the VaD category for research purposes [54].

Table 13. Perspectives on mixed dementia, as outlined by major diagnostic criteria

Guideline	Handling of Mixed Dementia
NINDS-AIREN	A diagnosis of AD with CVD should be assigned to patients who fulfill clinical criteria for possible AD, while also exhibiting clinical or neuroimaging evidence of CVD [14]
ADDTC	A diagnosis of mixed dementia should be made when stroke co-exists with a second systemic or brain disorder (e.g., AD or Parkinson's disease) that is thought to be causally related to dementia [86]

NINCDS-ADRDA	Cases of mixed dementia are categorized as possible AD if AD is considered to be the principal cause [21]
DSM-IV	There is no diagnostic code for mixed dementia. When there is evidence that dementia is due to multiple etiologies (e.g., AD and VaD), both diagnoses should be recorded [19].
ICD-10	A diagnosis of mixed dementia should be made when evidence of CVD co-occurs with a clinical presentation and history suggestive of AD [20].

In its monograph on ischemic VaD, the ADDTC specifies that a diagnosis of mixed dementia should be made when stroke co-exists with a second systemic or brain disorder that is thought to be causally related to dementia [86]. This definition is similar to that set forth by the NINDS-AIREN, which assigns a diagnosis of "AD with CVD" to patients who fulfill clinical criteria for possible AD, while also exhibiting clinical or neuroimaging evidence of CVD [14]. It differs, however, from the criteria proposed by the NINCDS-ADRDA, which assigns the category of possible AD to all cases of mixed etiology in which AD is considered to be the principal cause [21].

2.5.5 Vascular Cognitive Impairment – diagnosis

Current criteria for VaD have poor sensitivity for identifying cases at early stages, when treatment for dementia is most likely to be successful. In an effort to improve the detection of mild cases and increase the potential for treatment success, researchers have proposed the concept of VCI, which would presumably be diagnosed by very sensitive, rather than very specific, instruments. Although such instruments have yet to be developed, it has been suggested that methods used to identify VCI should place equal emphasis on all cognitive domains [54].

2.5.5.1 NINDS-CNS recommendations

To address the lack of diagnostic criteria for VCI, the NINDS and Canadian Stroke Network (CSN) recently convened a group of experts to formulate recommendations for the clinical diagnosis and research of this disease construct. From the outset of the workshop, it was recognized that existing data were insufficient to develop a definitive set of diagnostic criteria. Thus, the overarching goal of the workshop was to determine which data elements should be collected in studies that would aim to flesh out the definition of VCI. A basic assumption was that VCI would encompass a broad spectrum of cognitive deficits, ranging from VCIND to VaD to mixed dementia.

Among the results of the NINDS-CNS workshop, recommendations were made for 5-, 30-, and 60-minute neuropsychological test protocols that could be used to identify patients for VCI studies. These protocols were selected based on their ability to assess a wide range of cognitive domains, while simultaneously focusing on the evaluation of executive function. The 60-minute protocol was composed of numerous tests for executive/activation, visuospatial, language, memory/learning, and neuropsychiatric functioning. A subset of these tests was retained for the 30-minute protocol, with a selection of subtests from the MoCA [62] recommended for use in 5-minute screening evaluations. However, due to its insufficient sensitivity in detecting executive dysfunction and mild memory impairment, the MMSE was considered inappropriate for use in VCI assessment [60].

In addition to setting forth neuropsychological criteria, the NINDS-CNS participants also addressed the role of neuroimaging in VCI studies. Their conclusions emphasize the important descriptive function of neuroimaging in VCI, as it can provide vital information on the severity and location of brain atrophy, white matter hyperintensities, infarction, hemorrhage, and other manifestations of vascular disease. At the same time, however, the NINDS-CNS working group maintained that neuroimaging has limited value in VCI diagnosis, due to the lack of pathogomonic radiological features of VCI and the frequent overlap between vascular and degenerative pathologies. The experts recommended magnetic resonance imaging (MRI) as the optimal instrument for VCI assessment, and

cautioned against the use of computerized tomography (CT) due to the dangers of radiation exposure and limitations in measuring mild disease [60].

2.5.5.3 Potential biomarkers

As in AD and VaD, the diagnosis of VCI could be improved by the identification of biomarkers that differentiate between AD and vascular pathology. However, the heterogeneity of VCI subtypes and the prevalence of mixed dementia have hampered research in this area, such that only one test (the CSF Albumin Index) is currently clinically available for this purpose. Markers with potential utility in VCI, according to the NINDS-CNS Working Group, are listed in below (see Table 14). All are found in the cerebral spinal fluid (CSF), as no blood biomarkers have yet been identified.

Table 14. Candidate CSF biomarkers for VCI [60]

Marker	**Related Pathology**
Serum albumin ratio	Blood-brain barrier damage to intracerebral vessels
Sulfatide	White matter demyelination
Neurofilament	Axonal degeneration
Matrix Metalloproteases	Vascular disease with inflammation

2.5.6 Mild Cognitive Impairment – diagnosis

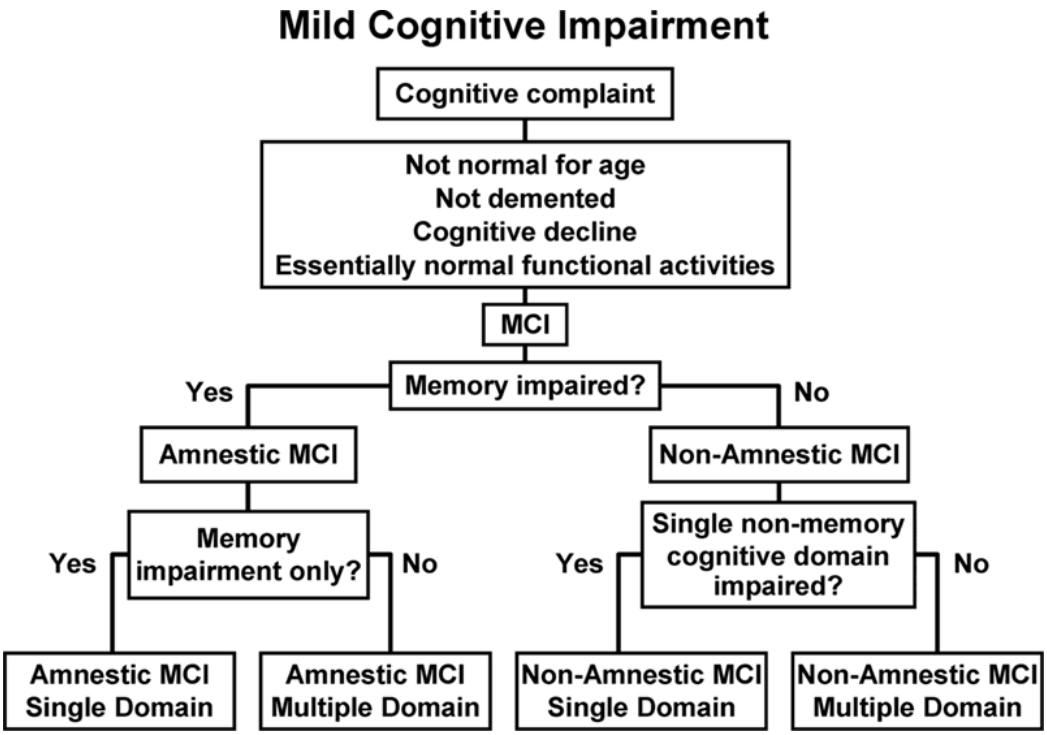
When individuals exhibit cognitive deficits that do not meet dementia criteria, they may be classified as having MCI or cognitive impairment no dementia (CIND). The rationale behind such classification is that MCI and CIND represent the early stages of dementia syndromes, and could thus be used to identify patients who are likely to progress to dementia over time. The construct of MCI, however, is still evolving, and according to the Canadian Consensus Conference on Dementia (CCCN), there is insufficient evidence to support widespread screening for MCI/CIND in unselected older people or individuals who lack dementia symptoms. Until more evidence is available, clinicians are generally advised only to maintain a high level of suspicion for dementia, and to follow-up on concerns of functional decline or memory loss reported by patients and caregivers [17]. Even in research settings, diagnoses of MCI or CIND may be made by clinical judgment after exclusion of dementia. This strategy was employed by both the CSHA and ACCORD studies, despite the fact that specific criteria for MCI have been developed [33].

2.5.6.1 Suggested diagnostic algorithms

Historically, diagnostic criteria for MCI called for the existence of subjective memory complaints and objective memory impairment in the absence of general cognitive dysfunction or interference with daily functioning. Although the

relevance of these criteria have held up over time, there has been increasing recognition that not all memory impaired individuals progress to dementia, and that dementia can develop from other clinical phenotypes. Such observations led to the identification of amnestic and nonamnestic MCI subtypes, for which criteria were developed at a 2003 international conference. The most current diagnostic algorithm breaks down the diagnosis of MCI even further, specifying not only the presence or absence of memory impairment, but also the number of domains with some degree of dysfunction (see Figure C). Still greater precision can be made by classifying MCI according to whether the etiology is presumed to be degenerative, vascular, psychiatric, or medical in nature [33]. Whether or not such diagnostic precision is clinically relevant, however, remains unclear, as data from the Canadian Study of Health and Aging (CSHA) indicated that use of specific diagnostic sets did not improve the prediction of dementia progression, relative to broader, more inclusive criteria [87].

Figure C. Current algorithm for diagnosing MCI and its subtypes [33]



2.7.6.2 Neuroimaging and potential biomarkers

An important issue in the diagnosis of MCI/CIND is the differentiation between patients whose deficits are precursors of dementia and those whose memory loss is more benign. In an attempt to address this issue (and more appropriately select patients for early treatment intervention), researchers have been looking for biomarkers that will predict which MCI patients will progress to AD and which will remain cognitively stable over time. To this end, urinary neural thread protein (NTP) has been targeted by a new diagnostic test (Nymox's AlzheimAlert) that has shown efficacy in detecting early AD [88]. Other promising diagnostic tools

include MRI measurements of hippocampal volumes, positron emission tomography (PET) imaging of glucose metabolism, and CSF measurements of total tau, phosphorylated tau, and Aβ42 [33,34,37]. In future, the novel PET tracer Pittsburgh Compound-B, which has been demonstrated to bind to cortical amyloid deposits in patients with AD [89], may facilitate diagnoses of AD at even earlier stages by identifying patients with Aβ plaques before the development of cognitive impairment. Another novel compound, 2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene) malononitrile (FDDNP), allows neuritic plaques and NFTs to be visualized by molecular imaging at preclinical stages [90].

2.6 EPIDEMIOLOGY

2.6.1 Dementia – epidemiology

2.6.1.1 Incidence and prevalence in Canada

The prevalence of dementia in 1991 was estimated at 8% among Canadians aged ≥65 years, with roughly half of dementia patients living in the community and half residing in institutional settings. As expected, the prevalence of dementia in Canada increased dramatically with age (see Table 15), exceeding 34% among persons aged ≥85 years [2] and reaching 58% by ages 95 years and older [23]. The percentage of females with dementia was generally similar to the percentage among men (8.6% vs. 6.9%), although the longer lifespan among Canadian

women translated into a far higher number of female vs. male dementia patients (171,400 vs. 81,200) [83]. When stratified by disease stage, prevalence rates were 2.3% for mild dementia, 3.1% for moderate dementia, and 2.6% for severe disease. The difference between males and females seemed to be particularly pronounced at moderate and severe dementia stages (see Table 16) [3].

Table 15. Age-standardized prevalence of dementia (all types) in Canada, by age and gender, 1991 [2]

Age Group	Men	Women	Total
65-74 years	1.9%	2.8%	2.4%
75-84 years	10.4%	11.6%	11.1%
85+ years	28.7%	37.1%	34.5%
Total	6.9%	8.6%	8.0%

Table 16. Prevalence of dementia (all types) in Canada, by gender and disease severity, 1991 [3]

Gender	Mild	Moderate	Severe
Men	2.1%	2.6%	1.4%
Women	2.4%	3.6%	3.5%
Total	2.3%	3.1%	2.6%

Between 1991 and 1996, the annual incidence of dementia in Canada was estimated at 2%, which translated into 60,150 new cases of dementia per year. As seen with prevalence rates, the incidence of dementia in Canada increased dramatically with age, but did not vary significantly according to gender (2.18% vs. 1.91%) [91]. When these figures were extrapolated to the population, researchers estimated that approximately 252,600 Canadians had some form of dementia in 1991, and that the prevalence would triple to reach an estimated 778,000 individuals over a 40-year period [2]. The most recent estimates provided by the Alzheimer Society of Canada [92] place the prevalence of dementia at 450,000 in 2006, with an additional 97,000 individuals expected to develop the condition in 2007. This rapid rise in dementia prevalence has exceeded the growth of general population, highlighting the need for more effective intervention [2].

2.6.2 Alzheimer's Disease – epidemiology

2.8.2.1 AD commonality and prevalence

Epidemiologists generally agree that AD represents the most common form of dementia, accounting for up to 75% of all dementia cases [93]. In Canada, AD was identified as a cause of dementia in 64% of cases identified by the CSHA, and in 77.9% of patients diagnosed in specialized referral centers [2,82]. The total age-standardized AD prevalence rate was calculated at 5.1%, indicating that 161,000 Canadian individuals had AD in 1991 [2]. Applying this rate to population

estimates, the prevalence of AD in Canada was reported at 279,000 in 2005 and projected to reach 509,000 by the year 2031 [2,94]. A substantial percentage of Canadians either know someone with AD (20-32%) or have a family member affected with the disease (21-26%) [92,95].

2.6.2.2 Rates of AD increase with age and female gender

As with dementia overall, the prevalence of AD increases substantially with age, with estimates ranging from 1% among Canadians aged 65-74 years to 26% among those aged 85 and older (see Table 17). In addition, there seems to be a marked variation in prevalence by gender, such that women are disproportionately affected [55]. In Canada, AD was estimated to affect 5.8% women aged ≥65 years, compared with 3.8% of men. This gender difference, which has also been observed in other nations, seems to be particularly pronounced at older ages, and stands in contrast to trends in VaD, which seems to predominate among men [2].

Table 17. Age-standardized prevalence of AD in Canada, by age and gender, 1991 [2]

Age Group	Men	Women	Total
65-74 years	0.5%	1.4%	1.0%
75-84 years	5.5%	7.8%	6.9%
85+ years	19.6%	28.8%	26.0%
Total	3.8%	5.8%	5.1%

2.6.2.3 Prevalence of AD in Canada and other countries

Prevalence rates of AD in the United States, Europe, and Asia are generally similar to rates reported in Canada. Pooled age-specific prevalence rates from 36 studies in these regions were as follows: 0.5% in people aged 60-65 years, 1.5% in those aged 65-69 years, 3% in those aged 70-74 years, 6% in thosee aged 75-79 years, and 12% in those aged 80-84 years [93].

There is some evidence, however, that the burden of AD in the US exceeds that in Canada, with figures indicating that AD affects 13% of US residents aged ≥65 years and 50% of those aged 85 years and older [96]. A study based on estimates among residents of Chicago, Illinois placed the US prevalence of AD at 4.5 million people in 2000, with a projected increase to 13.2 million by 2050 [97].

The fact that the prevalence of AD in Canada is roughly similar to or lower than that in other nations is interesting in light of the observed excess of dementia among Canadians. It has been speculated that this apparent discrepancy may be related to "an unusual balance" between AD and other dementia subtypes in the CSHA study. Worldwide, there appears to be a preponderance of AD in Caucasian populations (AD to VaD ratios = 3.3 in Canada, 3.0 in the UK, 2.0 in Italy, and 1.3 in Scandinavia), whereas VaD predominates in Asian nations (AD to VaD ratio = 0.6 in both Japan and China) [2].

2.6.3 Vascular Dementia – epidemiology

In comparison with AD, VaD has been the subject of far less epidemiological research. In fact, the CSHA is one of the few North American studies to publish population-based data specifically on VaD, yielding an age-standardized prevalence rate of 1.5% in the older Canadian population. Based on this rate, researchers estimated that 49,000 older Canadians had VaD in 1991, and that by 2031, VaD could affect as many as 144,000 Canadian residents [2].

Of all dementia cases identified in the 1991 CSHA, only 19% were attributed to VaD, indicating that VaD was 3.3 times less common than AD in the Canadian population [2]. Although not addressed specifically by this study, it has been suggested that "pure" VaD (i.e., VaD with no co-existing AD pathology) is even rarer than reported, perhaps accounting for less than 3% of all dementia cases [98]. Findings from the Canadian Collaborative Cohort of Related Dementias (ACCORD) study seem to support this contention, as a diagnosis of "pure" VaD was given to only 8.7% of Canadians presenting to a dementia clinic, whereas 18.7% were diagnosed with mixed dementia [82].

2.6.3.1 Rates of VaD

Like AD, the prevalence of VaD in Canada appears to increase with age, approaching 5% in the oldest subgroups. Unlike AD, however, VaD appears to be disproportionately common among men, despite the higher number of females in the elderly population. In the CSHA, age-standardized prevalence rates were calculated at 1.9% among men, compared with 1.2% among women. The greatest gender discrepancy was observed in the subgroup aged 75-84 years, where VaD was estimated to affect 3.1% of men, but only 1.9% of women (see Table 18) [2].

Table 18. Age-standardized prevalence of VaD in Canada, by age and gender, 1991 [2]

Age Group	Men	Women	Total
65-74 years	0.8%	0.4%	0.6%
75-84 years	3.1%	1.9%	2.4%
85+ years	5.2%	4.6%	4.8%
Total	1.9%	1.2%	1.5%

2.8.3.2 Incidence of VaD

Between 1991 and 1996, the CSHA identified 97 new cases of VaD among 8,623 Canadian residents, yielding an annual incidence rate of 0.25% when only

survivors were taken into account, and 0.38% when deaths during follow-up were also considered. The overall incidence of VaD was slightly higher in men than in women, and increased with age in persons of both genders (see Table 19). Extrapolating these data to the general population, it was estimated that 7,355 to 11,062 new cases of VaD developed during the five-year period [99].

Table 19. Annual incidence of VaD by age and gender, as estimated among survivors only and both survivors and decedents [99]

Age Group	**Women**		**Men**	
	Survivors	**Deaths included**	**Survivors**	**Deaths included**
65-69 years	0.07%	0.14%	0.12%	0.22%
70-74 years	0.07%	0.11%	0.31%	0.46%
75-79 years	0.38%	0.70%	0.35%	0.66%
80-84 years	0.53%	0.73%	0.53%	0.71%
85+ years	0.68%	0.93%	0.66%	0.83%
TOTAL	0.23%	0.35%	0.28%	0.42%

The 1.5% prevalence reported in Canada appears to fall at the lower end of the range reported in other countries [15], including the US, where prevalence of VaD among individuals aged 71 years and older has recently been estimated at 2.48% [100]. With regard to incidence, however, Canadian rates appear to fall in the middle range, exceeding those reported in France, Sweden, and the Netherlands, but lower than those found in the UK, Germany, Taiwan, and Japan (see Table 20) [101].

At present, it is unclear whether the apparent geographical variation in VaD incidence is result of genetic and/or environmental influences, or whether it reflects differences in study methodology and diagnostic criteria [101]. The fact that VaD appears to represent 50% of all dementias in Japan (compared with 4-20% in the Western world), however, has led to speculation that the excess of hypertension and stroke in Asia may lead to a disproportionately high occurrence of VaD in the Japanese population [15]. Alternately, researchers have pointed to increased rates of small vessel disease as contributing to the higher frequency of VaD observed in Blacks, Hispanics, and Asians [55].

Table 20. Age-standardized incidence ratios (SIRs) for VaD in Canada vs. other countries, as calculated from studies that did and did not include deaths during follow-up [101]

Methodology	**Country**	**SIR**
Survivors only*	Canada	Reference
	Taiwan	1.79
	China	1.40
	UK	2.68
	France	0.83
	Japan	1.58
Deaths included**	Canada	Reference
	Sweden	0.71 to 0.82
	The Netherlands	0.42
	Germany	1.23
	China	0.87

2.6.4 Mixed Dementia – epidemiology

While AD is widely accepted as the most common form of dementia, there is increasing consensus that AD often overlaps with other dementia subtypes, including VaD and frontotemporal dementia. According to autopsy studies, nearly

half of all dementia patients in the US and Europe have more than one form of the disease, with 11% of dementia cases attributed to a combination of AD and VaD (see Table 21) (Barker et al, 2002). Moreover roughly 50% of AD patients exhibit CVD on neuropathological assessment, and the majority of VaD patients show some degree of degenerative pathology [4,34]. The relatively common categorization of mixed dementia as VaD in epidemiological studies may have resulted in inflated estimates of VaD prevalence and a reduced appreciation for the concurrent influence of AD pathology.

Table 21. Distribution of "pure" and mixed dementia subtypes among 382 dementia patients in the State of Florida Brain Bank, 2004 (Barker et al, 2002)

Subtype		**Percentage of All Dementia Cases**
"Pure" Dementia (58%)	AD	42%
	VaD	3%
	Other subtypes	13%
Mixed Dementia (42%)	AD + VaD	11%
	AD + other subtype(s)	21%
	VaD + other subtype(s)	1%
	AD + VaD + other subtype	2%
	Other combinations	7%

2.8.4.1 Lack of data on mixed dementia in Canada

Although the exact frequency of mixed dementia in Canada has not been established, estimates from an autopsy study in the US place the prevalence of mixed AD/VaD at 23% of dementia patients [102]. In Canada, it is noteworthy that 18.7% of patients presenting to a dementia clinic in the ACCORD study were

diagnosed with mixed AD/VaD, and that the prevalence of mixed AD/VaD was almost three times higher in subjects aged >70 years than in younger patients. The relatively high estimates of mixed AD/VaD in the ACCORD study suggest not only that AD and VaD pathologies are more likely to exert a combined influence at older ages, but also that the process of referral to a dementia clinic may facilitate the often challenging mixed diagnoses [82].

2.6.5 Mild Cognitive Impairment– epidemiology

2.6.5.1 Prevalence

Although there are presently no data on the epidemiology of MCI in Canada, the CSHA investigated the prevalence of a related construct, CIND, and found that 16.8% of Canadians aged ≥65 years (21.3% of males; 13.5% of females) had cognitive dysfunction that did not meet dementia criteria [3,61]. In the ACCORD study, an even higher rate of CIND was found, such that 30.1% of Canadians presenting to a dementia clinic received a CIND diagnosis. The difference in CIND prevalence across the two studies suggests that CIND is more likely to be detected at a specialty center than in general practice [82].

Of note, the relative prevalence of CIND and dementia in the ACCORD sample varied markedly by age, such that rates of CIND exceeded those of dementia until the age of 60 years. The decreasing prevalence of CIND with age suggests that older individuals may tolerate a higher level of cognitive impairment before

seeking referral to a specialty clinic. Thus, public education may be needed to increase the likelihood that older persons will seek treatment at an early stage of cognitive decline, when treatment is most likely to be effective [82].

2.6.5.2 Variation in estimates of prevalence and progression

Although CIND and MCI are not synonymous constructs, the rates of CIND reported in the Canadian studies are in line with those reported for MCI in other populations. Across studies, estimates of MCI prevalence have varied widely, ranging from 5% to 25% among community dwelling individuals and from 6% to 85% in clinical settings [37]. A similar variation has been found in rates of conversion from MCI to dementia, which range from 5% to over 35% per year, depending on the criteria used to define MCI. Although progression to dementia is more common among MCI patients than in cognitively normal controls (1% to 7% annually), it is important to note that not all patients with MCI exhibit further decline. In fact, within the CSHA cohort, roughly 33% of subjects classified with CIND showed an improvement in cognitive status after five years of follow-up. Still, the rate of incident dementia among Canadians with CIND was more than three times higher than that of other individuals, suggesting that CIND is a precursor to more serious cognitive dysfunction (Linsday et al, 2004).

2.7 RISK FACTORS

The risk of dementia is generally thought to stem from the combined effects of many factors, including age, genetics, lifestyle, and medical and environmental features, many of which have been associated with both degenerative and vascular pathology. Because of its multifactorial nature, the task of identifying risk factors for dementia is a complicated one, with relative risks varying in accordance with the criteria used for study inclusion. To the extent that researchers aim to identify predictors of discrete dementia subtypes, it is imperative to select homogeneous samples for case-control studies. Given that many studies misclassify mixed dementia as either pure AD or VaD, caution must be used in assuming that the influence of a particular risk factor is on AD, VaD, or both (Alzheimer's Society of Canada, 2006).

Beyond these concerns, research on dementia risk is hampered by the fact that cognitively impaired individuals, almost by definition, have difficulty remembering and reporting accurate historical information. Because traditional interview-based approaches to obtaining history will not be useful in this population, alternative strategies are clearly needed. In the CSHA, researchers addressed this problem in two ways: first, by conducting baseline case-control analyses using retrospective data provided by informants; and secondly, by prospectively following non-demented subjects over five years to identify baseline predictors of incident dementia. Among the variables assessed by the

CSHA were medical history, family history, and health behaviors, as well as exposures to a range of substances [83].

Findings from the CSHA point to a number of factors that may influence the risk of VaD as defined by ICD-10 and NINDS-AIREN criteria (see Table 22 and Table 23). In many cases, the identified variables were similar to established risk factors for AD, including low education, ApoE genotype, heart disease, hypertension, and exposure to fertilizers and pesticides [2,99,103].

Although not specifically supported by CSHA findings, a number of other risk factors have been identified as common to AD and CVD (e.g., hypertension [104-106], hyperhomocysteinemia [107], systemic inflammation [108], smoking [109], diabetes [110,111], obesity [112,113], and the metabolic syndrome [114,115]), thus supporting the overlap between degenerative and vascular pathologies. While it is possible that these vascular factors play a causal role in the development of AD pathology, it is equally likely that they induce cerebrovascular pathology, thereby lowering the threshold at which plaques and NFTs will lead to dementia [34].

Table 22. Risk factors for prevalent VaD, as identified in a baseline case-control analysis of CSHA subjects [103]

Risk Factor		**Odds Ratio**
High blood pressure	High systolic	0.58
	High systolic + diastolic	1.42
	Normal	reference
Orthostatic hypotension		1.29
History of arterial hypertension		2.08*†
Cardiac symptoms		1.35
Body mass index	<20	2.02
	20-<25	reference
	25-<27	1.02
	27+	1.12
Medical history	Head trauma	1.50
	Alcohol abuse	2.45*
	Smoking	0.78
	Diabetes	1.67
	Arthritis	0.67†
	Heart condition	1.71*
	Migraine	1.45

Risk Factor		**Odds Ratio**
Current drug use	Aspirin	3.10*
	NSAIDs	0.71†
Occupational exposure	Pesticides and fertilizers	2.60*†
	Liquid plastics or rubbers	2.59*
Education	0-6 years	4.06*†
	7-9 years	1.28
	10+ years	reference

*Denotes statistical significance

†Designates those variables that were significantly associated with AD in either the CSHA case-control or prospective risk factor analysis [2,83]

Table 23. Risk factors for incident VaD, as identified in a prospective case-control analysis of CSHA subjects [99]

Risk Factor		**Odds Ratio**
Sex (male)		1.02
Rural residence		2.03*
Living in an institution		2.33*
ApoE4 allele		2.34*†
Diabetes		2.14*
Depression		2.41*
High blood pressure	Men	0.86
	Women	2.05*
Heart condition	Men	2.52*
	Women	0.71
Current or previous aspirin use		2.33*
Estrogen replacement therapy		0.25
Shellfish consumption (at least once per month)		0.46*
Regular exercise	Men	1.24†
	Women	0.46*†
Smoking (nearly every day)	Cigarettes	0.83
	Cigars	0.20*

Alcohol use (at least once a week)	Beer	0.66
	Wine	0.72†
	Spirits	0.88
Occupational exposure	Pesticides or fertilizers	2.05*†
	Plastic or rubbers	1.75

*Denotes statistical significance

†Designates those variables that were significantly associated with AD in either the CSHA case-control or prospective risk factor analysis [2,83].

2.7.1 Demographic Factors

2.7.1.1 Age

Of all the proposed risk factors for cognitive decline, age is almost universally regarded as the most important, with significant effects seen across all dementia disorders [34,37]. For each increasing year of age, the risk of VaD may increase by a factor of 5%, with an additional 18% increase observed in AD risk [99,116]. Given the rapid aging of the population, the risks conferred by advancing age could lead to a tremendous increase in dementia prevalence.

Although the association between age and dementia is largely undisputed, findings from the third wave of the CSHA indicate that this is not a simple relationship, and that cognitive decline is by no means a universal consequence of

aging. In fact, of the elderly non-demented individuals who participated in the CSHA, nearly 50% showed almost no change in cognitive status over a 10-year period. In addition, the CSHA found no impact of age on cognitive decline among subjects who had already developed dementia, indicating that older dementia patients do not progress more rapidly than do younger subjects. Although this finding of the CSHA has been replicated in some studies, it has been contradicted by others, leaving the question of how age impacts cognition after onset of dementia open to further research [83].

2.7.1.2 Gender

The impact of gender on dementia risk remains controversial, with some (but not all) studies pointing to an increased risk of AD among females and a preponderance of VaD among men [37]. In Canada, the risks associated with AD and VaD appear to be similar in men and women, and while the CSHA provided some evidence of faster cognitive decline in female subjects, the association between sex and cognitive decline was only seen in the institutionalized subgroup [83,99,116].

2.7.1.3 Low education

Low educational attainment has been identified as a risk factor for dementia in numerous studies, including the CSHA [2] and a case-control study conducted in Manitoba, Canada [116]. Such findings provide evidence that educational or

occupational attainment may provide a "cognitive reserve" against the clinical manifestation of the neuropathologic changes of AD [117]. Although most of the literature focuses on the link between education and AD [118], an association with VaD has also been documented, suggesting that education may lead to increased brain density and a subsequently higher threshold for brain injury-induced cognitive impairment in this condition as well [119].

2.7.2 Genetic Factors

2.7.2.1 Family history

Family history is often cited as a major risk factor for AD, with some evidence suggesting a two- to four-fold increase in AD risk among individuals with a family history of the disease [37]. Not all research, however, supports this conclusion, as an association between AD and a family history of dementia was found in the CSHA baseline analysis, but not in the prospective incidence study [83].

2.7.2.2 Apolipoprotein E4 genotype

A polymorphism in the apolipoprotein (ApoE) gene is an established risk factor for sporadic, late-onset AD, with up to 50% of cases attributed to the presence of the ApoE ε4 allele [120]. Given the strength of the association between AD and this polymorphism, recent research has focused on determining: (1) whether the ApoE

ε4 allele can be used to predict the development of non-AD dementias, and (2) whether ApoE ε4 genotype is a predictor of MCI-to-dementia progression.

Over the past few years, researchers from the CSHA have attempted to answer these questions, finding that the risk of VaD (but not VCI) is increased in ApoE ε4 allele carriers and that the ApoE genotype can predict progression from CIND to AD (but not VaD) dementia (see Table 24) [121,122].

In line with the CSHA analyses, the ACCORD study also investigated the impact of the ApoE4 genotype and found significantly increased risks of AD (odds ratio 6.3), VaD (odds ratio 7.4), amnestic CIND (odds ratio 3.2) and VCIND (odds ratio 3.4) among ApoE ε4 allele carriers. Notably, ACCORD data indicate that the proportion of ApoE ε4 alleles increases across the spectrum of normal cognition to CIND to dementia, supporting CIND as an intermediate stage between normal aging and significant cognitive deterioration [82]

Table 24. The impact of ApoE ε4 genotype on the 5-year incidence of AD and VaD among older Canadians with normal cognition (n = 1173) or CIND (n = 296) at baseline [122]

Baseline Status	Incident Diagnosis	Adjusted OR
Normal	AD	2.89
	VaD	3.13
CIND	AD	2.69
	VaD	NS

Overall, the data strongly support a link between the ApoE polymorphism and dementia development, suggesting that genetic testing could be used to identify individuals at increased risk of not only AD, but VaD as well. According to the CCCD, however, more information is needed before widespread ApoE screening can be recommended for either symptomatic or asymptomatic individuals. As such, the CCCD currently advocates that genetic testing be performed only when a patient's family history is consistent with autosomal dominant disease, or when an individual without such a history requires further reassurance or assistance.

2.7.3 Vascular Risk Factors

Among the most important risk factors for dementia development are those that also confer an increased risk of future vascular events. The influence of such vascular risk factors, which include hypertension, dyslipidemia, and smoking, has been studied both individually and cumulatively, with varying results. Logically, theories regarding the etiologies of AD and VaD would suggest that vascular risk factors would be more important in VaD development. On the other hand, the frequent co-occurrence of AD and VaD pathologies would anticipate a substantial overlap in vascular risk profiles across dementia subtypes. Support for both hypotheses may be found in a secondary analysis of the CSHA, which investigated the influence of a "vascularity index score" (i.e., the cumulative number of vascular risk factors present) on the risks of AD and VCI, which by definition included mixed dementia cases. According to this analysis, higher scores on the vascularity index conferred an increased risk of VCI, but not AD, suggesting that the influence of vascular factors may be reduced in AD when there is no vascular component [121].

2.7.3.1 Stroke

Data from epidemiological, clinical, and neuropathologic research all support a link between stroke and dementia or cognitive impairment, which might be expected given that stroke is an etiological cause of some VaD subtypes. According to experts, approximately 76% of patients with VaD and 56% of those

with VCI have experienced at least one infarction. This rate is far higher than the 5-7% incidence reported in AD patients, supporting stroke as an important predictor in differential diagnosis [15].

The likelihood of developing dementia within one year of index stroke may vary by age, ranging from 5.4% in patients aged >60 years to 10.4% in those aged >90 years. In the case of lacunar stroke, the risk of dementia may be even more pronounced, occurring at a rate of up to 23% within four years [119]. Other potential predictors of dementia among stroke patients include lower education, cortical atrophy, diabetes mellitus, African American race, comorbid disorders associated with hypoxemia (e.g., seizures and cardiac arrhythmia), ApoE ε4 genotype, and previous atherosclerosis or vascular disease [15].

2.7.3.2 Dyslipidemia

The term dyslipidemia refers to abnormalities in serum lipid levels, such as elevated low-density lipoprotein (LDL) cholesterol, reduced high-density lipoprotein (HDL) cholesterol, and elevated triglycerides, any of which can trigger the development of atherosclerosis and vascular disease. As with other vascular conditions, dyslipidemia appears to be a risk factor for both AD and VaD [15], with one study showing a three-fold increase in the risk of either "pure" VaD or mixed AD/VaD among elderly persons with elevated total or LDL cholesterol [119].

Although the mechanism linking dyslipidemia to dementia remains unclear, the impact of cholesterol on Aβ deposition is a prime suspect, with in vitro studies showing a marked inhibition of Aβ production following reduction of cholesterol levels [123,124]. Such research, as well as a meta-analysis of seven observational studies that documented reduced risks of cognitive impairment among statin users [125], suggests that lipid-lowering medications may be useful in dementia prevention [126]. However, no significant benefits of statins on cognitive endpoints were found in the recently reported LEADe trial of atorvastatin [127] or the PROSPER trial of pravastatin [128]. The impact of other statins on dementia risk is currently the subject of several major research projects [129].

2.7.3.3 Hypertension

Hypertension is an important risk factor for CVD and may also play a role in dementia development. The impact of hypertension, however, may vary according to dementia subtype, with the risks of AD or mixed dementia appearing to be most greatly affected [119]. With regard to "pure" VaD, the role of hypertension has been described as controversial, as not all studies have shown a connection [15]. In the CSHA, hypertension predicted an increased risk of VaD among women (odds ratio 2.05), but had no such effect in men [99]. In addition, several studies have shown a decline in blood pressure before dementia onset in AD patients, whereas no such change was observed prior to VaD onset [119].

According to some researchers, the association between hypertension and dementia may be a result of a hypertension-induced development of white matter lesions [130], which are common in age-related dementias [131]. Protection against dementia development has been found with some antihypertensive drugs, but there is currently disagreement over which class of antihypertensive is most effective for reducing dementia risk [132].

2.7.3.4 Heart disease

Coronary artery disease and myocardial infarction represent two additional vascular factors that have been linked to dementia risk in some studies. For example, among residents of Manitoba, Canada, neither heart attack nor other heart conditions was significantly associated with AD [116]. Moreover, with regard to VaD, the CSHA found the effects of heart disease to be gender-specific, reaching significance only in male subjects (odds ratio 2.52) [83,99].

2.7.3.5 Diabetes

Diabetes is not only an established risk factor for heart disease and stroke, but may also lead to the development of AD, VaD, and VCI [99,133]. In the CSHA, diabetes was associated with relative risks of 1.62 for VCI, 2.03 for VaD, and 1.68 for VCIND, but appeared to have no impact on the incidence of AD, mixed AD/VaD, or all dementias [133]. Further support for a link between diabetes and dementia was found in a 24-week treatment study in which the diabetes drug

rosiglitazone appeared to prevent cognitive decline among patients diagnosed with MCI or very mild AD. Although the mechanism behind the drug's neuroprotective benefits is unclear, it is possible that the rosiglitazone alters Aβ processing, either by reducing inflammation [134] or by modulating insulin activity [135].

Several hypotheses have been put forth to explain the link between diabetes and dementia. First, it has been suggested that diabetes induces micro- and macrovascular changes that trigger a reduction in cerebral blood flow and subsequent cognitive decline. Second, hyperglycemia has been implicated as having either direct effects on neuronal death or indirect effects through increased production of a substance associated with amyloid deposition, tau formation and oxidative stress. Finally, it has been speculated that insulin is essential for neuronal growth, and that the insulin changes associated with diabetes disrupt the normal neurogenesis process [119]

2.7.3.6 Systemic inflammation

A role for systemic inflammation in dementia development is supported by several lines of evidence, including epidemiological studies linking inflammatory biomarkers (e.g., C-reactive protein) to both CVD and AD [136,137], as well as experimental data indicating that AD pathology can trigger inflammatory processes that lead to neuronal damage [138]. Based on such findings, some

researchers believe that CRP and other markers of inflammation may be useful in predicting dementia risk [139]. Support for this theory was provided by the Honolulu Heart Disease Study, which found increased risks of both AD and VaD among Japanese-American men with elevated high-sensitivity CRP in mid-life [140]. Of note, the association between CRP and dementia was found to be independent of cardiovascular disease, as well as other vascular risk factors [140].

2.7.3.7 Metabolic syndrome

The term "metabolic syndrome" refers to a constellation of symptoms—obesity, low serum HDL cholesterol, higher serum triglycerides, hypertension, and elevated blood glucose—that appear to directly promote the development of atherosclerotic disease [141]. Given that many of the symptoms of this syndrome are known risk factors for dementia [132] and vascular diseases [141], it is not surprising that the metabolic syndrome represents an important predictor of not only AD [114,115], but also silent infarctions [142,143], which are associated with an increased risk of dementia and a decline in cognitive function [144]. Recognition that chronic inflammation is an integral component of the metabolic syndrome [145] provides further support for inflammation as a treatable target for dementia prevention.

2.7.3.8 Smoking

Although smoking is frequently cited as a predictor of VaD risk, the evidence supporting this association comes primarily from retrospective studies, and cannot

be considered conclusive [15,119]. When prospective data are considered, the impact of smoking on VaD appears to be minimal at best, with CSHA findings showing no correlation at all between smoking and the risk of VaD [83]. With regard to AD, an analysis of three additional Canadian datasets failed to find an effect of smoking after adjustment for confounding variables. It has thus been suggested that any association between smoking and AD may be limited to specific subtypes [146].

2.7.3.9 Head injury/Brain atrophy

Head injury and reduced brain size have also been cited as independent risk factors for AD, although the impact of head injury on AD risk failed to reach statistical significance in either the CSHA (odds ratio 1.66) or another population-based Canadian study (relative risk 1.59) [116,147]. With regard to brain size, it has been speculated that people with larger brains have a reduced risk of AD because they have more neurons to lose before symptoms occur. This hypothesis may also explain the putative link between AD and early cognitive ability, as individuals with lower intelligence may have smaller brains, fewer synaptic connections, and slower neurotransmission. [34,37].

2.8 PSYCHOSOCIAL BURDEN

By definition, the cognitive impairments associated with dementia are not benign, but rather carry a vast range of negative consequences, including functional disability, psychiatric disturbances, and ultimately death. As the cognitive symptoms of dementia increase, so too does the burden of illness, such that patients in the later stages of disease may require assistance for even the most basic everyday activities, including bathing, dressing, eating, and use of the toilet. Importantly, the burden associated with dementia may begin long before full symptom development, when patients are exhibiting only minor cognitive deficits [87]. By the time the final stages of dementia are reached, which may occur only a few years after symptom onset, individuals are often bedridden, having completely lost the ability to communicate and/or recognize loved ones [96]. Clearly, such deficits place tremendous financial and emotional strain on family members, who are often called upon to provide informal care and/or pay for residential treatment. The costs of dementia are thus far-ranging, impacting not only patients, but also family, friends, and society at large.

2.8.1 Disease progression

Although the course of dementia may vary according to patient characteristics and pathological subtypes, none of the dementia disorders can presently be considered curable, and no effective strategies currently exist for stopping or slowing long-term decline. This means that even though some patients may lead active and

fulfilling lives long after a dementia diagnosis, the ultimate prognosis is poor, regardless of disease subtype. For most patients, the duration of dementia ranges from three to ten years [37,96], with VaD portending a shorter survival [148].

For individuals with a diagnosis of MCI or CIND, outcomes are only slightly improved, and the likelihood of a progressive deterioration in cognitive and functional status is high. For example, even though a diagnosis of VCIND was associated with less progression in the CIVIC study, relative to VaD or mixed dementia, VCIND patients still exhibited an increased risk of progression, compared with matched controls [35]. Similar trends were observed in the CSHA, in which 47% of CIND patients who survived five years progressed to dementia during this time. The rate of progression in the CIND subgroup represented a 5.3-fold increase over that observed in cognitively normal controls [87].

2.8.2 Mortality

2.8.2.1 Dementia as a leading cause of death

Dementia is associated with a shortened life expectancy, and is cited as one of the leading causes of death in Canada, the US and worldwide. With regard to AD specifically, data from the Centers for Disease Control and Prevention (CDC) in the US place AD as the 7th leading cause of death for Americans of all ages, and the 5th leading cause for Americans aged 65 years and older. Importantly, the impact of AD on mortality appears to be on the rise, as the number of AD-

associated deaths in the US increased by 32.8% between 2000 and 2004, and may actually have been underestimated, given that many AD patients have co-existing medical conditions. Regardless of actual numbers, survival among AD patients appears to be reduced in all age groups, compared with the general population [96].

2.8.2.2 Mortality risks

According to data from the CSHA, the median survival among Canadians with dementia was only 3.3 years, with VaD conferring a 16% increase in the risk of death, relative to an AD diagnosis [148]. In comparison with cognitively normal individuals, mortality risks were increased not only among dementia patients, but also in those with a CIND diagnosis [87]. When stratified by residence and gender, the risks associated with CIND and dementia appeared even greater in institutional settings, particularly among female subjects (see Table 25). These findings from the CSHA are in line with other data suggesting that MCI-related mortality may be double that of the population having no cognitive impairment [37].

Table 25. Age-adjusted mortality ratios among CSHA subjects by residence, gender, and cognitive status [149]

Residence	Cognitive Status	Mortality Ratio	
		Men	**Women**
Community	Normal	1.0	1.0
	CIND	1.95	2.17
	Dementia	2.84	2.64
Institution	Normal	1.0	1.0
	CIND	3.09	3.52
	Dementia	5.02	6.03

2.8.2.3 Risk of mortality after stroke

The association between mortality and cognitive decline appears to apply not only to the general elderly population, but also to patients with a history of stroke. As seen in a US study, individuals who exhibited cognitive decline after stroke had increased risks of death, relative to cognitively stable stroke patients, regardless of whether cognitive decline was defined as low MMSE scores (relative risk 3.99), "post-stroke dementia" (relative risk 3.11), or either "post-stroke dementia" or AD with CVD (relative risk 3.22) [150]. Given that these categories all resemble VCI subtypes, such data suggest that the construct of VCI may be an important predictor of mortality following an index stroke.

2.8.3 Nursing home placement (NHP)

Because dementia by definition is associated with functional impairment, the risk for dependency is high, particularly at later disease stages. When the amount of assistance required by a dementia patient exceeds that available in the community, placement in a nursing home or other institutional facility becomes inevitable. In the US, an estimated 25-50% of all elderly users of hospitals, nursing homes, assisted living, home care, and adult day services carry a dementia diagnosis. Given that most US dementia patients do not have the financial assets to pay for even one month of nursing home care, Medicaid costs for nursing home residents with dementia are projected to rise from $21 billion in 2005 to $38 billion by 2025 [96].

2.8.3.1 NHP risks

The association between dementia and institutionalization is a well-recognized phenomenon, with increased risks of nursing home placement (NHP) seen in nearly all dementia subtypes and at all levels of disease severity. In the CSHA, the presence of any cognitive impairment was associated with a 29-fold increase in NHP risk, relative to normal cognition, while a diagnosis of AD increased the risk of institutionalization by a factor approaching 15 [151]. Among Canadians with VCI, the percentage of patients requiring long-term residential care ranged from 41.4% to 92.8% in the most severe stages, with increased risks of institutionalization seen in all VCI subgroups, including VCIND [35,152]. In the CSHA, rates of NHP

over five years of follow-up were 29% among patients with baseline CIND versus 14% in cognitive normal individuals [87]. The 2.5-fold increased risk observed in this analysis was in line with the two- to three-fold risk increase reported in MCI patients [37].

With regard to differences in NHP across dementia subtypes, there is some indication that risks may be increased in AD [61] and reduced in acute-onset patients who have a higher likelihood of vascular risk factors and/or a VaD diagnosis [153].

2.8.4 Disability

Related to the need for institutional care, the inability to attend to ADLs and instrumental ADLs (IADLs) is a common consequence of cognitive decline. According to a study conducted in the US, more than 69% of patients with probable AD may no longer be able to dress, groom, or wash themselves within 5 years of diagnosis, and roughly 68% may require care equivalent to that provided in long-term residential settings (Holtzer et al, 2003).

In another study of Medicare beneficiaries, 81% of all patients with AD or other dementia were found to be dependent in at least one ADL, with 32% exhibiting impairment in all activities. Importantly, the degree of functional impairment corresponded with both healthcare costs and risks of NHP in this population,

indicating that functional decline is a particularly important consequence of dementia [154].

2.8.5 Depression

Symptoms of depression may be present in as many as 63% of AD patients, with up to 20% exhibiting major depressive disorder [17]. In the CSHA, the prevalence of major depression was 3.2% for AD and 21.2% for VaD, indicating that depression is over eight times more common among VaD patients [155]. Data from the CIVIC study support these findings, indicating the progression of depressive symptoms over time may be significantly more frequent in patients with VCI (30%) than in those with AD (15%) or normal cognitive functioning (12%). The likelihood of progression of depressive symptoms does not appear to differ according to VCI subtype [35].

2.10.6 Behavioral disturbances

Behavioral signs and symptoms are a common manifestation of dementia, occurring in up to 90% of dementia patients and frequently contributing to increased caregiver distress [17]. In the CIVIC study, behavioral problems were identified in 55% of patients with VCI or AD, compared with 33% of those with normal cognitive functioning. Disturbances in judgment were common in both VCI (31%) and AD (22%), as were disruptions in other executive domains (39% for both subtypes), which contradicts the assumption that executive dysfunction is

a hallmark of VCI. Of the VCI subtypes, VCIND was associated with a lower incidence of behavior symptoms (43%), relative to patients with VaD or mixed dementia (64%) [35].

2.8.7 Comorbidities

Given that dementia is an illness of aging, the co-occurrence of other aging-related medical conditions among dementia patients is high, leading to increased costs and service utilization. In a sample of 25,109 Medicare beneficiaries aged ≥65 years with an AD diagnosis or at least one claim for an AD-specific drug, almost 95% had at least one medical comorbidity, with 35.4% exhibiting six to10 comorbid conditions, and 28.8% carrying 11 or more comorbid diagnoses [156,157]. Notably, comorbidity rates were higher for AD patients versus controls in almost all medical categories, including diabetes (odds ratio 1.21), heart conditions (odds ratio 1.16), and cerebrovascular (odds ratio 2.60), neurological (odds ratio 2.32), mental (odds ratio 5.08), and cognitive disorders (odds ratio 155.72) [156,157]. Such increased comorbidity rates may contribute to more frequent hospitalizations and increased rates of NHP among dementia patients [157-159].

2.8.8 Caregiver Burden

One of the most important issues associated with dementia is the burden that it places on caregivers. In Canada, family members and friends are the primary source of care for community-dwelling AD patients, and may also provide

significant assistance to AD patients living in institutional settings. In most cases, one person (typically a spouse or adult child) assumes the majority of caretaking responsibilities, which may include assisting the patient with basic activities, providing emotional and financial support, and mediating with other service providers. Primary caregivers in Canada provide an average of 19 more hours of informal support to AD patients than to nondemented elderly individuals [160].

2.8.8.2 Physical and psychological consequences of caregiving

Beyond the financial burden associated with caregiving, persons who provide care to dementia patients may also experience declines in physical and psychological health. Depression is reported by as many as 30% of AD caregivers, and may be particularly prevalent in caregivers with low social support. Because of the consuming nature of caretaking, many caregivers have little time or energy for social interactions and recreational activities, leading to a reduction in quality of life. In the US, providing care to dementia patients has been shown to be more stressful than caring for nondemented elderly persons [96], and in Canada, health problems have been identified more frequently among persons caring for dementia patients than among caregivers of healthy elders [83]. Key predictors of negative caregiver outcomes include the frequency of behavioral problems (e.g., aimlessness and aggression) exhibited by the care recipient, as well as the certain personality traits and a lack of social support [151,160].

2.9 ECONOMIC BURDEN

2.9.1 Canadian Cost Estimates

Beyond the clinical burden to patients, AD and other dementias impose tremendous financial strain on caregivers, as well as federal and state budgets. In Canada, the annual net economic cost of dementia was estimated at over $3.9 billion (or $13,900 per patient) in 1991 [161], with projections totaling $5.5 billion by the year 2000 [92]. These figures, which reflect the difference in costs incurred by CSHA subjects with and without dementia, represent the sum total of direct expenditures for drugs, hospitalization, institutional care, and research, combined with indirect cost estimates for unpaid services provided by informal caregivers (see Table 26). What is not reflected, however, are the indirect costs associated with missed work or the unquantifiable burden associated with emotional distress. In addition, because conservative cost values were used in categories that precluded direct measurement, it is likely that this research underestimates the true costs of dementia, and that Canadian society actually spends far more on dementia each year [161]. In fact, the Alzheimer Society of Canada predicts that AD and related dementias "may prove to have the highest economic, social, and health cost burden of all diseases" over the next 25 years [92]

Table 26. Net annual costs of dementia in Canada, 1991 [161]

Population	**Source of Costs**		**Net cost per patient**	**Total annual net cost**
Elderly dementia patients	Community-based services	Paid services	$4,970	$615 million
		Unpaid services	$5,130	$635 million
		Subtotal	**$10,100**	**$1.25 billion**
	Long-term care		$19,100	$2,180 million
	Drugs		$240	$60.6 million
	Hospitalization*		$0	$0
	Diagnosis		$250	$13.5 million
	Subtotal		**$13,900**	**$3.5 billion**
Younger dementia patients**				$389 million
Research***				$9.8 million
Total				**$3.9 billion**

* There was no significant difference in hospitalization days between dementia patients and controls.

** Based on the assumptions that 9-25% of AD patients are aged <65 years, and that costs for younger and older dementia patients are equivalent.

*** Based on the actual costs of dementia-related research conducted in Canada during 1991-1992

2.9.1.2 Cost variations by subtype and disease severity

Whereas the analysis set forth above focused on the net costs of any dementia (without consideration for cost differences across disease subtypes), a subsequent study investigated the costs associated specifically with VCI in the Canadian population. Once again using data from the CSHA, researchers found that the societal costs of VCI exceeded those of AD at the mild stage of disease, but were lower than those of AD among patients who had mild-to-moderate, moderate, or severe dementia (see Table 27) [152]. The generally higher costs observed in Canadian AD patients are line with reports from the US, which rank AD (but not VCI) among the top 10 most expensive illnesses [37].

Table 27. Mean annual per patient costs of VCI and AD by disease severity [152]

Dementia subtype	**Source of costs**	**Disease Severity**			
		Mild	**Mild-to-Moderate**	**Moderate**	**Severe**
VCI	Long-term care	$6,708	$7,944	$13,728	$31,104
	Community services	$2,184	$1,125	$1,728	$580
	Medications, physician fees	$310	$299	$299	$287

Dementia subtype	Source of costs	Disease Severity			
		Mild	**Mild-to-Moderate**	**Moderate**	**Severe**
	Unpaid net supervision time	$1,584	$468	$792	$948
	Unpaid direct care time	$4,236	$4,632	$3,516	$1,596
	TOTAL	$15,022	$14,468	$20,063	$34,515
AD	TOTAL	$9,451	$16,052	$25,724	$36,794

As reflected in the table above, the costs of VCI increase in direct proportion to disease severity, ranging from an annual $15,022 per Canadian with mild VCI to $34,515 per patient with severe cognitive deficits [152]. Similar trends have been found in studies of patients with AD and any dementia, with data from the multicenter Predictors study demonstrating a 13% annual increase in the direct costs of caring for an AD patient [96,162].

2.9.1.3 Nursing home placement (NHP) is a significant cost driver

Data from the CSHA indicate that long-term institutionalization is the most significant cost driver for both dementia in general and VCI in particular. With regard to overall dementia, the costs of NHP in Canada in 1991 were estimated at

$2.18 billion, or $19,100 per elderly dementia patient, which was roughly double the costs reported for community-based services (see Table 26). The costs attributed to NHP in this study accounted for almost two-thirds of total expenditures among elderly patients, suggesting that strategies to delay NHP may have tremendous cost-savings potential [161].

Among Canadians with VCI, long-term residential care was found to be the most significant cost driver at all levels of disease severity, indicating that even mild cases incur substantial institutionalization costs. Of note, however, the relative contribution of NHP to total costs appeared to increase as cognitive functioning declined, such that annual costs of NHP were only three times higher than those of community services among mild cases ($6,708 vs. $2,184), but nearly 54 times higher than those of community services among patients with severe disease ($31,104 vs. $580) (see Table 27). Such trends indicate that as spending increases for institutional placement, the costs of community services and unpaid direct care decline. Thus, the focus of costs appears to shift from informal to formal providers as VCI progresses [152].

2.10 PHARMACOTHERAPY

The currently available anti-dementia drugs in Canada include donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl), all of which act as cholinesterase

inhibitors (ChEIs). While these drugs are all approved for mild-to-moderate AD, only donepezil has received additional approval for treating more severe cases.

Recently available in Canada, the NMDA receptor antagonist memantine represents an alternative to ChEIs, but is generally used as second-line therapy for moderate-to-severe cases [163]. Other, less commonly used treatments include antioxidants (e.g., ginkgo biloba and vitamin E), nootropics (e.g., piracetam and aniracetam) and calcium-channel antagonists (e.g., nimodipine), all of which have demonstrated some modest efficacy in AD patients. Importantly, while all of the drugs mentioned above have symptomatic benefits, none have been found to prevent or reverse dementia progression.

2.10.1 Goals and Recommendations for Dementia Treatment

At the 1998 meeting of the CCCD, a group of experts outlined "reasonable" goals for dementia treatment, and set forth guidelines for the use of anti-dementia drugs (see Table 28). Among their most noteworthy recommendations, the CCCD participants placed great emphasis on the need for routinely monitoring medication response. Their guidelines indicate that drug-treated patients should be formally assessed every three months, and that observations of stabilization, improvement, and deterioration should be used to guide subsequent treatment decisions [17].

Table 28. CCCD Goals and Recommendations for Anti-Dementia Pharmacotherapy [17]

Goals	• To halt or slow cognitive and functional declines • To improve memory and other cognitive functions • To maintain or improve a patient's self-care abilities • To improve behavior, mood, quality of life, and general well-being in patients and caregivers
Guidelines	• Physicians should pursue continuing education on the administration and interpretation of functional and cognitive tests. • Patients should be monitored every 3 months after starting therapy. • Records should be kept to document stabilization, improvement, or deterioration over time. • Caregivers should keep written logs about patient's condition. • Primary care physicians who are unable to perform routine assessment should make appropriate referrals. • Physicians should be able to educate patients and families about dementia and treatment expectations.

Medication Recommendations	• Donepezil and rivastigmine are appropriate treatment options for mild to moderate dementia. • Neither donepezil nor rivastigmine should be used for AD prevention. • Vitamin E is not recommended for AD treatment or prevention. • Ginkgo biloba is not recommended for AD treatment or prevention.

2.10.2 Cholinesterase Inhibitors

The use of ChEIs in the treatment of AD can be traced back to 1986, when the ChEI tacrine hydrochloride became the first anti-dementia drug to demonstrate efficacy in a controlled clinical trial [164]. Although tacrine is no longer in use due to tolerability concerns, its approval by US regulators in 1993 heralded a wave of research into the effects of "second-generation" ChEIs, which were found to provide superior safety profiles. The benefits of the ChEIs donepezil, rivastigmine, and galantamine have since been demonstrated in several randomized, double-blind trials, leading this class to become the mainstay of AD therapy [165].

2.10.2.1 Mechanism of action of ChEIs

The rationale for using ChEIs in AD treatment derives from the cholinergic hypothesis, which posits: (1) that the cognitive symptoms of AD are caused by a loss of cholinergic neurons; (2) that the loss of cholinergic neurons is accompanied by a reduction in the neurotransmitter acetylcholine (ACh), which is required for memory formation; (3) that levels of ACh are further reduced by the enzyme acetylcholinesterase (AChE); and (4) that ChEIs can block the effects of AChE, thereby increasing the amount of ACh available for cholinergic neurotransmission [166]. The end result of this process is enhanced cognitive functioning—an effect that is supported by a growing body of clinical research [34].

2.10.2.3 Potential utility of ChEIs in VaD

Although the use of ChEIs in mild-to-moderate AD has been recommended by numerous guidelines (e.g., the CCCD), the general consensus among physicians is that the efficacy for these treatments is low [167], and the lack of approved medications for patients with non-AD dementias means that this population is greatly underserved. To address the latter concern, the developers of donepezil, rivastigmine, and galantamine have been actively testing these drugs in the treatment of VaD, with some promising results. In terms of development, donepezil appears to be farthest along, having been pre-registered for VaD as of 2005, and having exhibited benefits in cognition, behavior, and ADLs among VaD patients [7]. While the other two ChEIs have been less extensively tested,

some evidence suggests that these drugs may have efficacy in certain vascular subpopulations, which might be expected based on the presence of cholinergic dysfunction in VaD patients [7].

However, in a recently published, independently funded, review and meta-analysis of 6 trials of ChEIs and 2 of memantine, investigators concluded that the widespread use of ChEIs in patients with vascular dementia could not be supported because the drugs produced only "small benefits in cognition of uncertain clinical significance" in patients with mild to moderate VaD. Both published and unpublished data were included in the review. Trials were 6 months in duration with similar criteria for vascular dementia and outcome measures, and included a total of 3,093 drug-treated patients and 2,090 patients who were given a placebo. Some efficacy was found in terms of an increase in ADAS-cog (about the same in magnitude as has been found in AD trials) and MMSE measures. However, in the absence of a corresponding effect on global impression, functional, or behavioral outcomes, the clinical significance of the positive measures were undermined. Only donepezil showed both cognitive and global effects, but the data across studies were inconsistent [8].

To further clarify their findings with respect to the efficacy of ChEIs in VaD, Kavirajan and Schneider point out that their review illustrates the challenges inherent in designing clinical trials for VaD, including differences in diagnostic imaging techniques and the presence of coexisting AD. In addition, they

acknowledge the possibility that the small benefits found in VaD trials may actually be reflective of the effects on comorbid AD [8].

2.10.2.5 Reimbursement and utilization of ChEIs in Quebec

Under criteria set forth by the Régie de l'assurance maladie du Québec (RAMQ), reimbursement for ChEIs in Quebec requires a special authorization process, during which clinicians must justify both the initiation and continuation of treatment (see Figure D). Under most circumstances, authorization for an initial request is granted only for patients with an MMSE score indicative of mild-to-moderate dementia (10-26), although patients with higher scores may be considered with appropriate justification. After a 6-month initial prescription, the physician must provide proof that the medication has been of benefit to the patient, as evidenced by stabilization or improvement in symptoms, and a decline of no more than 3 points on the MMSE. At present, the maximum duration of RAMQ authorization for ChEIs is 12 months.

Figure D. RAMQ reiumbursement criteria for ChEIs [168]

For initiation of treatment:

- MMSE score must be between 10 and 26, or up to 27 or 28 with appropriate justification
- Medical documentation must be provided regarding degree of impairment in:
    - Cognitive function, including memory
    - Mood

- Behavior
- ADLs and IALDs
- Social interaction, including ability to participate in conversation

- Up to 6 months of therapy may by reimbursed

For continuation of treatment:

- MMSE score must be between 10 and 26, or higher or lower with appropriate justification
- No more than a 3-point decline on the MMSE over 6 months, or a greater decline with appropriate justification
- Stabilization or improvement in at least one of the following areas:
  - Cognitive function, including memory
  - Mood
  - Behavior
  - ADLs and IALDs
  - Social interaction, including ability to participate in conversation
- Up to 12 months of therapy may be reimbursed

According to a review of the RAMQ database, a total of 18,748 patients received at least one dispensation for a ChEI between January 1, 2000 and June 30, 2003. The majority of these patients (68%) were women, and the mean age was 79.2. In 74% of cases, ChEIs were prescribed by a general practitioner, and in 50%, treatment was discontinued within 216 days after initiation. Older patients and those who were dispensed <20 prescriptions during the year prior to the index ChEI prescription were at increased risk of treatment discontinuation. Other risk factors for discontinuing therapy included receiving the index prescription from a GP rather than a specialist (rate ratio 1.10) and being prescribed donepezil rather than galantamine (rate ratio 1.13) [169].

2.10.3 Donepezil in mild-to-severe AD

In Canada, donepezil is approved for use at two doses (5 and 10 mg daily) and in two forms (tablets and rapidly disintegrating tablets) [170]. Donepezil is indicated for mild, moderate and severe Alzheimer's dementia. Its approval in mild-to-moderate AD was based primarily on two 24-week trials and one 54-week placebo-controlled trial. Overall, data from these controlled clinical trials showed beneficial symptomatic effects of donepezil vs. placebo (see Table 29). Donepezil was also approval by Health Canada in June 2007 for severe AD [171], based on two 24-week placebo-controlled trials. According to the drug's product monograph, the most common adverse events associated with donepezil are nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, and resolved during continued treatment without the need for dose modification. An open-label study suggested that the frequency of these common adverse events was lower in patients who received an initial 5-mg daily dose for 6 weeks prior to increasing the dose to 10 mg/day than in patients who received the initial 5-mg daily dose for only 1 week before receiving 10 mg/day [170].

Table 29. Phase III trials supporting the use of donepezil for the treatment of mild-to-moderate AD [170]

Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
24 weeks	473	ADAS-cog	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF.
			Rates of improvement and stabilization were greater with donepezil 5 mg and 10 mg, compared with placebo.
		CIBIC-Plus	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF.
		CDR-SB	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF.

Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
24 weeks	818	ADAS-cog	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF. Effects were not sustained after 6 weeks of placebo washout.
		CIBIC-Plus	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF. Effects were not sustained after 6 weeks of placebo washout.
		CDR-SB	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF.
		Interview for Deterioration in Daily Functioning	Significant drug-placebo differences favored donepezil 10 mg, but not donepezil 5 mg, at week 24-LOCF.

Duration of Treatment	Number of Patients	Endpoint	Results
54 weeks	432	Clinically evident functional decline	Survival times were significantly longer with donepezil vs. placebo. Overall risks were 38% lower with donepezil vs. placebo.

LOCF = last observation carried forward

2.10.4 Donepezil in VaD and VCI

Beyond AD, donepezil has also been studied in patients with VaD/VCI, and is among the compounds farthest in development for a VaD indication. In 2004, the evidence regarding donepezil's effects in VCI was investigated in a Cochrane review, which concluded that the drug has both cognitive and functional benefits in patients with mild to moderate forms of VaD or mixed dementia. The review, which was based primarily on two 24-week, randomized, double-blind trials, emphasizes the potential value of donepezil as a short-term symptomatic therapy, but suggests that the drug may be effective in the longer-term as well. Importantly, donepezil was well tolerated at daily doses of 5 or 10 mg in these study patients (n = 1,216), and had a low incidence of adverse events [172].

2.10.5 Rivastigmine in mild-to-moderate AD

Like the other ChEIs, rivastigmine is an inhibitor of AChE, and has been approved for the treatment of mild-to-moderate AD in Canada [173,174]. Unlike the other ChEIs, however, rivastigmine's effects are not specific to AChE, but rather extend to butyrylcholinesterase (BuChE), which is thought to play a role in attentional processes. Perhaps because of this unique mechanism of action, the clinical profile of rivastigmine in mild-to-moderate AD includes not only benefits on cognition and daily functioning, but also efficacy in behavioral and neuropsychiatric disturbances [175].

In Canada, rivastigmine is available in capsule form (1.5 mg, 3 mg, 4.5 mg and 6 mg), as an oral solution (2 mg/mL), and as a transdermal patch (5 cm^2 and 10 cm^2 containing 9 mg and 18 mg rivastigmine base, respectively) for the symptomatic treatment of mild-to-moderate AD [173,174]. Its approval was based primarily on two studies, both of which were 26 weeks in duration and incorporated flexible maintenance-dose regimens. Outcomes on the ADAS-cog, CIBIC-Plus, and Progressive Deterioration Scale (PDS) all favored rivastigmine over placebo, with 6-12-mg doses providing superior results compared with lower dosing strategies. Common adverse events included nausea, vomiting, dizziness, diarrhea, anorexia, abdominal pain, fatigue, asthenia, and somnolence. These adverse events were generally mild in intensity, more frequent at higher doses, of short duration, and attenuated with continued dosing or discontinuation of rivastigmine. Common

adverse events in the single clinical trial with the patch formulation were nausea, vomiting, diarrhea, decreased weight, and dizziness. The overall incidence of adverse events in patients treated with the 10 cm^2 patch was lower than the rate in patients who received a 20 cm^2 patch (not a marketed dose) or the capsule formulation. [173,174].

Table 30. Phase III trials supporting the use of rivastigmine for the treatment of mild-to-moderate AD [173,174]

Duration of Treatment	Number of Patients	Endpoint	Results
26 weeks	699	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF. A greater treatment effect was noted for rivastigmine 6-12 mg than for 1-4 mg.
			Rates of improvement and stabilization were greater with rivastigmine 6-12 mg compared with placebo.

Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
		CIBIC-Plus	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF.
		PDS	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
26 weeks	725	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
			Rates of improvement and stabilization were greater with rivastigmine 6-12 mg compared with placebo.
		CIBIC-Plus	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
		PDS	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.

Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
24 weeks	1053	ADAS-cog	Significant drug-placebo differences favored rivastigmine 10-cm^2 and 20-cm^2 patch and 12-mg/day capsules at week 24-LOCF.
		ADCS-CGIC	Significant drug-placebo differences favored rivastigmine 10-cm^2 patch and 12-mg/day capsules, but not 20-cm^2 patch, at week 24-LOCF.
		ADCS-ADL	Significant drug-placebo differences favored rivastigmine 10-cm^2 and 20-cm^2 patch and 12-mg/day capsules at week 24-LOCF.
Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
26 weeks	699	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF. A greater treatment effect was noted for rivastigmine 6-12 mg than for 1-4 mg.

Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
			Rates of improvement and stabilization were greater with rivastigmine 6-12 mg compared with placebo.
		CIBIC-Plus	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF.
		PDS	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
26 weeks	725	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
		CIBIC-Plus	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF. Effects were not sustained after 6 weeks of placebo washout.

Duration of Treatment	Number of Patients	Endpoint	Results
		CDR-SB	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF.
		Interview for Deterioration in Daily Functioning	Significant drug-placebo differences favored donepezil 10 mg, but not donepezil 5 mg, at week 24-LOCF.
54 weeks	432	Clinically evident functional decline	Survival times were significantly longer with donepezil vs. placebo. Overall risks were 38% lower with donepezil vs. placebo.
Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
26 weeks	699	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF. A greater treatment effect was noted for rivastigmine 6-12 mg than for 1-4 mg.
			Rates of improvement and

Duration of Treatment	Number of Patients	Endpoint	Results
			stabilization were greater with rivastigmine 6-12 mg compared with placebo.
		CIBIC-Plus	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF.
		PDS	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
26 weeks	725	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
		CIBIC-Plus	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF. Effects were not sustained after 6 weeks of placebo washout.
		CDR-SB	Significant drug-placebo differences

Duration of Treatment	Number of Patients	Endpoint	Results
			favored donepezil 5 mg and 10 mg at week 24-LOCF.
		Interview for Deterioration in Daily Functioning	Significant drug-placebo differences favored donepezil 10 mg, but not donepezil 5 mg, at week 24-LOCF.
54 weeks	432	Clinically evident functional decline	Survival times were significantly longer with donepezil vs. placebo. Overall risks were 38% lower with donepezil vs. placebo.
Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
26 weeks	699	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF. A greater treatment effect was noted for rivastigmine 6-12 mg than for 1-4 mg.
			Rates of improvement and stabilization were greater with

Duration of Treatment	**Number of Patients**	**Endpoint**	**Results**
			rivastigmine 6-12 mg compared with placebo.
		CIBIC-Plus	Significant drug-placebo differences favored rivastigmine 6-12 mg and 1-4 mg at week 26-LOCF.
		PDS	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
26 weeks	725	ADAS-cog	Significant drug-placebo differences favored rivastigmine 6-12 mg but not 1-4 mg at week 26-LOCF.
		CIBIC-Plus	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at week 24-LOCF. Effects were not sustained after 6 weeks of placebo washout.
		CDR-SB	Significant drug-placebo differences favored donepezil 5 mg and 10 mg at

Duration of Treatment	Number of Patients	Endpoint	Results
			week 24-LOCF.
		Interview for Deterioration in Daily Functioning	Significant drug-placebo differences favored donepezil 10 mg, but not donepezil 5 mg, at week 24-LOCF.
54 weeks	432	Clinically evident functional decline	Survival times were significantly longer with donepezil vs. placebo. Overall risks were 38% lower with donepezil vs. placebo.

ADCS-ADL = AD Cooperative Study Activities of Daily Living Inventory;
ADCS-CGIC = AD Cooperative Study Clinical Global Impression of Change

2.10.6 Rivastigmine in VaD and VCI

The question of rivastigmine's efficacy in patients with VCI was addressed in a recent Cochrane Review [176], but remains unresolved due to a paucity of clinical data and a lack of unconfounded, randomized, placebo-controlled trials. At present, the most robust evidence supporting rivastigmine's use in VCI comes from small, open-label studies showing a range of benefits in patients with subcortical VaD, and from subgroup analyses of larger trials, which document the drug's efficacy in AD patients with hypertension or other vascular risk factors.

Although these findings clearly suggest that rivastigmine has potential in treating VCI or subcortical VaD, experts agree that further research is needed before any recommendations can be made [175,176].

2.10.7 Galantamine in mild-to-moderate AD

Galantamine represents a third option for the treatment of mild-to-moderate AD in Canada, where it has been approved in both tablet (4 mg, 8 mg, and 12 mg) and extended-release capsule (8 mg, 16 mg, and 24 mg) forms [177]. Support for galantamine's use in mild-to-moderate AD can be found in four randomized double-blind, placebo-controlled trials, including one which compared immediate-release galantamine to the extended-release formulation (see Table 31). Results showed significant benefits of galantamine over placebo on measures of cognition, functioning, and caregiver-rated ADLs, when given at doses of 16-32 mg/day for up to six months. In general, there appeared to be few efficacy differences between immediate- and extended-release galantamine, although the extended-release formulation did not differentiate from placebo on the CIBIC-Plus after 24 weeks of administration. The most common adverse events in the dose-escalation trial were nausea, vomiting, diarrhea, and anorexia. These events tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose. Administration of galantamine with food, the use of anti-emetic medication and ensuring adequate fluid intake may reduce the impact of these events [177].

Table 31. Phase III trials supporting the use of galantamine for the treatment of mild-to-moderate AD [177]

Duration of Treatment/ Formulations/ Dosages	**Number of Patients**	**Endpoint**	**Results**
21 weeks Immediate-release galantamine 8 mg, 16 mg, and 24 mg, given in twice daily doses	978	ADAS-cog	Significant drug-placebo differences favored galantamine 16 mg and 24 mg daily (but not galantamine 8 mg daily) at week 21.
			Rates of improvement and stabilization were greater with galantamine 16 mg and 24 mg daily (but not galantamine 8 mg daily), compared with placebo.
		CIBIC-Plus	Significant drug-placebo differences favored galantamine 16 mg and 24 mg daily (but not galantamine 8 mg daily) at week 21.
		ADCS-ADL	Significant drug-placebo differences favored galantamine 16 mg and 24 mg daily (but not galantamine 8 mg daily) at week 21.

Duration of Treatment/ Formulations/ Dosages	**Number of Patients**	**Endpoint**	**Results**
26 weeks Immediate-release galantamine 24 mg and 32 mg, given in twice daily doses	636	ADAS-cog	Significant drug-placebo differences favored galantamine 24 mg and 32 mg daily at week 21.
			Rates of improvement and stabilization were greater with galantamine 24 mg and 32 mg daily, compared with placebo.
		CIBIC-Plus	Significant drug-placebo differences favored galantamine 24 mg and 32 mg daily at week 21.
24 weeks Extended-release galantamine 16 mg or 24 mg, given once daily	(number of patients not included in the Ortho publication)	ADAS-cog	Significant drug-placebo differences favored galantamine extended-release at week 24.
		CIBIC-Plus	The effects of galantamine extended-release did not differ significantly from placebo.
		ADCS-ADL	Significant drug-placebo differences favored galantamine extended-release 24 at week 24.

ADCS-ADL = AD Cooperative Study Activities of Daily Living Inventory

2.10.5.2 Galantamine in VaD and VCI

Beyond these pivotal trials, galantamine has also been investigated in two randomized, placebo-controlled studies of patients who could be classified as having VCI. In the first trial, galantamine was assessed in patients who met criteria for either VaD or AD plus CVD, with results indicating that the drug had cognitive, functional, and behavioral benefits in the entire cohort and the AD plus CVD subgroup, but not among patients with "pure" VaD. By contrast, the second trial investigated only patients who met VaD criteria, and documented benefits of the drug on measures of both cognition and executive functioning. Although Health Canada did not find sufficient evidence for a VCI indication (Janssen Ortho Inc, 2007), the authors of a recent Cochrane Review considered galantamine to be possibly beneficial in the VCI population. Regardless of its potential benefits, however, the risks associated with galantamine are of concern, as the drug has been associated with increased rates of adverse events and withdrawal, compared with placebo [32].

2.11 CONCLUSIONS

The field of dementia research is evolving at a rapid pace, and significant progress has been made in unraveling the complexities of this devastating disorder. Over the past few decades, a number of important discoveries have been made, including the recognition that VaD may arise from a wide range of cerebrovascular injuries (e.g., subcortical white matter changes), the finding that AD and VaD may share common pathogenic pathways (e.g., a cholinergic

deficit), and the observation that patients with milder forms of cognitive impairment may also have poor outcomes (e.g., institutionalization and death). As a result of such advances, researchers are learning to better differentiate between the dementia subtypes while appreciating the etiological overlaps across dementia disorders. In addition, they are recognizing the importance of early detection, and identifying risk factors not only for the onset of cognitive impairment, but also for the risk of progression to dementia after initial decline.

Based on recent findings, a new paradigm is emerging in which AD and VaD are no longer viewed as dichotomous entities, but rather as opposite ends of a spectrum of dementia disorders. The concept of VCI, which encompasses VaD, VCIND, and mixed dementia, represents an important outgrowth of this emerging paradigm, recognizing that AD and VaD often co-exist and that it is often difficult (if not impossible) to identify which is the primary contributor to cognitive decline. Although VCI is a nonspecific construct and may overlook the subtle distinctions between vascular etiologies, it nonetheless serves to identify a population of patients whose cognitive decline has a vascular component, and who may benefit from similar treatment interventions.

Regardless of subtype, dementia is clearly a debilitating disease, affecting not only cognition, but also the ability to perform everyday tasks. Many patients with AD, VaD, and even milder forms of cognitive dysfunction are at increased risk of disability and nursing home placement, which is extremely costly to both

individuals and society. It is thus promising that in some studies the currently available AD drugs (i.e., the cholinesterase inhibitors) have been shown to delay institutionalization and reduce the accompanying costs in both AD and VCI patients. Such benefits point to possible cost benefits of the cholinesterase inhibitors, which may extend beyond AD patients.

With regard to the future of dementia research, investigators have called for a better characterization of non-AD dementias, a clearer understanding of the convergence between AD and CVD, and more sensitive tools for identifying early cognitive impairment [4,15]. It is hoped that advances in these areas will facilitate the development of disease-modifying drugs, while improving the detection of patients who are most likely to benefit from either preventive or treatment interventions. Given the aging of the population and the anticipated surge in dementia patients, the importance of continued research cannot be underestimated.

Retrospective epidemiological analyses of administrative databases containing information on drug claims and medical services may provide valuable insight into the effectiveness of AD treatments and which populations may benefit most from such treatments. However, the retrospective nature of these studies subjects them to a variety of potential limitations which need to be carefully considered in study design and interpretation of results. The most important biases that may occur in epidemiological studies are discussed in the next chapter.

3.0 BIAS IN EPIDEMIOLOGIC RESEARCH

3.1 OVERVIEW

Scientific evidence regarding factors that increase the risk of Alzheimer's disease or prevent its occurrence is primarily based on observational studies of human populations. Due to their non-experimental nature, these epidemiological studies are subject to a variety of study limitations potentially leading to bias. Bias in epidemiologic research is any systematic error that distorts an estimate of the relationship between exposure and outcome. Biases are generally categorized into three types. Selection bias refers to errors that occur in identifying the study population. Information bias, also known as observation bias, consists of error in ascertaining data on exposure or outcome. Immortal time bias is a form of information bias in which a time-dependent exposure is treated as a time-invariant factor, and is of particular concern in retrospective cohort analyses. Confounding occurs when the relationship between exposure and outcome is affected by another factor [11].

Minimization of bias is imperative for the design of epidemiologic studies, given that its presence raises doubts about the quality and credibility of results. Whereas the effects of confounding may be controlled at the time study data are analyzed, it is critical to prevent selection bias and information bias at the design stage in order to avoid compromising study validity [12].

The interpretation of epidemiologic data should take into account the possibility of bias. Key contributors to bias include the type of study design, which may be susceptible to particular forms of bias, and the conduct of investigators during study implementation. Although quantitative analysis of the magnitude of potential bias is not always possible, the likely effect of the error on study findings can often be deduced either at the design or at the analysis phase of the study [11].

This chapter discusses common types of bias in pharmacoepidemiologic research and provides examples to illustrate them. Methods for preventing or correcting bias during the design, conduct, and analysis of epidemiologic research are also described. Given the large number of possible biases [178], the three main categories and frequently encountered subtypes are covered here: selection bias (i.e., referral bias, self-selection, prevalence bias, protopathic bias, publication bias), information bias (i.e., misclassification bias, detection bias, recall bias, immortal time bias, loss to follow-up), and confounding.

3.2 SELECTION BIAS

Selection bias occurs when a patient sample is identified that has a different relationship between drug exposure and outcome than the target population. This type of error can be introduced during the design or implementation stages of a study [178]. Case-control and retrospective cohort designs are particularly

vulnerable to selection bias, due to the fact that both exposure and outcome have already occurred at the time the investigation is conducted. Thus, exposure status may influence the selection of cases and controls in case-control studies, and outcome may affect the identification of exposed and non-exposed subjects in retrospective cohort studies. Selection bias is less likely in prospective cohort studies, in which exposure is determined prior to outcome [11]. The inclusion of patients in a study sample in a way that is systematically different from the actual distribution in the target population is very difficult to take into account in the data analysis, and therefore must be avoided as far as possible at the design and implementation stages [12].

Several common forms of selection bias are presented below and illustrated with examples from the epidemiologic literature. Methods for preventing and, when possible, correcting for selection bias are discussed at the end of the section.

3.2.1 Referral bias

The use of healthcare databases to obtain epidemiologic data poses a risk of introducing referral bias. This error arises when patients referred to a healthcare institution (e.g., a hospital) are not representative of cases that originate in the community [178].

Women who experience leg pain, for example, may be more likely to receive a referral for in-hospital testing for venous thrombosis if they report the use of oral contraceptives to their primary care physicians. Awareness among healthcare providers of a possible contraceptive-related risk of thrombotic disease would thus result in the diagnosis of more cases of venous thrombosis in contraceptive users than non-users, and hospital databases would show a biased association between exposure and adverse outcome. After the publication of study data suggesting a positive association between a drug and a disease, the behavior of healthcare providers may change, increasing the risk of referral bias in subsequent studies. In such instances, the referral bias is termed *popularity bias* or *publicity bias* [12].

Referral bias may be demonstrable even when the reasons for it are not apparent. Sorenson and colleagues evaluated the claim, made in previous case-control and cohort studies, that supportive care at a tertiary medical center improves survival in patients with amyotrophic lateral sclerosis (ALS), a devastating neurological disease with a poor prognosis. The authors examined data on 132 patients treated at a tertiary ALS center within a general hospital. Forty-two of these subjects were local residents who received ALS care at the hospital as the sole inpatient facility in the area. The other 90 subjects were referred to the ALS center from more distant geographic regions.

Although both groups of patients had similar demographic characteristics, experienced a similar disease course, and received the same medical care for ALS, the referral patients had a significantly (p=0.007) longer median survival time after diagnosis than the local patients (29 months versus 18 months). In the absence of an obvious explanation, Sorenson and colleagues attributed the gap to "as yet unknown prognostic factors" that differed between the local and referral populations. They concluded that the apparent benefits of ALS treatment at a tertiary care center, as suggested by previous research, are likely attributable to referral bias, although no likely source for such bias has yet been identified. Regarding the results of their own study, Sorenson and colleagues speculated that the difference in survival rates may have been due to the fact that the referral patients were delayed in their first clinic visit until several months after diagnosis, which may have excluded patients with an especially short survival from this group [179].

3.2.2 Self-selection

Self- selection bias refers to the selective participation of certain subsets of individuals, and is primarily of concern when a large percentage of individuals asked to participate in a study decline to participate. If factors related to non-participation (for example, younger, more educated people and women have been found to be more likely to participate) are also correlated with exposure or disease occurrence, this would result in a bias that may either mask or enhance

true associations. Self-selection of study participants presents a particular risk of bias for retrospective, interview-based case-control studies. In such investigations, exposure and outcome have already occurred at the time of recruitment, and decisions to participate may therefore be related to both exposure and outcome.

In a typical example, mothers of children with birth defects are approached to participate in an interview-based study of potential associations between adverse pregnancy outcomes and medication use [12]. It is plausible to assume that mothers who smoked during pregnancy are less likely to participate. This would result in a biased association of medication use and birth defects, for example, if mothers who smoked were less likely to use medications during pregnancy and more likely to give birth to children with adverse outcomes. Consequently, medication use among mothers of children with birth defects would be underestimated, resulting in a biased association of medication use and adverse outcome.

In contrast, the use of databases on active workers may result in the underestimation of disease and mortality rates associated with exposures of interest. Self-selection occurs prior to the study, given that the actively employed are generally healthier than the overall population, which includes the retired and disabled. Such bias is termed the *healthy worker effect* [180].

Study investigators can avoid self-selection bias by employing methods to capture all cases in a population, such as using registry data. Approaches for minimizing selection bias in general are described in section 3.2.6.

3.2.3 Prevalence bias

The use of prevalent cases of disease in case-control and cross-sectional studies raises a potential for prevalence bias, also known as incidence-prevalence bias or Neyman's bias. Prevalence bias arises when mortality from a disease is affected by the exposure under study. In an investigation of a potential link between smoking and the occurrence of acute myocardial infarction (AMI), for example, the investigators might interview AMI patients one week following the event to obtain their smoking status. If smoking increases mortality in the first days after AMI, however, the interviews would miss a disproportionate number of smokers who had already died from their AMI, and the study would thereby underestimate the association between AMI and smoking [178]. The use of incident cases avoids the potential for prevalence bias, although incidence data may be difficult to obtain for conditions that have a gradual onset, such as Alzheimer's disease [181].

A similar error of particular interest for observational pharmacoepidemiologic studies is *survivor treatment selection bias*. Patients who live longer are more likely to try different medications than those who die sooner from an illness. A

correlation in a patient database between longer survival and use of a medication may lead to the erroneous conclusion that an ineffective treatment increased survival, whereas longer life in fact caused use of the treatment. Glesby and Hoover discuss this problem in relation to studies of AIDS therapies, and suggest statistical methods to mitigate the bias. Multivariate regression techniques, for example, may be used to adjust for prognostic factors and time of treatment initiation, thereby eliminating the effects of variables other than medication use. Better statistical approaches to the problem, however, are needed [182].

3.2.4 Protopathic bias

Protopathic bias arises when drug exposure is affected by the early signs and symptoms of the disease of interest, resulting in confusion of cause and effect. Such error is attributable to the fact that many diseases are not diagnosed until late after the first manifestations of illness. The appearance of bloody stools, for example, may lead individuals to discontinue taking aspirin. Patients later diagnosed with colon cancer would not be listed as aspirin users at the time of diagnosis, and the potential association between drug and outcome would be underestimated [12].

Conversely, early symptoms of an illness may cause patients to start taking a drug, leading to the biased conclusion that use of the medication is positively

associated with the disease. Patients are likely to be prescribed a proton pump inhibitor for the relief of gastrointestinal symptoms, which may be the first indicator of as yet undetectable gastric cancer [183].

The use of lag time provides one way to control for protopathic bias in the analysis of postmarketing pharmacoepidemiologic data. In this method, a specific period of time prior to disease diagnosis is excluded from the assessment of drug exposure in order to account for the possibility of a disease-induced increase in drug use. Tamim and colleagues recently pointed out that no scientific criteria to determine the appropriate length of lag time have been developed. Using data from a previous case-control study of proton pump inhibitors and gastric cancer, they proposed a method for ascertaining the optimal amount of lag time to be used in an exposure assessment. A range of different lag times were applied to the study data, and commonly used statistical techniques were employed to select the lag time at which the association between proton pump inhibitor use and gastric cancer stabilized. According to the authors, this approach can be easily implemented and incorporated into future study manuscripts [183].

3.2.5 Publication bias

Selection bias can also occur after a study has been conducted, in the form of publication bias. Studies that produce statistically significant results are more

likely to be published in peer-reviewed journals, whereas null results are less likely to be communicated. Publication bias is attributable to both study investigators and journal editorial boards; authors may be less enthusiastic about pursuing publication of statistically nonsignificant findings, and editorial boards may be more prone to reject such articles. Publication bias can create the erroneous impression that a drug is more efficacious than is actually the case, by causing a disproportionate number of statistically significant studies to be available. Similarly, the risk of adverse events may be exaggerated as a consequence of publication bias against data that do not support a significant association between exposure and adverse outcome [184].

In order to explore factors relevant to publication bias, Timmer and colleagues examined a random sample of abstracts submitted to Digestive Diseases Week, an important annual event in the field of gastroenterology. The sample included abstracts on 326 controlled clinical trials, 336 other clinical research reports, and 174 basic science studies. Subsequent publication of findings in a medical journal was ascertained by a database search and a mailed questionnaire to the authors of each abstract. Significant predictors of publication in a peer-reviewed journal were acceptance of the abstract for publication at the meeting and multicenter status of the research (i.e., the abstract had authors from >3 research centers). Studies that did not produce statistically significant results were significantly less likely to appear in journals deemed to be “high impact” publications in the field [185].

A related form of bias is *reference bias*, also known as *citation bias*, in which the authors of an article selectively cite statistically significant studies and omit non-significant findings. Even in the absence of reference bias on the part of their authors, meta-analyses are vulnerable to the effects of pre-existing publication bias, as only published studies can be included [184].

Gøtzsche evaluated the presence of reference bias in articles that reported double-blind trials of non-steroidal anti-inflammatory drugs in rheumatoid arthritis. A total of 111 study reports were examined. For each article, Gøtzsche determined which drug was under evaluation in the trial, and counted the number of previous studies of the drug that were cited in the article. He then ascertained the total number of previous studies of the drug that were available to the authors at the time the article was written, and determined whether the outcome in each was positive or negative. In 22 of the 111 articles, the authors had cited a disproportionate number of studies with a negative outcome for the drug, compared to the total number of studies that were available at the time. The authors of 44 studies, however, had cited a disproportionate number of studies with a positive outcome, indicating a significant citation bias in favor of drug efficacy [186].

3.2.6 Avoiding selection bias

Selection bias is difficult to control for during data analysis and must be prevented as far as possible in the design of the study. In addition to the strategies mentioned above for avoiding specific types of selection bias, the application of a few general principles can maximize the probability of obtaining a study sample representative of the target population. Random sampling of both cases and controls (or of exposed and non-exposed patients in cohort studies) is desirable. Well-codified accrual procedures that can be followed in the same way by different study investigators should be established. Recruitment of consecutive patients provides a way to avoid self-selection, and using a geographic definition of incident cases can reduce referral bias [12].

Selection bias is in principle fairly easy to correct mathematically, but this is rarely achievable in practice. Two necessary preconditions for such a procedure are that the factors affecting subject selection have been measured and that the joint distribution of these factors in the entire source population is known. Such conditions rarely obtain in retrospective studies, and thus selection bias does not "lend itself readily to quantitative resolution." [187]

3.3 INFORMATION/OBSERVATION BIAS

Information bias, also known as observation bias, refers to systematic error in the collection of data on exposure or outcome. As with selection bias,

information bias can be introduced during the design or implementation of a study, and is more difficult than confounding to correct at the analysis stage. Information bias can occur in retrospective case-control or cohort studies, but may also compromise data collection in prospective investigations. Several common subtypes of information bias are discussed below, followed by a brief overview of methods for preventing or adjusting for such errors.

3.3.1 Misclassification

Misclassification of exposure occurs when study subjects are assigned the wrong exposure status. Given that some inaccuracy in data collection is inevitable, misclassification has the potential to arise in almost all epidemiological studies. If such error applies to both study groups equally, it is termed *random* or *nondifferential* misclassification. In a case-control study of spermicide use and adverse pregnancy outcomes, for example, exposure was defined as use of the agent within 600 days prior to birth. This definition would misclassify the exposure status of subjects who used spermicide before that period, and the error would apply to both cases and controls. Random misclassification increases the statistical similarity of the two study groups and therefore tends to produce an underestimation of the actual association of disease and exposure [11].

When misclassification of exposure applies to one study group more than the other, the error is said to be *nonrandom* or *differential*. For example, this type of error may occur in case-control studies in which knowledge of disease status affects the quality of information sought for previous exposure. (See more on this in the subsequent section "Detection bias.") Depending on the source of nonrandom misclassification, the actual relationship between exposure and outcome may be either exaggerated or underestimated [12].

In addition to bias due to systematic error in the measurement of exposure or covariates, epidemiological studies can be biased due to incorrect classification of disease status, or disease misclassification [178,188-191]. For mortality studies, death certificates are commonly used to assess outcomes but the quality of the cause of death may be variable [192]. In studies of non-fatal outcomes, sources include disease registries (e.g., cancer, congenital malformations, occupational disease notifications), health system records (e.g., hospital admissions, general practice records), health insurance claims, standardized questionnaires (e.g., by asking the question: "have you ever been told by a doctor that you had…"), and physiological measurements. The potential for error is present in all methods for assessing outcomes.

In a mortality study, a specific cancer recorded on the death certificate as the underlying cause of death may instead have been metastatic disease for which the exposure of interest would not be etiologically relevant, or the underlying death

cause may differ entirely. Medical records, although an important source of clinical data for study participants, are intended for patient care and not systematically recorded for research purposes. The quality of clinical information from medical records is variable; incorrect information may be supplied by patients or it may be incorrectly recorded, medical records may be incomplete, the physician's handwriting may be illegible, or the abstractor's interpretation of the data in the medical record may be incorrect [193-195]. The increased utilization of electronic health records is believed to improve quality of care and patient safety [196] and may benefit clinical research as well. In United States studies using hospital discharge data, the phenomenon known as "DRG creep" may affect the accuracy of diagnosis data collected. DRG creep arises in United States studies when a patient's illness is upcoded into the highest treatment category possible in order to increase hospital income by obtaining more reimbursement than would otherwise be due [197]. Subjects' self-report of past illness is affected by the type of medical condition, with recall being more accurate for well-defined and relatively easily-diagnosed diseases and less accurate for diseases characterized by complex non-specific symptoms. Physiological measurements may be affected by the use of inaccurate instrumentation, such as using only one size blood pressure cuff to take measurements on all adults regardless of body type [191].

In a discussion of antibiotic resistance studies, Harris and colleagues illustrate the complexity of the challenges posed by misclassification bias. The authors describe two case-control studies designed to identify factors associated with

the emergence of antibiotic-resistant Pseudomonas aeruginosa in a single hospital. In the first investigation, cases were patients with positive cultures for the resistant organism, and controls were randomly selected from all patients admitted to the institution. Harris and colleagues note that control patients were subject to misclassification, however, as some were not administered bacterial cultures and thus may actually have been cases infected with resistant P. aeruginosa. This nonrandom misclassification bias would be expected to result in the underestimation of associations between risk factors and outcome.

A second study was designed to avoid the misclassification bias. As in the previous study, control group patients were selected randomly from all hospital patients, but also had to have received at least one bacterial culture, which would confirm the absence of resistant P. aeruginosa in this group. As Harris and colleagues note, however, elimination of the misclassification bias introduced the potential for selection bias. Specifically, patients who receive bacterial cultures tend to be sicker than those who do not. The control group in the second study, therefore, had more severe illness than the control group in the first study and presumably also had a disproportionately higher share of risk factors. As a consequence, estimates of the associations between risk factors and antibiotic resistance were even lower in study two than in study one [198].

Information on the sensitivity and specificity of the method employed to determine diagnosis may be used to assess potential bias due to disease misclassification. Estimates of positive and negative predictive values may also be

informative for this purpose, and are commonly used for treatment decisions and communication of disease risk to patients [199-202]. These measures of diagnostic accuracy assume that a gold standard for diagnosing illness exists. For example, one study determined the validity of hospital discharge data on acute myocardial infarction by using a gold standard diagnosis which considered symptoms, cardiac biomarkers, and electrocardiographic evidence [203]. Another study assessed the validity of dementia status in a disease registry using a well-established two-stage diagnostic process as the gold standard, and found that about half of the dementia patients were not recognized as such in the disease registry [204].

Sensitivity represents the probability that a test is positive for disease (or, in record linkage studies, that a medical record or death certificate noted the disease) given that someone truly has disease. Conversely, specificity is the probability that a test is negative for disease when someone truly is without disease. The most helpful methods for classifying disease are those with high sensitivity and specificity. Predictive values measure the usefulness of a diagnostic test, sign or symptom. The positive predictive value (PPV) represents the probability that someone with a positive test truly has disease or will develop it in the future, whereas the negative predictive value (NPV) indicates the probability that an individual with a negative test does not have disease or remains disease-free [200-202]. While predictive values have a more intuitive clinical interpretation than sensitivity and specificity, they are influenced by the prevalence of disease in the population in which the test was administered. As the population prevalence

increases, the PPV will increase and the NPV will decrease. Therefore, it is not appropriate to apply the predictive values from one study population to another if they differ in underlying disease prevalence. Sensitivity and specificity are not affected by disease prevalence in the source population.

Identification of outcomes should be consistent between the exposed and unexposed to avoid information bias. If errors in classification of disease status are made, the rate of such errors should be the same for exposed and unexposed participants, i.e., disease misclassification should be non-differential. This is best accomplished by blinding those who are responsible for determining outcomes to the exposure status of participants. For non-differential misclassification to be present, the sensitivity and specificity of determining outcome should be exactly the same in the exposed and unexposed group. With this type of bias, measures of association in epidemiological studies will on average be underestimated, i.e., there will be bias towards the null [189,200,201]. However, a measure of association will be unbiased in the presence of non-differential misclassification when specificity for detecting the outcome is 100 percent (i.e., everyone without disease is correctly classified as such) and sensitivity is less than perfect [189]. These observations apply to case-control studies or during follow-up in cohort studies, but not to the measurement of disease at baseline in cohort studies excluding people with prevalent disease from follow-up (because they are not at risk of disease). In this situation, non-differential misclassification of disease at baseline can lead to over- or

underestimation of measurements of association, which highlights the need for highly sensitive tests for disease at baseline to excluded all diseased subjects from follow-up [205].

The impact of non-differential error in disease classification was illustrated in a case-control study of prostate cancer [206]. Large autopsy studies have found that about 30 percent of men have been found to have unsuspected prostate cancer, which would result in recruiting these men with indolent disease as controls for prostate cancer cases. Assuming non-differential disease misclassification, Godley and Schell reported that statistical power drastically reduced with an increasing error rate necessitating the need to increase the size of the study population by as much as three-fold to detect the hypothesized difference [206]. The authors speculated that this methodological limitation is partially responsible for the lack of evidence for protective or harmful risk factors for prostate cancer.

When errors in outcome assessment are more or less common among exposed as compared to unexposed participants, the misclassification of disease is said to be differential by exposure status. If disease misclassification is only approximately non-differential or more obviously differential, the impact on measures of association is less predictable. Jurek and colleagues found that small deviations from non-differential error in exposure measurement (and, by extension, in outcome measurement) could inflate measures of association by

four-fold or reduce them by half [200]. In another simulation study, Chyou found that differential misclassification likely overestimates an exposure effect. The magnitude of bias appeared to depend not only on exposure status but also on the true magnitude of association and the proportion of misclassification [207].

Disease misclassification is best avoided through proper study design as it is seldom possible to fully control for bias in the statistical analysis. Outcomes should be clearly defined, specific, and measurable [192,208]. The diagnostic accuracy of methods employed should be determined in validation studies prior to initiating the epidemiological investigation. Investigators assessing outcomes should be unaware of participants' exposure status to reduce the possibility of false-positive associations.

3.3.2 Detection bias

Detection bias describes a situation in which procedures for assessing exposure or outcome are dissimilar between study groups. Like recall bias (see below), detection bias is considered to be a source of differential misclassification bias, but may be conceptualized as a distinct topic due to its importance for study design and conduct.

Both retrospective and prospective studies are vulnerable to detection bias. Awareness of disease status in a case-control study may influence data collection,

in that the investigators search more thoroughly for evidence of exposure among the cases. In cohort studies, follow-up may be more extensive for exposed patients. For example, women who take postmenopausal hormone therapy are likely to see their physicians more frequently than other women, and thus to receive a greater number of assessments for cancer or cardiovascular disease. Alternately, use of a drug associated with adverse gastric effects may result in more frequent diagnostic imaging in the exposed patients, leading to greater detection of other prevalent conditions (e.g., gallstones) in this group. If exposure or disease is systematically detected more accurately in one of the study groups, differential misclassification will result [12].

Interviewer bias closely resembles detection bias but refers specifically to investigator error during the conduct of patient interviews. In case control or cohort studies, knowledge of the hypothesized relation between exposure and outcome may lead the interviewer to prompt study subjects in subtle ways. Verbal cues and gestures may elicit anticipated responses [178].

3.3.3 Recall bias

Retrospective studies are especially susceptible to the recall bias of study participants. Patients who have experienced an illness may reflect more thoroughly on possible causes of their condition, and subjects who were exposed to a possible risk may report subsequent symptoms with a greater

degree of accuracy. Family members or other caregivers display similar tendencies when interviewing on behalf of study subjects [11].

In a recent study, Andrews and colleagues reviewed case notes on children diagnosed with autism in two different periods. The first set of notes was drawn from the years before mid-1998, when a widespread media discussion took place on a possible association between measles, mumps, and rubella (MMR) vaccination and risk of autism. The second set was taken from the years following this debate. At the time of diagnosis, parents were asked when they first noticed possible symptoms of autistic regression. Parents interviewed after the 1998 event recalled the first regressive symptoms shortly after MMR vaccination more often than those interviewed before widespread concern over this possible association [209].

3.3.4 Immortal time bias

Epidemiological cohort studies are frequently used to evaluate the efficacy, effectiveness and safety of medical interventions in specific patient populations. Randomized controlled trials are considered the gold standard for assessing treatment effects, but these studies are limited in their ability to generalize their findings to populations beyond the specific patient population studied and lack sufficient sample size to examine long-term outcomes beyond those of primary interest. Observational cohort studies, in particular those utilizing administrative

databases with routinely collected information on exposure such as medications or occupational toxins, address these limitations but need to be designed carefully because they are themselves subject to a variety of biases that may hamper interpretation. Specifically, immortal time bias has recently been suggested as an important source of systematic error in observational studies of inhaled corticosteroid treatment in patients with chronic obstructive pulmonary disease and asthma [210-216], multidisciplinary care and mortality among patients with chronic kidney disease [217], interferon-β treatment in multiple sclerosis [218], and statin therapy and the risk of dementia [219,220].

Immortal time bias, also referred to as survival bias [221] or survivor treatment bias [182], is a form of information bias and refers to an error in the statistical analysis of cohort data in which a time-dependent exposure is treated as a time-invariant factor [222,223]. In its basic form, cohort members who are first exposed toward the end of follow-up would be classified as exposed for the entire follow-up period. In studies of therapeutic effects, this approach ignores the fact that patients who live longer have more probability to receive a certain treatment. That is, many patients who received treatment are healthier than those who did not, because inherent to the design of the study they are required to survive to the date of treatment whereas patients who die sooner have less time to select treatment and are therefore more likely to remain untreated [182]. Thus, the rate of disease among patients who did not receive treatment may be artificially greater than among those who were treated. If the statistical analysis

does not account for a difference in treatment probability, immortal time bias will make the treatment appear more effective than it truly is [222] or in some cases suggest a health benefit when in truth the treatment may actually be harmful [216]. Another form of immortal time bias, which we call "follow-up bias" (not to be confused with "bias due to loss to follow-up"), may occur when patients are followed for different study durations due to differences in the time specific medications were available for prescription. That is, patients who are prescribed drugs that were available earlier may have a longer duration of follow-up, possibly resulting in different outcomes. This form of potential bias may be circumvented by ensuring the same maximum duration of follow-up for all patients.

Immortal time bias will be discussed in more detail in the context of our analysis of cerebrovascular disease in Alzheimer's disease patients (Chapter 6).

3.3.5 Avoiding information/observation bias

The potential for information bias can be reduced through careful attention to the design of data collection instruments and the procedures used by study interviewers. Questionnaires should be constructed using specific, closed-ended questions that leave little room for interpretation by the interviewer or subject. Standardized training in data collection procedures, such as physical examinations and interviews, limits the likelihood of detection bias. If possible,

interviewers should be blinded to the disease status of subjects when determining exposure in a case-control study, or to the exposure status of subjects when ascertaining outcome in a cohort study. Investigators can minimize the potential for recall bias on the part of subjects by concealing the hypothesis of the study. In an investigation evaluating the association between alcohol consumption and cardiovascular disease, for example, interviewers may ask about other risk factors in addition to alcohol use, such as exercise, smoking, and diet, to mask the study purpose.

The use of dummy variables with a known relationship to exposure or outcome provides a way to assess for detection bias or recall bias. In a case-control study of the association between aspirin use and cardiovascular disease, the interviewer might inquire about the use of other types of analgesic. If cases and controls differed in their use of aspirin but not other analgesics, the investigators would find support for the conclusion that there was a real difference in aspirin intake between the study groups. On the other hand, if the reported use of both aspirin and the other medications was increased among cases, a suspicion of detection or recall bias would be warranted [11].

Inclusion of multiple data sources allows independent verification of exposure or disease status [11]. Opportunities for improving the quality of data are expected from the increase in use of electronic medical records that encompass both clinical and administrative information [224].

Compared to selection bias, misclassification bias is more amenable to correction during data analysis [187]. According to Gustafson and Greenland, several methods of controlling for misclassification have been described in the literature. Most study investigators, however, "rely on intuition to comment qualitatively on how misclassification might impact their findings," rather than conducting a formal statistical analysis of the impact of the bias. Given that the effects of misclassification are difficult to estimate intuitively, Gustafson and Greenland call for greater use of such analysis in future studies [225].

3.4 CONFOUNDING

Confounding refers to the effect of the exposure under study being mixed with the effect of a third factor that is associated with the exposure and independently affects the risk of developing the disease [11]. The extraneous factor is the confounding variable, such as age or sex.

For instance, in a study of the risk of heart disease in people who exercise frequently and those who do not, confounding would occur if the people who exercised frequently smoked less than those who did not exercise. Participants who exercise might thus have a lower risk of heart disease because they smoked less, and not because they exercised more.

Confounding is an important concept in pharmacoepidemiology because, if present, it can cause an over- or under-estimate of the observed association between exposure and disease. The distortion introduced by a confounding factor can be large, and it can even change the apparent direction of an effect. However, confounding is easier to adjust for in the analysis compared to selection and information bias.

The key issue for interpretation is whether adequate steps have been taken to identify and control for possible confounders. Even in the best studies it may be hard to totally exclude the possibility of confounding by some unknown factor. One of the main advantages of randomization is that it controls for known confounders.

3.4.1 Necessary conditions for confounding

If no other biases are present, three conditions are necessary for a factor to be a confounder [180]:

1) *Must be a risk factor for the disease*

A confounder is a factor which is predictive of disease in the absence of the exposure under study. Note that a confounder need not be a genuine cause of disease, but merely "predictive." Therefore, surrogates for causal factors (e.g., age) may be regarded as potential confounders, even though they are rarely directly causal factors.

2) *Must be associated with the exposure under study in the source population*

A confounder is associated with exposure in the source population at the start of follow-up (i.e., at baseline). In case-control studies this implies that a confounder will tend to be associated with exposure among the controls. An association can occur among the cases simply because the study factor and a potential confounder are both risk factors for the disease, but this does not cause confounding in itself unless the association also exists in the source population.

3) *Must not be affected by the exposure or the disease*

Thirdly, a variable which is affected by the exposure or the disease (e.g., an intermediate in the causal pathway between exposure and disease, or a symptom of disease) should not be treated as a confounder because to do so could introduce serious bias into the results [226].

For example, in a study of high fat diet and colon cancer, it would be inappropriate to control for serum cholesterol levels if it was considered that high serum cholesterol levels were a consequence of a high fat diet, and hence a part of the causal chain leading from diet to colon cancer. On the other hand, if serum cholesterol itself was of primary interest, then this should be studied directly, and a high fat diet would be regarded as a potential confounder if it also involved exposure to other risk factors for colon cancer. Evaluating this type of possibility requires information external to the study to determine whether a factor is likely to be a part of the causal chain. Intermediate variables can sometimes be used in the analysis, but special techniques are then required to avoid adding bias [227].

3.4.2 Confounding by indication

Confounding by indication is a frequent problem in pharmacoepidemiology. This term refers to the fact that patients at particular risk of an adverse outcome tend to receive specific drugs. For example, in a comparison of gastrointestinal bleeding rates in patients treated with selective COX-2 inhibitors and those using standard NSAIDs, the risk may appear to be higher with COX-2 inhibitors. This is due to the patients rather than the drug, however; COX-2 inhibitors are selectively prescribed to patients at high risk. The same methods used to control for confounding in general are used for confounding by indication.

3.4.3 Control of confounding

Avoidance of confounding bias is limited by the source of data used to describe practice patterns, especially when using administrative databases to compare outcomes among patients who receive different treatments. Confounding bias arises from many factors such as the treatment under study, comorbid diseases, severity of illness, and patient, physician and environmental factors. Factors such as these are likely to influence treatment decisions but are difficult to capture in recorded data [228]. Pharmacoepidemiologists who use administrative databases cannot adjust for imbalances in prognostic factors that are not captured or poorly categorized. Clinical details from patient charts may be

needed to permit full adjustments. Further data collection might solve this issue, but this is not always possible. Confounding can be controlled in the study design, in the data analysis, or both.

3.4.3.1 Control of confounding at the design stage

Control at the design stage involves three main methods: randomization, restriction and matching [180]:

Randomization

As random allocation to exposure categories is not an option in studies using administrative data, it will not be discussed further.

Restriction

Confounding can be controlled for by restricting the study population to those who are unexposed to one or more confounding variables.[11] Another approach is to restrict the study to narrow ranges of values of the potential confounders, e.g., by limiting the study to white males aged 35-54. Restriction of some sort is always part of study design, since virtually all studies deal with delimited geographical area and specific age range, though the motive may be feasibility rather than avoidance of confounding. If it is known or suspected that an association is strongest in a particular population subset, then it may make sense to focus the study on that group. Or, if there are few data available that

apply to a particular population, it may make sense to restrict study participants to persons in that population. This approach has a number of conceptual and computational advantages, but may severely limit the number of potential study subjects and the generalizability of the study, as effects in younger or older people will not be observable.

Matching

A third method of control involves matching study subjects on potential confounders. Matching involves constraining the control group (for case-control studies) or the unexposed group (for cohort studies) such that the distribution of the confounding variables within these groups is similar or identical to the corresponding distribution within the other study group [12]. Matching can be viewed as imposing a "partial restriction" on the values of the confounding variables, since only the control or unexposed group is restricted.

For example, in a cohort study one would match a white male non-exposed subject aged 35-39 with an exposed white male aged 35-39. This will prevent age-sex-race confounding in a cohort study, but is seldom done because it may be very expensive. Matching can also be expensive in case-control studies, and does not prevent confounding in such studies, but it can be beneficial, though, since if important potential confounders are similarly distributed in cases and controls, the comparison of these two groups can be more statistically efficient – with the same number of participants, the confidence interval for the odds ratio estimate will be narrower, therefore more precise. In some cases, matching

can lead to reduced statistical efficiency. If the matching variables are strongly associated with the exposure, then the exposure prevalence in matched controls will be more similar to that in cases than would occur for an unmatched control group, thereby diminishing the observed strength of association between exposure and disease. If the matching factors are not strong risk factors for the disease, then "overmatching" has occurred and a true association may be completely hidden [11].

Matching may actually reduce precision in a case-control study if it is done on a factor which is associated with exposure, but is not a risk factor for the disease of interest. However, matching on a strong risk factor will usually increase the precision of effect estimates. Techniques for analyzing matched data include conducting the data analysis separately for each level of confounder (stratified analysis) and using conditional logistic regression.

3.4.3.2 Control of confounding in the analysis

Some confounders should be controlled for in the study design stage, rather than in the analysis, particularly when the confounder is very strong and when the anticipated sample size is large enough to allow it. When study investigators cannot control for confounding in the design (and this is possible only rarely), they adjust for confounders in the analysis [11].

Common methods of adjusting are: stratification, modeling/multivariate analysis, standardization, and instrumental variable analysis. A fifth method consists of balancing by propensity score. This method avoids the problem of sparse cells and allows many potential confounders to be taken into account.

Stratified analysis

This technique involves stratifying the data according to the levels of the confounder(s) and calculating an effect estimate which summarizes the association across all strata [229]. It is usually not possible to control simultaneously for more than two or three confounders in a stratified analysis because as the number of strata grows large, understanding and interpreting the results may present a major challenge, especially if the results vary from one stratum to another without any obvious pattern [230]. Such strata are uninformative; thus, fine stratification is wasteful of information. This problem can be mitigated to some extent by the use of multiple regressions which allows for simultaneous control of more confounders by "smoothing" the data across confounder strata. Despite these limitations, stratified analyses are a popular approach to control for confounding.

Modeling/multivariate analysis

Modeling, also known as multivariate analysis, consists in identifying possible confounders, measuring them, and then statistically controlling for them. The relationship between risk factors and outcome is modeled mathematically to

allow the assessment of many factors simultaneously [12]. This approach, although the most common in practice, is far from optimal. First, researchers can never be sure that all the confounders have been identified, and second, some might have been measured inadequately. Another limitation is that the results from these analyses rely on the linearity of the model [231].

An important consideration when using regression adjustment is proper specification of the model, which can be difficult when several potential confounders exist. One solution is to summarize covariate information using a propensity score (discussed below) which then can be used as a single covariate [232].

Standardization

Standardization controls confounding by application of a standard distribution of confounding variables to all exposure groups [233]. There are two methods of standardization, direct and indirect. In direct standardization, the stratum-specific event rates in study populations are applied to the distribution of confounding variables present in a "standard" or "reference" population. In indirect standardization, a set of stratum-specific event rates is selected from the reference population and applied to the distribution of the confounding variables in the study population [229].

For example, in an adjustment for age using direct standardization, the external standard is an age distribution. This can be the world age distribution, country or province age distribution, or can be the distribution in one of the populations

being compared. Stratum-specific event rates (i.e., age-specific rates) of each study population are then extrapolated to the number of individuals in the corresponding stratum in the standard population. In indirect age standardization, the external standard is a set of age-specific event rates in the reference population, which are then applied to the age distribution in the study sample. What distinguishes standardization from other stratified methods of controlling for confounding is use of an external standard as the basis for comparison.

Instrumental variables analysis

The core of the method is to use one or more instrumental variables to isolate the effect of treatment variation that is independent of unobserved patient characteristics [234]. Instrumental variables are observable factors that influence treatment but do not directly affect patient outcomes. The use of this method enables statistical pseudo-randomization and accounts for any residual confounding [235].

There are two key assumptions of the instrumental variable technique: that the instrument has no independent effect on the outcome and that variation in the instrumental variable causes substantial variation in the treatment variable.[236] If the instrumental variable fulfills these two assumptions, and the sample size is adequate, a reasonably good estimate of the effect of the treatment on the outcome variable can be obtained.

The most challenging part of applying the instrumental variable approach is finding 'good' instruments which influence the choice/quantity of treatment yet do not introduce further bias by being directly correlated with treatment outcome.

Propensity scores

One technique that is gaining ground in adjustment to control for confounding by indication is the propensity score. The propensity score is defined as the probability of being assigned to a particular treatment conditional to the observed covariates [237]. The basic idea of propensity score methods is to summarize the observed covariate information for each subject as a single score (propensity score), which is used to match or group subjects into subclassifications [238]. When covariates contain no missing data, the propensity score can be derived from a discriminant analysis or multivariable logistic regression in which those variables that are significantly associated with exposure are included. It is important that the outcome variable is not included as a covariate [231].

Matching, stratification, and regression adjustment are three of the most common techniques that use propensity scores to make an adjustment for covariates prior to (matching and stratification) or during (stratification and regression adjustment) the calculation of treatment effect. All three methods

calculate the propensity score in the same manner but differ in the way the estimated score is applied [238].

An important advantage of these methods over regression adjustment is that the investigator may discover that there is essentially no overlap in the distributions of the covariates in the treated and control groups. In that case, there is no hope of drawing valid causal inferences from these data without making strong external assumptions involving extrapolation.

Despite the broad utility of propensity score methods, when addressing causal questions from observational studies, it is important to keep in mind that even propensity score methods can only adjust for observed confounding covariates and not for unobserved ones. Another limitation of propensity score methods is that they work better in larger samples. A final possible limitation of propensity score methods is that a covariate related to treatment assignment but not to outcome is handled identically to a covariate with the same relation to treatment assignment but strongly related to outcome.

3.4.4 Limitations of methods to control for confounding

Unknown and unmeasured potential confounders can be controlled only through randomization. This unique advantage of randomized designs is a primary reason for their particular strength. Even for potential confounders that

are controlled (through restriction, matching, stratified analysis, modeling, etc.), limitations or errors in the conceptualization, measurement, coding, and model specification will compromise the effectiveness of control. Such incomplete control results in "residual confounding" by the potential confounder. Residual confounding, like uncontrolled confounding, can lead to bias in any direction (positive or negative, away from the null or towards the null) in the adjusted measure of effect between the study factor and outcome. Even if measurement error in the potential confounder is nondifferential (i.e., independent of the study factor and outcome), the bias in the association of primary interest can be in any direction. It is important to be aware of these limitations while planning observational studies whether using administrative data or not.

4.0 ORIGINAL STUDIES OF CHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE

4.1 BACKGROUND

As comprehensively described in Chapter 2, dementia is a widespread public health problem that affects tens of millions of individuals worldwide, and is a leading contributor to disability, institutionalization, and death in the elderly population. As of 2001, a Delphi panel of experts estimated that 24.3 million people aged 60 years and older had dementia, yielding a global prevalence rate of 3.9% among older individuals [1]. Because the prevalence of dementia increases with age [239], experts anticipate that the aging of the world population will trigger a surge of 4.6 million new dementia cases per year, such that 81.1 million patients may be diagnosed with dementia by the year 2040 [1]. An estimate of global economic burden placed the direct medical costs of dementia at more than $150 billion in 2003 alone [240]. Clearly, a growing number of elderly dementia patients has grave health economic implications.

Among the various forms of dementia, AD is widely considered to be the most common, accounting for up to 76% of all dementia cases [2]. The next most common dementia subtype is thought to be vascular dementia (VaD) [241-244], which was identified in 19% of Canadian dementia patients [2]. Traditionally, AD and VaD have been construed as discrete entities, with AD representing a

progressive, irreversible, degenerative disorder, and VaD conceptualized as the product of stroke and other forms of cerebrovascular disease (CVD) [245]. Challenging this traditional notion, however, accumulating evidence suggests that AD and VaD share common pathophysiological mechanisms, and that the two subtypes frequently co-exist [98]. When a patient presents with dementia in the context of CVD, it may be difficult to determine whether the CVD is the primary cause of cognitive decline (as in VaD), a contributor to AD pathology (as in AD with CVD), or simply an unrelated phenomenon. Difficulties in differentiating between VaD and AD with CVD (or "mixed dementia") have led some researchers to lump both groups together under the classification of VaD or, more recently, vascular cognitive impairment [4].

Studies comparing dementia subtypes generally find a higher mortality rate in patients with vascular forms of dementia (VaD or AD with CVD), compared with AD alone [148,246,247]. In addition, stroke patients who develop dementia (VaD or AD with CVD) have exhibited an increased risk of death, relative to those without cognitive decline [150]. Taken together, these data suggest that AD and CVD may be associated with a high death rate in combination than alone, and raise the question of whether anti-dementia treatment has differential effects on mortality and other important outcomes in patients with and without CVD.

The cholinesterase inhibitors (ChEIs) donepezil, rivastigmine, and galantamine have been approved for the treatment of AD in Canada, based on evidence obtained from randomized controlled trials showing a beneficial effect on symptomatic progression. Although some studies have found similar benefits of ChEIs in VaD [242,244,248-250], the evidence to date has been deemed inconclusive to merit this indication. Diagnostic uncertainty in patients presenting with dementia following CVD creates an important treatment dilemma, as it remains unclear whether the presence of CVD, which might be associated with more complex functional gaps and higher disease burden, is sufficient to deny a patient access to ChEI treatment. To address this question, we conducted the retrospective cohort study of ChEIs in patients with dementia described in Chapter 5 and the methodological analysis of the impact of bias presented in Chapter 6.

4.2 OBJECTIVES & HYPOTHESIS

The retrospective cohort study reported in Chapter 5 was designed to facilitate treatment decisions by examining whether co-existing CVD is associated with outcomes of AD patients receiving ChEIs. The outcomes of interest included mortality and nursing home placement (NHP), which has been identified as one of the most significant cost drivers for dementia [251] and vascular cognitive impairment [152].

Based on the current literature, we hypothesize that times to death and NHP are shorter among ChEI-treated patients with CVD than in those without CVD. Accordingly, the primary objective of the retrospective cohort study reported in Chapter 5 was to determine whether concomitant CVD significantly decreases time to the composite outcome of death or NHP (or, stated differently, whether the hazard ratio for death and NHP, comparing patients with CVD to those without, is greater than one). Secondary objectives of this study were to determine whether concomitant CVD significantly decreases time to the separate outcomes of death or NHP, and to identify predictors of death or NHP during and after ChEI treatment in AD patients with and without CVD.

As detailed in section 3.3.4, observational cohort studies may be subject to immortal time (and follow-up) bias unless appropriate analytic methods that circumvent these biases are undertaken. However, the potential impact of these biases in studies of patients with AD has not previously been assessed. We hypothesized that retrospective analyses using the RAMQ databases of outcomes in AD patients associated with ChEI treatment would yield misleading results if these biases were not avoided. Thus, the primary objective of the methodological analysis of the RAMQ databases reported in Chapter 6 was to evaluate the impact of immortal time bias on the estimated risk of death or NHP among AD patients who took rivastigmine or galantamine compared to those who were prescribed donepezil. A secondary objective of this study was

to examine whether an unbiased analysis would suggest differences in effectiveness among the three ChEIs.

5.0 A RETROSPECTIVE STUDY OF CHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE AND ALZHEIMER'S DISEASE WITH CEREBROVASCULAR DISEASE

5.1 INTRODUCTION

In the Province of Québec, Canada, the Régie de l'Assurance Maladie du Québec (RAMQ) is the provincial government agency responsible for public health programs, including reimbursement of prescription claims and physician services. Data for this study were extracted from two of the RAMQ administrative databases, the prescription claims database and the medical services database. These databases contain a unique identifier for each patient making it possible for subject information to be linked to medical services consumed and to prescribed medications dispensed as part of the public reimbursement scheme. Eligible beneficiaries of the drug reimbursement program are persons 65 years and older, those on social assistance, or working individuals not enrolled in an employer-sponsored drug reimbursement program. The validity of the prescription claim database as sources of accurate information on drugs dispensed to seniors in Québec has been established [252].

5.2 METHODS

5.2.1 Study Population

A retrospective cohort study of patients was undertaken using RAMQ databases—drug claims and medical services—to examine the time to NHP or death for patients 66 years of age or older (universal drug coverage starts at age 65), diagnosed with AD with or without CVD, who had been treated with a ChEI between July 1, 2000, and June 30, 2003.

Data obtained from RAMQ included all patients who had received at least one dispensation of a ChEI between January 1, 2000, and June 30, 2003. From the extracted data, a cohort of patients who met the following inclusion criteria was created:

- At least one dispensation of a ChEI between July 1, 2000, and June 30, 2003;
- A complete drug reimbursement coverage for the year prior to the date of the first dispensation of a ChEI (index date);
- 66 years of age or older (because coverage starts at age 65 years, this allowed for the one year of coverage prior to the index date).

The index date for each patient was defined as the date of the first prescription for a ChEI. Patients in a nursing home at the time of the index date were excluded.

From the resulting cohort, two study groups—AD and AD with CVD—were defined as follows:

AD:

- at least one dispensation of a ChEI;
- diagnosis of AD on the basis of an ICD-9 diagnostic code for AD (290.0-290.4, 290.8, 290.9, 331.0, 331.2);
- no diagnosis for stroke;
- no endarterectomy;
- no diagnosis for transient ischemic attack (TIA) in the six months preceding the index date;
- patients with a diagnosis of myocardial infarction (MI) or peripheral vascular disease (PVD) (lifetime) were included.

AD with CVD:

- at least one dispensation of a ChEI;
- a diagnosis of AD was not required (this allowed capture of not only patients with mixed dementia, but also those with pure VaD);

- diagnosis of stroke (ICD-9 codes 430–438) or endarterectomy (ICD-9 code V151)(lifetime), or TIA (ICD-9 code 435.9) within the six months prior to the index date.

These criteria are likely to clearly distinguish between AD and AD with CVD except in the subset of AD patients with CVD in whom CVD is subclinical (i.e., not yet symptomatic) and therefore undiagnosed. Such patients would be incorrectly assigned to the AD-only subgroup.

5.2.2 Assessment of ChEI Medication Use

Three ChEIs are approved for use in Canada and are reimbursed by RAMQ: donepezil (first dispensation in database, April 19, 2000), galantamine (listed on the Quebec formulary and therefore available in the database since October 2, 2000), and rivastigmine (available in the database since June 2, 2002). In order for a patient's first prescription claim for one of these ChEIs to be paid by RAMQ, the prescribing physician must submit a form with the clinical diagnosis (AD, Lewy body dementia, mixed dementia, or other type of dementia, which must be specified), the patient's score on the mini-mental state examination (MMSE)—accepted if between 10 and 26—and report on the patient's level of impairment within five domains: cognition, mood, behaviour, autonomy, and social interaction. For further reimbursements to be approved, the physician must, at 6- to 12-month intervals, record a decline in MMSE

score of no more than 3 points per 6-month period, as well as stabilization or improvement in three of the five clinical domains.

5.2.3 Outcome Assessment

The study's primary endpoint was time to the composite of NHP and death. Secondary endpoints included the following: time to NHP and time to death. An additional secondary outcome was the amount of variability in death or NHP during and after ChEI treatment in AD patients with and without CVD that was explained by different potential confounding factors.

A first survival analysis was done among patients with continuous ChEI use. Continuous use was defined as renewal of ChEIs before the end of the prescription plus a grace period (50% of the prescription duration) plus overlap. An overlap was observed when a patient renewed a prescription before its end and was defined as the number of days between the actual date of renewal and the estimated end date of the prescription. A second survival analysis was performed among patients who discontinued the ChEI therapy.

5.2.4 Statistical Analysis

Bivariate analyses compared the characteristics of AD patients with and without CVD. T-test and chi-square test were used for continuous and categorical comparisons, respectively.

Kaplan-Meier estimators were used to estimate the probability of NHP, death and NHP/death for AD patients with and without CVD during the ChEI therapy and after the discontinuation of the ChEI therapy. A log-rank test was performed to measure the difference between the two groups. This analysis was adjusted for several factors including the index drug (donepezil, galantamine, rivastigmine); the socio-demographic variables: age at index date and gender; and use of healthcare services measured by the number of hospitalizations, the number of days of hospitalization, the number of visits to a general practitioner (GP), the number of visits to a specialist, and the number of visits to an emergency room (ER) during the year preceding the index date. In addition, the impact of several different comorbidities, including diabetes and cardiovascular conditions, was included in the model using the Chronic Disease Score (CDS), calculated based on the use of medications in the year prior to the index date [253]. To quantify this score, medications for the treatment of specific chronic diseases were assigned a weighting factor based on the seriousness of the condition for which they were prescribed, and a patient's CDS was determined by adding up the appropriate weighting factors for each medication. Medications that are frequently used only for symptom management (e.g., analgesics, anti-inflammatory drugs, antidepressant agents) were not included in the score. The scoring rules used to calculate the CDS are shown in Table 32. The overall score ranged from 0 to 21. Moreover, since patients in the AD with CVD group were not required to have a diagnosis of AD, the presence or absence of a diagnosis of AD before or at the

index date was controlled for in the analysis. Because diagnosed urinary incontinence increases the risk for admission to a nursing facility [254], the presence or absence of a diagnosis of urinary incontinence on the basis of ICD-9 code was also included as an exploratory variable in the analysis.

Table 32. Scoring rules used to calculate the Chronic Disease Score from claims in the RAMQ database for medications for chronic diseases [253]

Chronic disease	Score for medication class(es)
Heart disease	One class = 3
	Two classes = 4
	Three classes = 5
Respiratory illness	One class = 2
	Two or more classes = 3
Asthma	Glucocorticoids = 3
	Cromolyn = 2
Rheumatism	3
Rheumatoid arthritis	3
Cancer	3
Parkinson's	3
Hypertension	Beta blockers, diuretics = 1
	Other antihypertensives = 2
Diabetes	2

Chronic disease	Score for medication class(es)
Epilepsy	2
Acne	1
Ulcers	1
Glaucoma	1
Gout, hyperuricemia	1
High cholesterol	1
Migraines	1
Tuberculosis	1

Cox regression analyses were used to identify predictors of NHP or death, among patients with either continuous or discontinuous ChEI therapy. Adjusted rate ratios were calculated to assess the independent effects of group status (AD vs. AD with CVD), index drug (donepezil vs. galantamine vs. rivastigmine), and sociodemographic variables, on the primary outcome measure.

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

5.3 RESULTS

The RAMQ databases provided information on 17,940 patients who met the inclusion/exclusion criteria; 13,512 were included in the AD group, while 4,428 were classified as having AD with CVD. In the group with AD alone, 629 patients (4.7%) had had a TIA more than six months before their index date, or had experienced PVD or MI within their lifetime. In the AD with CVD group, 4,211 patients (95.1%) had incurred stroke only, 79 (1.8%) had experienced TIA only, and 138 (3.1%) had a history of both TIA and stroke.

Table 33 shows demographics and characteristics of the study groups at index date. There was a greater number of women ($p<0.05$) in the group with AD only, which is consistent with observations of a female predominance in AD and a predominance of males in vascular forms of dementia [2]. Donepezil was dispensed as the index drug for the majority of patients in both the AD and AD with CVD groups (82% and 78% respectively, $p<0.05$).

Table 33. Patient demographics, index drug, and index year

	AD (n=13,512)	AD with CVD (n=4,428)
Age (years)*		
mean ± SD	79.4 ± 6.2	80.3 ± 6.0
Age group: n (%)		
66–75 years*	3,718 (27.5)	967 (21.8)
76–85 years*	7,477 (55.3)	2,532 (57.2)
86–95 years*	2,268 (16.8)	920 (20.8)
96 + years	49 (0.4)	9 (0.2)
Women: n (%)*	9,343 (69)	2,783 (63)
Index drug: n (%)		
donepezil*	11,025 (82)	3,468 (78)
galantamine*	1,008 (7)	389 (9)
rivastigmine*	1,479 (11)	571 (13)
Chronic Disease Score (CDS)	3.80 ± 3.10	4.58 ± 3.30

	AD (n=13,512)	AD with CVD (n=4,428)
Incontinence (%)	1,323 (10)	580 (13)
Year of index date (%)		
2000*	3,172 (24)	883 (20)
2001	3,619 (27)	1,205 (27)
2002*	4,518 (33)	1,560 (35)
2003*	2,203 (16)	780 (18)

*$p<0.05$

AD: Alzheimer's disease; CVD: cerebrovascular disease

Relative to patients with AD alone, those in the AD with CVD group were dispensed significantly more drugs (in addition to the index ChEI) during the year prior to index date ($p<0.05$) (Table 34). Of these additional medications, the majority were cardiovascular drugs such as anti-platelets, anti-hypertensives, and lipid-lowering agents.

Table 34. Prescriptions for medications, other than ChEIs filled in the year prior to index date

	AD (n=13,512)	AD with CVD (n=4,428)
Dispensations		
mean* ± SD	60 ± 86	83 ± 95
Other medications dispensed: n (%)		
Statins*	2,489 (18)	1,149 (26)
NSAIDs	3,584 (27)	1,221 (28)
anti-hypertensive*	8,222 (61)	3,239 (73)
anti-platelets*	191 (1)	495 (11)
Antipsychotic*	2,095 (16)	759 (17)

*$p<0.05$

AD: Alzheimer's disease; CVD: Cerebrovascular disease; NSAIDs: Non-steroidal anti-inflammatory drugs

In terms of healthcare resource utilization during the year prior to the index date (Table 35), AD with CVD patients were hospitalized significantly more frequently and for significantly longer periods of time ($p<0.05$) than were the patients with AD alone (3.6 vs. 2.2 days respectively). In addition, the AD with CVD patients were more likely than those with only AD to have seen a

specialist or visited the ER in the year prior to the index date, despite having been followed for a shorter time by the prescribing physician. ($p<0.05$).

Table 35. Healthcare resource use/patient in the year prior to index date

	AD (n=13,512)	AD with CVD (n=4,428)
Hospitalizations (all causes)*		
mean ± SD	0.7 ± 1.4	1.1 ± 1.7
Days of hospitalization*		
mean ± SD	2.2 ± 5.7	3.6 ± 7.3
Specialty of physician prescribing ChEI at index date: n (%)		
GP	10,029 (74)	3,238 (73)
Neurologist	1,934 (14)	697 (16)
Geriatrician	760 (6)	254 (6)
Psychiatrist	509 (4)	146 (3)
Internist	125 (1)	44 (1)
Other	128 (1)	44 (1)

	AD (n=13,512)	AD with CVD (n=4,428)
Duration of follow up (days)*		
mean ± SD	533 ± 334	496 ± 325
GP visits*		
mean ± SD	5.4 ± 4.9	6.3 ± 5.5
Specialist visits*		
mean ± SD	3.9 ± 5.2	5.0 ± 6.0
Emergency room visits*		
mean ± SD	1.0 ± 2.0	1.7 ± 2.5

*$p<0.05$

AD: Alzheimer's disease; CVD: cerebrovascular disease; ChEI: cholinesterase inhibitor; GP: general practitioner

Six hundred patients reached the main study endpoint (NHP or death) within the study's time frame. In the group with AD only, a total of 430 patients (3.2%) reached the study endpoint (159 patients died and 271 were admitted to a nursing home), compared with 170 patients (3.8%) in the group with both AD and CVD (52 had died and 118 had been placed in a nursing home for a total 170). For the composite endpoint of NHP or death, 1,000-day survival rates differed significantly between groups (Figure E: AD: 86%, AD with CVD: 84%, $p=0.0072$) and among those who discontinued ChEI therapy (Figure F: AD: 78%, AD with CVD: 77%, $p=0.0011$). The large sample sizes yielded by the RAMQ database likely account for the statistical significance of these differences between patients with AD and those with AD with CVD despite their small absolute magnitude. Of the secondary endpoints, time to death was shorter for AD patients with versus without CVD ($p<0.01$), but time to NHP did not differ between groups.

Figure E. Time to death or NHP among patients with continuous ChEI use (adjusted for covariates)

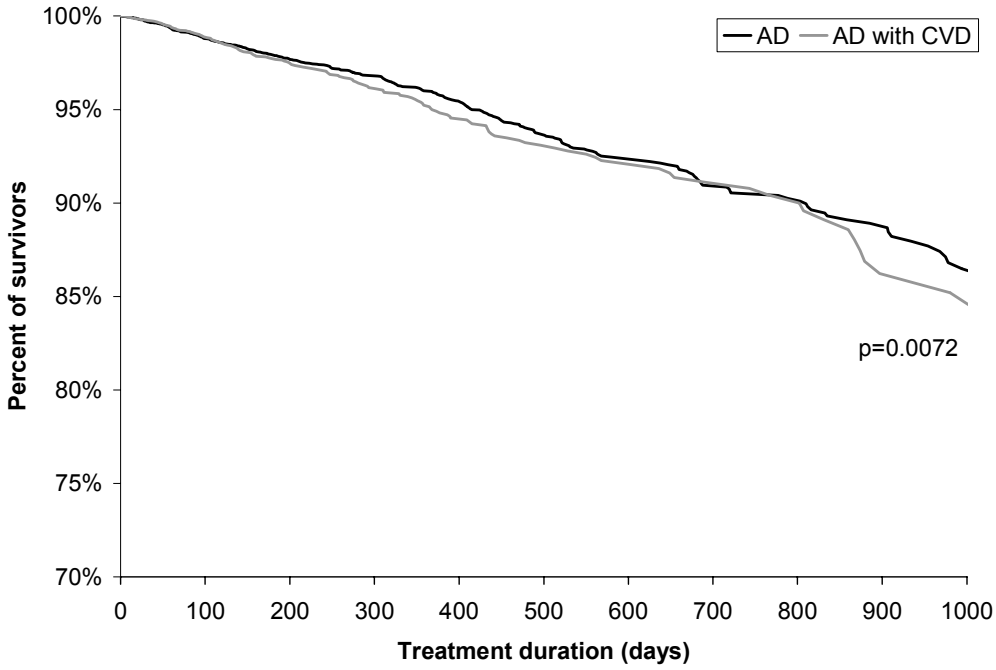
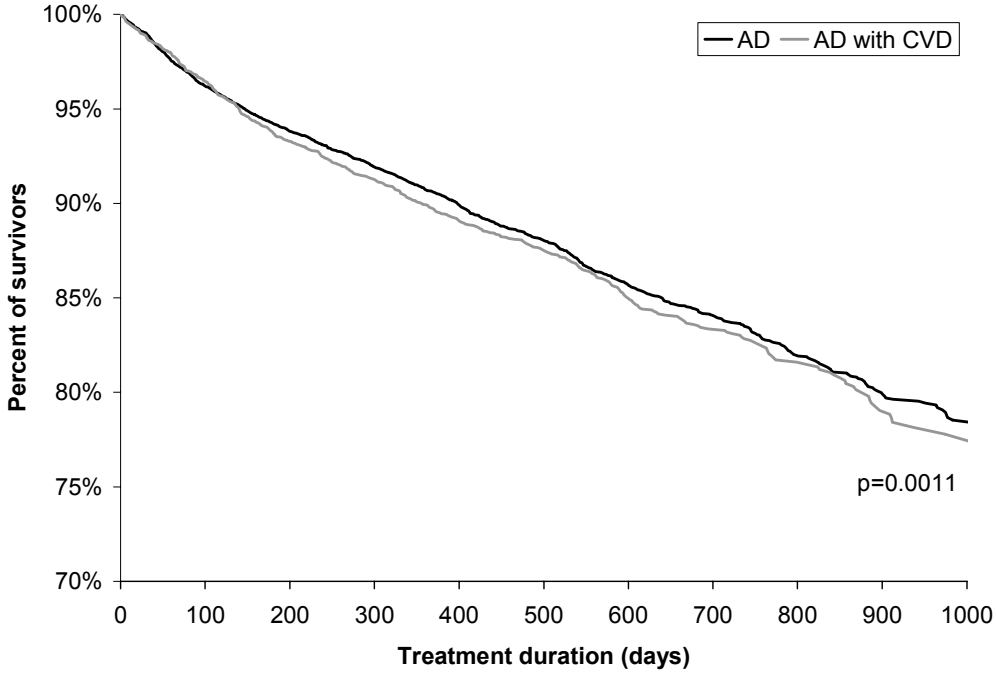


Figure F. Time to death or NHP among patients who discontinued ChEI therapy (adjusted for covariates)



Using Cox regression models, adjusted rate ratios were calculated to determine which, if any, factors predicted time to NHP or death among patients with either continuous or discontinuous ChEI use (Table 36). In this analysis, rate ratios for each factor were adjusted for all other variables simultaneously. For patients who persisted on ChEI treatment, significant risk factors included increased age, male sex, use of rivastigmine as the index drug, a diagnosis of AD at or before the index date, and the occurrence of hospitalizations and ER visits in the year prior to the index date ($p<0.05$). For patients who discontinued ChEI therapy, index dispensations of galantamine and

rivastigmine were found to delay NHP or death by 63% and 42%, respectively, whereas higher age, male sex, increased CDS, and diagnosis of AD at or before the index date were identified as negative prognostic factors ($p<0.05$). A classification of AD with CVD did not predict the study endpoint in either regression analysis.

Table 36. Results of multivariate analyses comparing adjusted rates of the primary endpoint (time to nursing home placement or death) between patients with AD and those with AD with CVD. Rate ratios for each factor are adjusted for all other variables. Results are stratified by ChEI use (continuous vs. discontinuous).

Factor	Continuous use of ChEIs Rate Ratio (95% CI)	Discontinuous use of ChEIs Rate Ratio (95% CI)
Patient group		
AD	1.00 (reference)	1.00 (reference)
AD with CVD	1.08 (0.90–1.30)	1.05 (0.95–1.16)
Index drug		
Donepezil	1.00 (reference)	1.00 (reference)
Galantamine	0.99 (0.68–1.45)	0.37 (0.28–0.48) *
Rivastigmine	1.39 (1.09–1.78) *	0.58 (0.49–0.69) *

Factor	Continuous use of ChEIs Rate Ratio (95% CI)	Discontinuous use of ChEIs Rate Ratio (95% CI)
Age (years)		
66–75	1.00 (reference)	1.00 (reference)
76–85	1.74 (1.39–2.17)*	1.44 (1.28–1.62)*
86–95	2.58 (1.98–3.35)*	2.07 (1.81–2.38)*
≥ 96	6.46 (2.82–14.81)*	2.89 (1.54–5.43)*
Sex		
Female	1.00 (reference)	1.00 (reference)
Male	1.29 (1.09–1.53) *	1.48 (1.35–1.62) *
Chronic Disease Score (CDS)	1.02 (0.99-1.05)	1.04 (1.02-1.05)*
Resource use/person in year prior to index date		
Hospitalizations (all causes)	1.08 (1.03–1.13)*	1.03 (0.99–1.06)
Duration of hospitalization (days)	1.01 (0.99–1.02)	1.00 (0.99–1.01)
visits to GP	1.00 (0.99–1.02)	1.01 (0.99–1.01)
visits to specialist (all)	1.00 (0.98–1.02)	1.01 (1.00–1.02)
visits to emergency room	1.04 (1.01–1.08)*	1.02 (0.99–1.04)

Factor	Continuous use of ChEIs Rate Ratio (95% CI)	Discontinuous use of ChEIs Rate Ratio (95% CI)
Diagnosis of urinary incontinence before or at index date		
No	1.00 (reference)	1.00 (reference)
Yes	1.097 (0.85-1.42)	0.89 (0.77-1.04)
Diagnosis of AD before or at index date		
No	1.00 (reference)	1.00 (reference)
Yes	1.20 (1.01–1.42)*	1.26 (1.15–1.39) *

*p<0.05

AD: Alzheimer's disease; CVD: Cerebrovascular disease; ChEI: cholinesterase inhibitor

This study also examined the differences in secondary outcomes for AD patients with versus without CVD. As shown in Table 37, small, but statistically significant differences between AD and AD with CVD groups were found in unadjusted rates of NHP among patients with continuous ChEI use (0.2% vs. 0.3%, p=0.009) and death among patients who discontinued ChEI treatment (0.09% vs. 0.10%, p=0.0007). No differences between groups were found in other secondary outcomes.

Table 37. Results of univariate analyses comparing unadjusted rates of secondary outcomes (nursing home placement or death) between patients with AD and those with AD with CVD. Results are stratified by ChEI use (continuous vs. discontinuous).

	AD (n=13,512)	AD with CVD (n=4,428)	p-value
Death with continuous ChEI use (%)	159 (0.01%)	52 (0.01%)	0.9898
NHP with continuous ChEI use (%)	271 (0.02%)	118 (0.03%)	0.0090
Death with discontinuous ChEI use (%)	1,183 (0.09%)	463 (0.10%)	0.0007
NHP with discontinuous ChEI use (%)	301 (0.02%)	91 (0.02%)	0.4955

AD: Alzheimer's disease; CVD: Cerebrovascular disease; ChEI: cholinesterase inhibitor; NHP: nursing home placement

5.4 DISCUSSION

After application of the study's inclusion/exclusion criteria, information was extracted for 13,512 patients with AD only and for 4,428 patients with AD with CVD. There were more women than men in the AD-only group, which reflects the usual demographics of the diseases. The AD patients with CVD in the

study population tended to be somewhat older than the patients with AD alone. Donepezil was the most frequently dispensed ChEI in both groups of patients, which can be explained by the fact that it was the first to market and the only ChEI available until October 2000.

In contrast to what was expected based on previous evidence, rates of NHP, death, and NHP/death were virtually identical for AD patients with and without CVD, after adjustment for covariates. Although some of the differences between AD and AD with CVD patients reached statistical significance, the absence of large absolute differences suggests that these statistical findings are attributable mainly to the large sample sizes. Although greater statistical power is an advantage of using large administrative claims databases like those of the RAMQ, it increases the need to carefully judge the clinical significance of differences rather than only their statistical significance. Similar cautions have been raised regarding the clinical vs. statistical significance of efficacy results from large clinical trials of ChEIs in patients with AD [255]. The small differences revealed in the present study suggest that there is little clinically relevant association between co-occurring CVD and survival or NHP among AD patients receiving ChEIs, and that expectations of poorer outcomes should not be used to deny AD patients access to potentially beneficial ChEI therapy. This finding has important implications to the healthcare system and prescribing physicians, who may be reassured about the appropriateness of

providing ChEIs for patients presenting with AD symptoms and a recent history of CVD.

Given the disease burden associated with cardiovascular disease, it is not surprising that the data revealed that AD with CVD patients used healthcare resources to a greater extent than the patients with AD alone. Relative to patients in the AD group, those with AD with CVD were hospitalized more often, spent a greater number of days in the hospital, had a higher number of specialist and ER visits, and received significantly more additional medications ($p<0.05$) during the year prior to the index ChEI prescription. By contrast, patients with AD only had a longer duration of follow-up, relative to AD with CVD patients, which may reflect earlier initiation of ChEI therapy in patients thought to have AD in its "restrictive" form. Regardless of CVD status, patients were largely dispensed the same medications: antihypertensives, cholesterol-lowering drugs, NSAIDs, and anti-psychotics. Patients in the AD with CVD group were dispensed more antiplatelet drugs, compared with AD only patients, but the difference was not significant.

This study included patients who received donepezil, rivastigmine, or galantamine, all of which increase cholinergic function in the central nervous system. Evidence from randomized controlled trials suggests that the three ChEIs included this study have clinically detectable benefits not only in AD [242,244,249,256], which is associated with cholinergic deficits in the basal forebrain

and neocortex [257], but also in VaD [242,245,248,256,258,259], which may be associated with cholinergic losses in all sectors of the cerebral cortex [245]. Given the diagnostic uncertainty in patients who develop dementia following CVD, it is possible that the AD with CVD group in this analysis included a subset of patients for whom VaD was the true cause of dementia. Thus, the lack of clinically relevant difference between AD and AD with CVD groups in this study may support previous findings of ChEI benefits in AD and VaD patients. However, it is not possible to estimate the proportion of patients in the AD with CVD group who may have had VaD because the detailed clinical signs and symptoms diagnostic for VaD (reviewed in Section 2.7.3 above) are not recorded in the RAMQ database.

The finding that index ChEI was a statistically significant predictor of NHP or death may be due either to differences in efficacy or to differences in the clinical characteristics of the individuals to whom the different ChEIs are prescribed. Given that the indications of the three ChEIs at the time the data were collected were similar (i.e., mild-to-moderate AD; the severe AD indication for donepezil was not approved until June 2007), the latter explanation seems unlikely. Furthermore, while one trial has suggested greater functional benefits of rivastigmine compared with donepezil [260], evidence on the relative efficacy of donepezil versus galantamine is conflicting [261,262], and most head-to-head comparisons find little difference between the effectiveness of ChEIs [263,264]. Thus, it is possible that the finding of an association between

index ChEI and death or NHP was simply an artifact, due to only a few patients remaining in these cells throughout the study period.

A number of possible biases may have affected the results of this study. As with any retrospective database study, it was necessary to rely on existing records, which may be less accurate or complete than data collected in a randomized trial. The RAMQ databases used for data extraction are large and have been validated for accuracy and comprehensiveness [252]. Nevertheless, they are those of a public payer and are designed primarily for drug and physician services reimbursement. As a result, the ICD-9 coding may, in some cases, be unreliable. To reduce this effect, data were drawn only for subjects who had received a dispensation of a ChEI—medications approved solely for the treatment of AD patients. This approach helped to reduce selection bias by ensuring that all patients receiving ChEIs were included even if a diagnosis of AD had not been formally coded. In all cases, the presence of an AD diagnosis was tracked, and its impact examined.

As stated, the classification and diagnosis of dementia continues to be difficult, with overlap between AD, VaD, and what is termed AD with CVD or "mixed dementia." As a result, it is possible that systematic selection (misclassification) bias may have affected our results. To minimize this, the research was based on clearly defined criteria, selected to increase the likelihood that AD was the primary cause of dementia in the AD group and that

CVD had contributed to cognitive decline in patients classified as AD with CVD. Nevertheless, it remains possible that recent stroke was causally unrelated to dementia in some "AD with CVD" patients, and that CVD may have been an important contributor to cognitive decline in "AD only" patients with a cerebrovascular event in the distant past or with undiagnosed CVD. Indeed, because of its high prevalence, subclinical CVD may underlie many cases of cognitive impairment [265]. On the basis of imaging studies, for every patient in the US who experienced a symptomatic stroke in 1998, an estimated 12 other individuals had subclinical infarcts and 2.5 had asymptomatic microhemorrhages [266]. Inability to assess the potential impact of such subclinical cases of CVD is an inherent limitation of the present study, because the claims data in the RAMQ databases are generated only for treated conditions.

A related limitation applies to the calculation of the CDS on the basis of reimbursed medications for chronic conditions. The method we used has been applied in previous retrospective studies using the RAMQ databases [267,268]. However, it should be acknowledged that this method will not capture medical conditions for which no prescriptions are recorded, potentially resulting in an underestimation of the degree of comorbidity for some indeterminable percentage of patients. Conversely, the CDS score for a patient may be incorrect in cases where a drug was prescribed off-label for a condition with a different weighting than the indicated condition.

A previous retrospective cohort study of elderly individuals revealed that, even after adjusting for comorbid conditions, diagnosed urinary incontinence increased the risk for NHP two-fold in women, and over three-fold in men [254]. Furthermore, clinical trials of some (though not all) antimuscarinic agents used for urinary incontinence therapy have shown an increased risk for cognitive impairment [269-271]. Urinary incontinence was not a significant predictor of time to NHP or death in the present study, in which this condition was identified on the basis of ICD-9 codes. A more definitive assessment of the potential influence of this variable would have required scoring of dispensations for medications used to treat urinary incontinence, in addition to ICD-9 codes. However, since urinary incontinence was an exploratory variable and not a primary focus of the present study, this more labour-intensive analysis was not performed.

In an earlier analysis, AD patients with cardiovascular disease had been excluded, but this rendered the AD group unrepresentative of the overall AD patient population. The reality is that many AD patients do have cardiovascular conditions [272-274]. To better reflect the real world, AD patients were included who had a history of PVD or MI, or who had experienced a TIA more than six months before the index date.

Confounding bias, where some of the variables are related both to the exposure and to the outcome, was handled though the use of regression models controlling for a large number of covariates. However, because MMSE scores for the patients included in this study were unavailable to the researchers, some may have been more severely affected by their disease than others, thus affecting their outcomes. Furthermore, the RAMQ database did not contain information on smoking and Body Mass Index, which may also have had influenced study results. Finally, the duration of ChEI therapy was not documented in this study, raising the possibility of unequal treatment lengths in the two study groups. Given that nearly 28% of Canadians in a previous study discontinued donepezil within seven months of an initial prescription [275], it is possible that a sizable proportion of patients in the current analysis did not receive ChEIs long enough to achieve optimum benefits.

The length of the observation period, the large number of subjects, and the strict inclusion/exclusion criteria are, however, strengths of this study and would be hard to equal in a randomized trial. Further research with a control group is needed to clarify the findings of this study. One possible control group would include AD patients with or without recent CVD, who have not received ChEI treatment, although such patients would be difficult to identify in a retrospective database. Comparisons between patients with and without ChEI treatment would help to clarify whether ChEIs have actual benefits on survival

or NHP in patients with AD, while also examining whether the magnitude of such benefits differs according to CVD status.

5.5 CONCLUSIONS

The presence of co-existing CVD in this analysis was not associated with a clinically relevant reduction in time to death or NHP among AD patients treated with ChEIs. The lack of relevant clinical difference between AD patients with and without CVD in this study was unexpected based on previous findings, and suggests that patients who develop symptoms of AD after CVD should not be denied access to ChEIs solely based on expectations of early death or nursing home care.

6.0 ASSESSMENT OF IMMORTAL TIME BIAS IN A RETROSPECTIVE STUDY OF ALZHEIMER'S DISEASE

6.1 INTRODUCTION

As mentioned in the literature review, immortal time bias is a form of information bias and refers to an error in the statistical analysis of cohort data in which a time-dependent exposure is treated as a time-invariant factor [222,223]. In clinical settings, the immortal time phenomenon was first recognized in the early 1970s when heart transplant studies incorrectly demonstrated a survival benefit of heart transplantation based on statistical analyses which did not account for the inbuilt survival advantage among those undergoing the surgery [223]. Some early occupational cohort studies also suffered from this bias thereby masking the deleterious health effects of vinyl chloride and asbestos [223]. Others have demonstrated that bias from immortal time is responsible for the observation that popes have a longer life expectancy than artists [276], and that Oscar winners live longer than less successful performers [277]. For example, Oscar winners had to survive long enough to win whereas performers who did not win had no minimum survival requirement. Analyses that credit the immortal years before winning toward survival after winning will incorrectly conclude that Oscar winners outlive their peers [277].

Based on a review of recent observational studies of medication effects, Suissa published a comprehensive description of the bias in pharmacoepidemiology for a variety of cohort designs: time-based cohorts, event-based cohorts, exposure-based cohorts, multiple-event-based cohorts, and event-exposure-based cohorts [223]. These cohort definitions vary in the way patients are eligible for cohort entry and in the definition of exposure status. End of follow-up is in all cohort designs defined by the occurrence of an event or the end of the study period, whichever comes first. In *time-based cohorts*, cohort entry is defined by a time point (usually a calendar date). In these studies, exposure is defined by a prescription or an average number of prescriptions during follow-up, and the time between cohort entry and the first prescription is inappropriately credited toward survival after treatment. *Event-based cohorts* are characterized by cohort entry based on the date of a clinical event, such as first diagnosis or hospitalization for a given condition. Exposure is defined by a given number of prescriptions within a certain period after cohort entry, for example, two or more prescriptions for a certain drug within 90 days after first diagnosis. In this situation, the time between cohort entry and the second prescription is "immortal". Analyses will be biased if this time is considered exposed because it underestimates the event rate among exposed patients. In *exposure-based cohorts*, subjects who receive the treatment of interest are considered exposed and enter the cohort at the time they start the treatment. All other patients are considered unexposed and enter the cohort when they start a comparison treatment or are first diagnosed with a particular condition. Given this definition of exposure, exposed patients may also have undergone the comparison

treatment and would have been considered unexposed if they had died prior to receiving the medication under study. Thus, the preexposure time period is immortal which, if not accounted for as unexposed time, will lead to study bias because it will result in an overestimation of the event rate among the unexposed. In *multiple-event-based cohorts*, cohort entry is defined by requiring completion of several events over time such as a minimum number of diagnoses or prescriptions. If follow-up time starts at the first of the events, subjects who die after the first event will be considered unexposed. Consequently, the time between the first and last required event is immortal and will provide an artificial survival advantage to the exposed group. Finally, in *event-exposure-based cohorts* patients enter the cohort based on the first diagnosis of a condition and exposure is defined by a treatment of interest on the same day as the diagnosis. Thus, patients who are hospitalized or first diagnosed and receive a prescription on the same day are considered exposed, whereas those who did not receive a prescription on the day of diagnosis or hospitalization and were not treated with the medication of interest during follow-up are classified as unexposed. In this design, patients who were not treated at diagnosis but received the prescription during follow-up are excluded from the analysis, thereby not considering their immortal unexposed person-time and mortal person-time. This approach overestimates the event rate in the unexposed group and underestimates the event rate in the exposed group, therefore leading to a spurious health benefit of treatment.

Several authors have recommended corrections in study design and statistical analysis to mitigate immortal time bias in cohort studies of drug effects. In general, cohort studies should include follow-up time prior to treatment initiation, and immortal time should be correctly classified with regards to exposure by using time-dependent analyses [223]. Initially, three different approaches were proposed to alleviate immortal time bias [182]. In the design phase, patients could be classified as treated or untreated at the start of the study without considering subsequent changes in treatment status (i.e., intention-to-treat analysis). However, this approach may lead to conservative estimates of treatment benefit if a substantial number of patients switch to treatment during follow-up [182]. Other recommended solutions involve the use of multiple regression techniques, in particular Cox proportional hazard regression since most cohort studies involve the analysis of time-to-event data [278]. Immortal time bias can be eliminated by using treatment initiation as a time-dependent covariate to adjust for the time at which treatment is initiated. Typically, proportional hazard models in observational treatment studies assume that once treatment has started, the patient remains exposed for the duration of follow-up. If data are available, a better approach would be to consider information on all prescriptions after entry into the cohort [279]. As an alternative to regression analysis, a modified Kaplan-Meier survival analysis could be conducted accounting for immortal time by simultaneous use of left-truncation and right-censoring [182].

In addition to these approaches controlling for immortal time bias, the "new-user design" has been proposed to handle bias introduced by immortal time and other difficulties related to the probability and timing of treatment initiation in pharmacoepidemiologic studies [280-283]. In studies with this design, all patients in a defined population who start treatment with the medication of interest are identified and follow-up begins at the time of treatment initiation. Patients who received the specific treatment during a minimum period prior to the new treatment initiation are excluded from the study. Unexposed patients, that is, those not under treatment and eligible for follow-up, are usually individually matched to exposed patients by time of new treatment and demographic variables that may impact the outcome. Follow-up of the comparison group starts at the same time as follow-up of the newly-treated patients.

In one of the most comprehensive assessments published to date, Zhou and colleagues described five methods to examine the impact of immortal time bias in the context of evaluating the effectiveness of statins for secondary prevention in elderly patients who survived an acute myocardial infarction [221]. The data sources for establishing this cohort and obtaining information on treatment were the hospital discharge summary database and the physician and prescription claims databases in Quebec, Canada. Death information was available from provincial death registries. A retrospective cohort was established of elderly patients who were discharged alive with a diagnosis of acute myocardial infarction between 1996 and 2000. Survival data was

available until 2002. Patients who filled at least one statin prescription less than 90 days after discharge were considered exposed, and patients were classified as unexposed otherwise. The event of interest was a recurrent acute myocardial infarction or death due to any cause.

In their analysis of bias due to immortal time, they described two methods introducing the bias and three methods controlling for the bias [221]. The first biased method **(*method 1*)** classified statin use as a binary variable based on the presence or absence of treatment initiation within 90 days after discharge. Follow-up was from the date of discharge until a study endpoint or the end of follow-up. Immortal time prior to the first prescription was inappropriately considered as exposed in this analysis and gives users an artificial survival advantage. The second biased method **(*method 2*)** also classified statin use as a binary variable based on the use of statins within 90 days of discharge. However, the date of start of follow-up differed from the previous approach. For statin users, follow-up started on the day of treatment initiation whereas for non-users the day of start of follow-up was randomly selected between the day of discharge and 90 days post discharge. Both groups were then followed from the start of follow-up until the study event or end of follow-up. Non-users who died prior to the randomly selected day of start of follow-up were excluded from this analysis. If the start of follow-up was on average substantially later among non-users than among users, this would give an artificial survival advantage to the non-users.

Zhou et al. also described three correct methods for analyzing their data, two of which relied on an appropriate classification of exposure time and one was based on a time-dependent Cox regression variable [221]. In one approach **(*method 3*),** statin use was represented by a binary variable as described above, that is, taking a value of 1 for those who initiated a statin within 90 days after discharge and taking a value of 0 for patients who did not. Both users and non-users were followed from 90 days post discharge until the occurrence of an event or the end of follow-up. Thus, this requires that patients in both groups survived for at least 90 days which eliminates a survival advantage for either group. In another method **(*method 4*)**, statin use was considered a binary variable as above, and follow-up started at the time of first prescription among users. For non-users, the start of follow-up was randomly selected based on the distribution of the number of days from discharge to dispensing time among users. This approach ensures that the start of follow-up, expressed as the number of days post discharge, is on average the same for users and non-users thereby removing a survival advantage. Finally, a regression method was utilized in which a time-dependent variable for statin initiation was used to classify users and non-users **(*method 5*)**. Statin use took the value of 0 until the time of first prescription, if any, after which the statin use variable took the value 1. This approach correctly classified follow-up prior to treatment as unexposed. As mentioned previously, this method could be improved by

considering changes in treatment after the first prescription since the number of prescriptions and patterns of use likely vary among users.

In analyses where the end of follow-up was restricted to one year post discharge, the authors found that the risk of recurrent acute myocardial infarction or death among statin users was 10 to 38 percent lower than the risk among non-users, depending on how which approach was taken to define exposure and start to follow-up. Assigning an artificial survival advantage to users (method 1) resulted in a statistically significantly 38 percent reduced risk, whereas introducing this survival advantage to non-users resulted in a much smaller health benefit; a 10 percent risk reduction which was not statistically significant. The correct analytic approaches yielded a much more consistent statistically significant reduction in risk of 20-22 percent. Differences in health benefit across methods were stronger when the duration of follow-up was limited to six months post discharge (42 percent reduction to one percent increase in risk among users), while less variation in results was seen when the duration of follow-up was lengthened to two years post discharge (20 to 32 percent risk reduction) [221].

Others have corroborated these findings [222,284]. This speaks to the importance of controlling for this bias in pharmacoepidemiology as it can significantly influence the interpretation of results [222,223,285]. For example, studies demonstrating an increased risk of mortality due to treatment would have found

an even stronger hazard if the time-dependent initiation of treatment had been correctly considered. Similarly, studies demonstrating no treatment effect would likely have shown an increased risk of death. Studies showing a health benefit of treatment may have continued to do so, but with a more conservative estimate, or they may have demonstrated a lack of effect or even an adverse effect after correcting for the bias [222]. Therefore, it is especially prudent to consider the potential for immortal time bias in studies reporting unexpectedly large beneficial treatment effects [286].

Although bias from immortal time has been recognized in clinical research for several decades, this bias is still common [284] and has recently appeared in a variety of observational studies examining the effects of medications in computerized healthcare databases. The impact of bias due to immortal time is particularly well illustrated in observational treatment studies of patients with chronic obstructive pulmonary disease (COPD). The prescription of inhaled corticosteroids in this population is controversial [287-290]. However, several studies have in recent years found reduced rates of COPD-related morbidity and all-cause mortality among COPD patients taking inhaled corticosteroids as compared to COPD patients who take other medications, which may have important implications for prescription consideration.

Sin and Tu identified a cohort of 22,620 patients aged 65 and older diagnosed with COPD between 1992 and 1997 from the Ontario version of the Canadian

Institute for Health Information hospital discharge database [212]. Information on prescription medication, including inhaled corticosteroids, was obtained from the Ontario Drug Benefit database. Exposed patients were those who received inhaled corticosteroid therapy within 90 days post discharge. The beginning of follow-up was defined as the date of discharge from COPD and end of follow-up was determined by the first repeat hospitalization of COPD, mortality from any cause, 365 days after discharge from the COPD admission, or the end of the study period, whichever occurred first. Patients who died before 30 days post discharge were excluded from the analysis. The authors found a 26 percent reduction in the risk for a combined event (either repeat COPD hospitalization or all-cause mortality) among inhaled steroid users as compared to unexposed patients. In this study, the 90-day exposure period represented immortal time since users were by design required to survive until treatment initiation whereas non-users could experience the event at any time during this exposure window. After accounting for this bias, Suissa found no benefit of inhaled corticosteroid use with a 6 percent reduction in risk that was not statistically significant [216]. Despite a rebuttal by Sin and Tu [211], Samet in an editorial concurred that their findings should be dismissed for the time being [279].

In another analysis addressing the effectiveness of inhaled corticosteroids in the treatment of COPD, Soriano and colleagues in the UK General Practice Research Database compared three-year survival between 1,045 treated COPD patients and 3,620 COPD patients over the age of 50 who regularly used other

bronchodilators but were not treated with inhaled corticosteroids [215]. Users were defined as those who received three or more corticosteroid prescriptions over a 6-month period whereas non-users received three of more prescriptions of select bronchodilators (not inhaled corticosteroids or long-acting β_2-agonists) during this time period. All patients in the analysis were required to survive for at least six months; follow-up was defined as the period between six months after the date of being newly diagnosed with COPD by a physician until the time of death or censoring. The rate of death was 52 percent lower among exposed patients as compared to patients treated with other bronchodilators. In this study, immortal time was introduced by not accounting for the time during which users of inhaled corticosteroid users may have been treated with regular bronchodilators (i.e., the analysis did not account for unexposed time among the treated patients). After Suissa replicated this bias in another cohort of 3,524 newly-treated COPD patients identified from computerized databases of Saskatchewan Health and subsequently accounted for unexposed person-time, no survival benefit due to inhaled corticosteroids was found [291].

Other examples of potential immortal time bias in the assessment of treatment effectiveness include studies of interferon-β in multiple sclerosis [218], and multidisciplinary care of patients with chronic kidney disease [217]. In both instances, beneficial effects of treatment were substantially overestimated. Li and colleagues further demonstrated the large impact of this bias in a study of

statin therapy and subsequent risk of dementia, resulting in a 50 percent risk reduction when in truth the treatment had no effect [219]. Unfortunately, even studies properly accounting for immortal time remain susceptible to potential errors in the definition of exposure status and follow-up time, such as time-dependent analyses using broad units of time or immeasurable time bias [292-295]. Therefore, in spite of the methodological improvements in the analysis of observational data on treatment effects, their results should be carefully scrutinized before they are allowed to influence clinical practice.

To examine the extent to which the findings reported in the previous literature also apply to AD studies, we evaluated the impact of immortal time bias and follow-up bias in our retrospective analysis of the RAMQ databases comparing the risk of death or NHP among AD patients who take rivastigmine or galantamine to those who were prescribed donepezil. We used seven Cox proportional hazard regression models which varied in the definition of the index date (start of follow-up) and the duration of follow-up.

6.2 METHODS

6.2.1 Study Population and Measures

The study setting, study population and variables used in this analysis were described in detail in Chapter 5 and are briefly summarized here. From the RAMQ databases, we included all patients 66 years of age or older who had a

diagnostic code for AD (ICD-9 codes: 290.0-290.4, 290.8, 290.9, 331.0, 331.2) or who had received at least one dispensation of a ChEI between January 1, 2000, and June 30, 2003. We assessed patients' time to the composite of NHP and death in relation to the use of donepezil (first dispensation in RAMQ database, April 19, 2000), galantamine (available in the RAMQ database since October 2, 2000), and rivastigmine (available in the RAMQ database since June 2, 2002).

6.2.2 Statistical Analysis

Similar to Zhou and colleagues [221], we evaluated the impact of immortal time (and follow-up) bias (see section 3.3.4) in our retrospective analysis of the RAMQ databases using a series of Cox proportional hazard regression models. The models varied in the definition of the index date (start of follow-up) and the duration of follow-up.

The hazard of a combined event (death or NHP) in the three different medication groups was compared (reference: donepezil) in an analysis without immortal time bias **(analysis 1)**, and in models introducing immortal time and follow-up bias **(analysis 2)**, immortal time bias only **(analysis 3)**, follow-up bias only **(analysis 4)**, and models that correct for these biases **(analyses 5-7)**. In analysis 1, the index date (or start of follow-up) was at the entry of galantamine in the database (June 2, 2002), thereby eliminating immortal time

from July 1, 2000 to June 2, 2002. The duration of follow-up for all patients was from June 2, 2002 until event occurrence or the end of the study (June 30, 2003), whichever occurred first. In analysis 2, both immortal time and follow-up bias are introduced by starting follow-up at the beginning of the study (July 1, 2000) and following people until an event or the end of the study (June 30, 2003), whichever came first. In this analysis, immortal time is introduced by requiring those on rivastigmine (October 2, 2000) or galantamine (June 2, 2002) to have survived until these drugs were in the Québec formulary. Due to differences in the date of entry into the database, more immortal time was introduced for galantamine than for rivastigmine. Follow-up bias was introduced by allowing a longer duration of follow-up for patients who were prescribed a medication found earlier in the database. Analysis 3 introduced immortal time but not follow-up bias by defining the beginning of the study as the index date, and limiting follow-up for all patients to the time of an event or one year after the index date (June 2, 2003), whichever occured first. Analysis 4 introduced follow-up bias but not immortal time bias by defining the index date as June 2, 2002 and following patients until June 30, 2003. In analysis 5, immortal time bias introduced in model 2 was corrected by starting follow-up at June 2, 2002. Analysis 6 corrected follow-up bias in model 2 by limiting the duration of follow-up to a maximum of one year from the index date. In analysis 7, both biases introduced in analysis 2 were corrected by starting follow-up on June 2, 2002 and ending follow-up on June 2, 2003 (unless an event occurred prior to this date).

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

6.3 RESULTS

Table 38 demonstrates the impact of immortal time (and follow-up) bias on the association between type of ChEI therapy and death or NHP. In the unbiased analysis, no association between medication type and outcome was found. Introduction of bias due to immortal time and differential follow-up resulted in an apparent beneficial effect of galantamine and, to a lesser extent, rivastigmine on a combined event of death or NHP. The observed bias was primarily due to immortal time; follow-up bias appeared to have little effect as no association with medication type was found in models in which only this type of bias was present.

Table 38. Adjusted rate ratio for death or NHP during ChEI therapy: assessment of impact of immortal time bias

	Rate ratio* (95% CI)
Analysis 1: Baseline (no ITB and no FUB)	
(no. of events = 189)	
Donepezil	1.000
Rivastigmine	1.182 (0.801 – 1.744)
Galantamine	0.988 (0.652 – 1.499)
Analysis 2: Introduction of both biases (ITB and FUB)	
(no. of events = 602)	
Donepezil	1.000
Rivastigmine	0.812 (0.637 – 1.036)
Galantamine	0.381 (0.262 – 0.555)
Analysis 3: Introduction of ITB only	
(no. of events = 602)	
Donepezil	1.000
Rivastigmine	0.852 (0.639 – 1.137)
Galantamine	0.527 (0.356 – 0.780)

	Rate ratio* (95% CI)
Analysis 4: Introduction of FUB only (no. of events = 212)	
Donepezil	1.000
Rivastigmine	1.268 (0.885 – 1.817)
Galantamine	0.959 (0.642 – 1.431)
Analysis 6: Second analysis with correction of FPB only (no. of events = 426)	
Donepezil	1.000
Rivastigmine	0.852 (0.639 – 1.137)
Galantamine	0.527 (0.356 – 0.780)
Analysis 7: Second analysis with correction of ITB and FUB (no. of events = 189)	
Donepezil	1.000
Rivastigmine	1.155 (0.783 – 1.703)
Galantamine	1.060 (0.692 – 1.623)

6.4 DISCUSSION

We did not find an association between ChEI treatment type and death or NHP. After we introduced immortal time bias, however, a strong beneficial effect of

galantamine compared to donepezil was observed. The impact of immortal time bias on hazard ratios was smaller for rivastigmine than for galantamine, which is consistent with the shorter immortal time for the former (July 1, 2000 – October 2, 2000) as compared to the latter (July 1, 2000 – June 2, 2002) medication. Our findings of the impact of immortal time bias are consistent with the bias reported in previous retrospective observational database studies of inhaled corticosteroid treatment in patients with chronic obstructive pulmonary disease and asthma [210-216], multidisciplinary care and mortality among patients with chronic kidney disease [217], interferon-β treatment in multiple sclerosis [218], and statin therapy and the risk of dementia [219,220]. In these studies, an apparent treatment benefit disappeared, as it did in our study, after properly accounting for unexposed person-time in the analysis either by modeling exposure as a time-dependent factor or adjusting the index date such that immortal time is eliminated. Thus, care is required in the interpretation of retrospective database studies, in particular when unexpected beneficial treatment effects are reported.

6.5 CONCLUSIONS

Dementia is a widespread public health problem that affects tens of millions of individuals worldwide. Costs to the world economy are upwards of $150 billion per year. The consequences of dementia are grave, ranging from

declines in cognition and daily functioning to complete functional dependence, institutionalization, and ultimately, death.

Scientific evidence regarding factors that increase the risk of AD or prevent its occurrence is primarily based on observational studies of human populations. Due to their non-experimental nature, these epidemiological studies are subject to a variety of study limitations potentially leading to bias. Bias in epidemiologic research is any systematic error that distorts an estimate of the relationship between exposure and outcome. Biases are generally categorized into three types. Selection bias refers to errors that occur in identifying the study population. Information bias, also known as observation bias, consists of error in ascertaining data on exposure or outcome. Immortal time bias is a form of information bias in which a time-dependent exposure is treated as a time-invariant factor, and is of particular concern in retrospective cohort analyses. Confounding occurs when the relationship between exposure and outcome is affected by another factor [11].

Minimization of bias is imperative for the design of epidemiologic studies, given that its presence raises doubts about the quality and credibility of results. Whereas the effects of confounding may be controlled at the time study data are analyzed, it is critical to prevent selection bias and information bias at the design stage in order to avoid compromising study validity [12].

The interpretation of epidemiologic data should take into account the possibility of bias. Key contributors to bias include the type of study design, which may be susceptible to particular forms of bias, and the conduct of investigators during study implementation. Although quantitative analysis of the magnitude of potential bias is not always possible, the likely effect of the error on study findings can often be deduced [11]. The present methodological analysis reveals that immortal time bias in a retrospective analysis of the RAMQ database can lead to the incorrect conclusion that different ChEIs differ in their effectiveness in terms of time to death or NHP among patients with AD. Correcting for immortal time bias yields the qualitatively different conclusion that the ChEIs are equivalent for this endpoint.

7.0 ORIGINAL STUDIES OF CHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE: DISCUSSION

Globally, over 24 million individuals are estimated to have dementia [1]. In most studies in Western countries, 50% to 70% of the total dementia prevalence is attributed to AD, and 20% to 30% to VaD, with a smaller percentage accounted for by other forms of dementia [93]. Traditionally, AD and VaD were considered to be discrete entities [245]. However, AD and VaD share common pathophysiological mechanisms, and frequently co-exist [98]. Given the high prevalence of dementia with a vascular component, there is a clear and urgent need for effective therapy for this patient population. However, identifying which therapeutic strategies are most appropriate to treat dementia depending on its etiology (i.e., AD, VaD, or a combination of the two) has posed a longstanding challenge to clinicians [10], and remains unresolved [8]. Thus, additional research is required to compare outcomes of treatment in patients with different forms of dementia.

Studies comparing dementia subtypes generally find a higher mortality rate in patients with VaD or AD with CVD than in those with AD alone [148,246,247]. Conversely, stroke patients who develop dementia (VaD or AD with CVD) exhibit an increased risk of death, compared to those without cognitive decline [150]. Taken together, these data suggest that AD and CVD may be associated with higher mortality in combination than alone, and raise the question of whether anti-

dementia treatment may have differential effects on mortality and other important outcomes in patients with and without CVD.

To address this question, we conducted the retrospective cohort study of ChEIs in patients with dementia described in Chapter 5. Rates of NHP, death, and NHP/death were virtually identical for AD patients with and without CVD, after adjustment for covariates. Although some of the differences between the AD and AD with CVD groups reached statistical significance, the absence of large absolute differences suggests that these statistical findings are not clinically significant. The small differences revealed in the present study suggest that there is little clinically relevant association between co-occurring CVD and survival or NHP among AD patients receiving ChEIs. This finding has important implications for clinical practice, as it suggests that prescribing ChEIs for patients presenting with AD symptoms and a recent history of CVD is a rational therapeutic strategy. However, since retrospective studies are susceptible to several types of bias, as explained in Chapter 3, these results require verification in prospective, randomized, placebo-controlled trials that include the endpoints of death and NHP.

Previous prospective trials of ChEIs in patients with vascular forms of dementia have yielded conflicting results [8]. For example, in the combined analysis of 2 identical randomized, placebo-controlled trials with 1219 enrolled VaD patients, donepezil was associated with significant improvements on the MMSE, ADAS-

cog, CIBIC-plus, CDR-SB, and ADFACS [296]. Conversely, in a randomized, placebo-controlled trial in 799 VaD patients, galantamine yielded significant improvements in ADAS-cog, but not CIBIC-plus or ADCS-ADL [297]. Discrepant results may arise from focus on different endpoints, differences in patient populations, and possible differences in the efficacy of different ChEIs in patients with VaD.

A definitive answer to the question of whether ChEIs are meaningfully effective in this patient population will require testing in large, long-term, prospective, randomized, placebo-controlled trials using efficacy measures sensitive to the disease course and symptomatology of VaD. However, clinicians should not be expected to postpone treating their dementia patients until such trials might be conducted. In the interim, treatment decisions can be informed by the results of other study designs, such as prospective open-label trials and retrospective observational studies. For instance, in the absence of randomized, controlled trials of rivastigmine focused on patients with mixed dementia, physicians may refer to results of an open-label study in which rivastigmine was associated with stabilization of ADAS-cog, MMSE, and GDS scores over 26 weeks in 119 patients with mixed dementia [298]. Although the present retrospective cohort analysis did not use detailed clinical measures of efficacy such as those employed in clinical trials, the outcomes of death and NHP are clearly relevant to both patients and clinicians.

The results reported here are also valuable because these outcomes were observed in real-world practice. Even after results of randomized, controlled trials are available, there remains a niche for naturalistic studies, because results seen in the closely supervised conditions of randomized trials, with their rigorous inclusion and exclusion criteria, may not always apply in routine clinical practice with unselected patients. For example, verification of the efficacy of rivastigmine in AD as shown in randomized, placebo-controlled trials was recently provided by the EXPLORE study, a naturalistic, open-label study in 3800 AD patients receiving rivastigmine in regular clinical practice [299]. At 6 and 12 months of follow-up, a higher percentage of patients improved than deteriorated on all six subscales of a Clinical Global Impression of Change scale.

Our finding of similar outcomes of ChEI therapy in AD patients with and without co-existing CVD contrasts to expections of poorer outcomes in the former group, based on previous evidence. For example, in a recent double-blind, randomized, placebo-controlled trial of 710 patients diagnosed with probable VaD, rivastigmine showed a significant treatment effect on the Vascular Dementia Assessment Scale, ADAS-cog, and MMSE, but this was attributable to efficacy seen in the subgroup of older patients, who were assumed to be more likely to have AD [300]. The trial investigators suggested that ChEIs were ineffective in patients with VaD in the absence of concomitant AD. Unfortunately, due to limitations of the data available for our retrospective analysis comparing patients with AD only with those with AD with CVD, it is not possible to determine what

percentage of patients in the latter category may have had dementia with primarily vascular causes as opposed to dementia primarily due to AD.

A number of novel therapeutic strategies are currently under investigation for their potential as dementia therapy. These include statins [126], beta-secretase inhibitors [301], gamma-secretase inhibitors [302], peroxisome proliferator-activated receptor gamma (PPARγ) agonists [303], serotonin 6 ($5\text{-}HT_6$) receptor antagonists [304], receptor for advanced glycation end products (RAGE)/Aβ blockers [305], Aβ immunotherapy [306], medium-chain triglycerides [307], and various experimental approaches to counteract tau neurotoxicity [308]. In the near future, randomized clinical trials will hopefully clarify the role of these strategies in the treatment of AD and other forms of dementia. While randomized controlled trials demonstrating symptomatic improvement and/or disease-modifying effects would be required for regulatory approval of any new dementia therapy [9], such carefully supervised and selective trials may not capture all outcomes of concern to patients and clinicians in real-world practice. By examining endpoints like survival and institutionalization in different patient subgroups, retrospective analyses of administrative healthcare databases—such as the present research—could provide valuable insight into the post-marketing effectiveness of future dementia treatments.

Similar retrospective cohort studies carried out in future will need to be designed with care to avoid biases to which such studies are susceptible. Although bias

from immortal time has been recognized in clinical research for several decades, this bias is still common [284] and has recently appeared in a number of observational studies examining the effects of medications in administrative healthcare databases.

However, no previous study has explored the impact of immortal time bias in studies of dementia treatments. The retrospective cohort analysis reported in Chapter 5 was designed from the outset to avoid immortal time bias. To demonstrate the impact immortal time bias would have had on our conclusions, we conducted a methodological analysis in which we used seven Cox proportional hazard regression models that varied in the definition of the index date and the duration of follow-up.

In the retrospective cohort analysis, we did not find an association between ChEI treatment type and death or NHP. Introduction of immortal time bias resulted in the apparent superiority of galantamine compared to donepezil. Subsequently removing the influence of immortal time with appropriate adjustment of the definition of index date and follow-up period returned the model results to their original state. These findings support demonstrations of the impact of immortal time bias reported in previous retrospective observational database studies of inhaled corticosteroid treatment in patients with chronic obstructive pulmonary disease and asthma [210-216], multidisciplinary care and mortality among patients with chronic kidney disease [217], interferon-β treatment in multiple sclerosis [218],

and statin therapy and the risk of dementia [219,220]. In these studies, an apparent treatment benefit disappeared, as it did in our study, after properly accounting for unexposed person-time. Thus, the present methodological analysis reinforces the need for care in the design and interpretation of retrospective database studies to avoid misleading conclusions as a result of immortal time bias.

8.0 ORIGINAL STUDIES OF CHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE: CONCLUSIONS

Dementia is a widespread public health problem that affects tens of millions of individuals worldwide. Annual costs to the world economy are upwards of $150 billion. The consequences of dementia are grave, ranging from declines in cognition and daily functioning to complete functional dependence, institutionalization, and ultimately, death.

Although AD is the most common cause of dementia, dementia associated with CVD accounts for a significant percentage of cases. Although three ChEIs are approved in Canada to treat AD dementia, the role of these agents in the therapy of other forms of dementia remains poorly defined. The retrospective analysis of the RAMQ administrative databases reported in Chapter 5 was undertaken to assess whether concomitant CVD worsened the prognosis for patients with AD receiving ChEIs. The presence of co-existing CVD in this analysis was not associated with a clinically relevant reduction in time to death or NHP among AD patients treated with ChEIs. This finding suggests that patients who develop symptoms of AD after CVD should not be denied access to ChEIs solely based on expectations of early death or institutionalization. This conclusion requires confirmation from prospective, randomized, placebo-controlled trials of adequate duration and using clinically relevant outcome measures in patients with clearly defined VaD and mixed dementia.

Retrospective epidemiologic analyses such as the study reported in Chapter 5 are susceptible to a number of types of bias that need to be taken into account to avoid misleading results and conclusions. Key contributors to bias include the type of study design and the conduct of investigators during study implementation. The methodological analysis reported in Chapter 6 reveals that introduction of immortal time bias into a retrospective analysis of the RAMQ database can lead to the incorrect conclusion that different ChEIs differ in their effectiveness in terms of time to death or NHP among patients with AD. Correcting for immortal time bias yields the qualitatively different conclusion that the ChEIs are equivalent for this endpoint. This represents the first demonstration of the potential impact of immortal time bias in any retrospective study of therapy for dementia. The results highlight the need to carefully avoid introducing immortal time bias into retrospective analyses of administrative databases.

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