Heart Disease and Dementia: A Population-based Study

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There are conflicting reports on the possible positive association between coronary disease and dementia. The objectives of this study were to examine the association between coronary disease, as measured by myocardial infarction and cardiac death, and dementia in a population-based study. By use of the record-linkage system of the Rochester Epidemiology Project, 916 cases of dementia and 916 age (±1 year)- and sex-matched controls were identified in Rochester, Minnesota, between 1985 and 1994. From the same population, the authors identified all subjects who experienced a myocardial infarction (defined using standardized criteria) during the period 1979–1998. For myocardial infarction occurring prior to the index year of dementia, the authors used conditional logistic regression (case-control analysis), while for myocardial infarction and death occurring after the index year, they used competing risk survival analysis to account for informative censoring (cohort analysis). Before the index year, the odds ratio for myocardial infarction among cases with dementia compared with controls was 1.00 (95% confidence interval (CI): 0.62, 1.62; \( p = 1.00 \)). After the index year, patients with dementia had a 46% decreased risk of subsequent myocardial infarction (hazard ratio = 0.54, 95% CI: 0.36, 0.82; \( p = 0.004 \)) and an 18% decreased risk of cardiac death (hazard ratio = 0.82, 95% CI: 0.70, 0.95; \( p = 0.010 \)). There was no evidence of a positive association between dementia and preceding myocardial infarction, while there was a decreased risk of myocardial infarction and cardiac death following dementia.

case-control studies; cohort studies; death; dementia; myocardial infarction; odds ratio; survival analysis

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases.

The burden of coronary disease has shifted toward elderly persons in recent decades (1). In an aging population, the prevalence of cardiovascular diseases and dementia is increasing, and both diseases have substantial impact on society and public health. Dementia is a progressive disease that affects a large number of individuals in Western countries; its prevalence doubles every 5 years after the age of 60 (2, 3).

The existence of a link between atherosclerosis and dementia has been suggested because these diseases share conventional and genetic risk factors (4–10). Some studies reported that after myocardial infarction patients had a higher risk of cognitive impairment as a result of brain hypoperfusion; therefore, myocardial infarction could be in the causal pathway to dementia (11). However, other findings are discrepant (12). A cross-sectional study of 4,971 participants in the Rotterdam Study detected a positive association between cognitive impairment and prior myocardial infarction (13). The Bronx Aging Study, a prospective cohort study, yielded a fivefold increase in the risk of dementia among elderly women with a history of myocardial infarction (14). On the other hand, the Honolulu-Asia Aging...
Study, a prospective cohort study, found no association between myocardial infarction and later cognitive impairment among 3,734 Japanese-American men (15). These conflicting results led to the formulation of the alternative hypothesis that atherosclerosis and dementia may be independent but convergent diseases caused by the same factors (4) and characterized by similarly long latency. Under this hypothesis, subjects with dementia should have a higher burden of coronary disease compared with dementia-free counterparts, and this excess risk could manifest itself both before and after the onset of dementia.

Using two complementary approaches, we undertook this study to comprehensively examine the association between dementia and clinical heart disease as measured by myocardial infarction and cardiac death. A matched case-control study nested within a population-based cohort was designed to assess the risk of myocardial infarction preceding the onset of dementia, and a cohort study examined the occurrence of myocardial infarction or cardiac death after the onset of dementia.

MATERIALS AND METHODS

Study population—the Rochester Epidemiology Project

Rochester and Olmsted County, Minnesota, are relatively isolated from other urban centers, and nearly all medical care is delivered to local residents by a few providers. The characteristics of the population of Olmsted County are similar to those of US Whites (16). According to census data, the population of Olmsted County was 106,479 in 1990 (16) and increased to 124,277 in 2000 while becoming ethnically more diverse.

The Mayo Clinic provides approximately half of the primary care and nearly all specialty care for the community. The Olmsted Medical Center and its affiliated hospital, along with the Mayo Clinic, provide comprehensive care in virtually every specialty. Each provider in the community uses a dossier medical record system, whereby all medical information for each individual is accumulated in a single file. Through the Rochester Epidemiology Project, medical diagnosis, surgical interventions, and other key information from the dossier are routinely abstracted and coded according to the H-ICDA, Hospital Adaptation of ICDA (H-ICDA) (17), based on the International Classification of Diseases (ICD). The computerized indices allow the linkage of medical records from all sources of care used by the population, which provides an infrastructure to analyze disease determinants and outcomes.

Identification of dementia cases

Standardized methods in place through the records-linkage system of the Rochester Epidemiology Project were used for case finding (18–20). We searched for 112 specific H-ICDA codes that might indicate dementia in Rochester, Minnesota, between 1985 and 1989 and for 132 codes for the period 1990–1994. Cases of dementia in the general population may remain undetected for a number of years but may be diagnosed at some point during their natural history. To increase the likelihood of capturing these individuals, the indices were searched for the study interval and for 6 additional years. The medical records of each potential case (defined by the presence of at least one of the study codes) were screened by trained nurse abstractors (18, 19). A neurologist confirmed the presence of dementia, classified the dementia by type, and determined the year of onset (18). We used the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV (21) criteria that, for dementia, require three items: 1) memory impairment as a prominent early feature, 2) at least one of aphasia, apraxia, agnosia, or disturbance of executive function, and 3) loss of function representing a significant decline from a previous level and sufficient to interfere with social or occupational activities. Abstraction and interpretation of medical records were standardized and operationalized to increase reliability (19). For inclusion, subjects were required to reside in Rochester in the year of onset of dementia and for at least 1 preceding year.

Controls and referent subjects

All 916 patients with dementia were individually matched by age (±1 year) and sex to a general population referent subject drawn randomly from all the subjects residing in Rochester and free of dementia in the index year (year of onset of dementia in the matched patient). The list of all Rochester residents from whom potential referent subjects were drawn was provided by the records-linkage system and was based on the enumeration of all individuals in contact with the system at least once in the 3 years after the index year. Potential referent subjects were selected randomly among all residents fulfilling the matching criteria. Referent subjects were used as controls in case-control analyses for myocardial infarction preceding dementia and as unexposed referents in survival analyses for myocardial infarction and cardiac death following the onset of dementia.

Ascertainment of cardiovascular diseases

Myocardial infarction. Myocardial infarction was ascertained by using standardized surveillance methods described in detail elsewhere (22, 23). In brief, the complete medical records of all patients discharged from Rochester hospitals in the period 1979–1998 with diagnoses compatible with a myocardial infarction in the ICD, Ninth Revision (24), were reviewed by trained nurse abstractors. These discharge diagnosis codes included 410 (acute myocardial infarction), 411 (other acute and subacute forms of ischemic heart disease), 412 (old myocardial infarction), 413 (angina pectoris), and 414 (other forms of ischemic heart disease).

The abstractors validated the diagnosis of myocardial infarction by use of standardized criteria relying on cardiac pain, biomarker values, and Minnesota coding of the electrocardiogram (25). This approach allows categorizing myocardial infarction as definite, probable, and suspect. For the purpose of this analysis, we used the categories definite and probable myocardial infarction, which have
been commonly used in epidemiologic studies (22, 23). Details about the reliability of these criteria were published elsewhere (1, 23). The ascertainment of myocardial infarction was performed by investigators who were kept unaware of the dementia status of the subjects.

Cardiac death. Follow-up was provided by passive surveillance through the community medical records (inpatient and outpatient). This process is quite complete because more than 90 percent of the population receives care at the Mayo Clinic or the Olmsted Medical Center, and residents are seen on average every 3 years at the Mayo Clinic (16). The ascertainment of death involved the review of death certificates filed in Olmsted County, autopsy reports, obituary notices, and electronic files of death certificates obtained from the Section of Vital Statistics, Minnesota Department of Health (23, 26). All cause-of-death entries listed in the death certificate were used (27–29). Cardiac death was defined by using ICD, Ninth Revision, codes 390 through 398 and 401 through 429 or the corresponding ICD, 10th Revision, codes I00 through I13 and I20 through I51 (30). All codes listed anywhere in the certificate were considered (underlying, intermediate, final, and other cause of death). The Mayo Clinic and the Olmsted Medical Center institutional review boards approved all aspects of the study.

Statistical analyses

For the myocardial infarction occurring before the index year, we used a matched case-control design and performed conditional logistic regression, reporting the odds ratio and 95 percent confidence intervals. We first analyzed all myocardial infarctions preceding the index year in cases and controls. To evaluate the long-term association between dementia and myocardial infarction, we repeated the analysis after excluding myocardial infarctions occurring within 2 and 5 years prior to the index year.

For myocardial infarction and cardiac death occurring after the index year, we used a cohort design. Survival was assessed using survival analysis adjusted for competing risks, a method that accounts for informative censoring (31). A proportional subdistribution hazards regression model was used to estimate the hazard ratios and 95 percent confidence intervals in the presence of competing risks (31, 32). The model adjusted for age and sex to remove possible residual confounding.

RESULTS

Study population

Between 1985 and 1994, 916 subjects with dementia and 916 age (±1 year)- and sex-matched referent subjects without dementia were identified, for a total of 1,832 subjects. Of the patients with dementia, 663 (72 percent) were women, and the median age at diagnosis was 82 years (range: 38–102). The age and sex distributions were similar in cases and referents (or controls), reflecting the matching. The median duration of follow-up after the index year obtained through the records-linkage system was 6.1 years (range: 0.4–19.5) for dementia subjects and 8.2 years (range: 1.1–19.5) for referent subjects (p < 0.001).

Myocardial infarction and dementia

The frequency of myocardial infarction preceding dementia was 36 of 916 subjects (3.9 percent) among the cases and 36 of 916 subjects (3.9 percent) among the controls, yielding an odds ratio of 1.00 (95 percent confidence interval (CI): 0.62, 1.62; p = 1.000) (table 1). When patients with myocardial infarction within 2 years of the index year were excluded along with their matched subject, the frequency of myocardial infarction was 25 of 896 subjects (2.8 percent) among the cases and 25 of 896 subjects (2.8 percent) among the controls (odds ratio = 1.00, 95 percent CI: 0.57, 1.76; p = 1.000). When patients with myocardial infarction within 5 years prior to the index year were excluded along with their matched subject, the frequency of myocardial infarction was 11 of 872 subjects (1.3 percent) among the cases and 14 of 872 subjects (1.6 percent) among the controls (odds ratio = 0.96, 95 percent CI: 0.63, 1.45; p = 0.831).

After the index year, 35 (4.0 percent) patients with dementia and 64 (7.3 percent) referent subjects developed a myocardial infarction (table 2). The risk of experiencing a myocardial infarction, accounting for the competing risk of death, was lower among patients with dementia compared with referents (hazard ratio = 0.54, 95 percent CI: 0.36, 0.82; p = 0.004).

As expected, subjects with dementia with myocardial infarction were more frequently admitted to the hospital from nursing homes compared with their dementia-free counterparts (33 percent vs. 8 percent, p = 0.002). They were also admitted more promptly after the onset of

| TABLE 1. Case-control analysis for myocardial infarction prior to dementia, Rochester, Minnesota, 1985–1994 |
|--------------------------------------------------|---------------|----------------|-----------------|-----------------|-----------------|
| Risk factor                                      | No. of cases  | No. of controls | Odds ratio      | 95% confidence interval | p value         |
| Myocardial infarction, all events                | 36            | 36             | 1.00            | 0.62, 1.62         | 1.000           |
| Myocardial infarction >2 years prior to index year | 25           | 25             | 1.00            | 0.57, 1.76         | 1.000           |
| Myocardial infarction >5 years prior to index year | 11            | 14             | 0.96            | 0.63, 1.45         | 0.831           |

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not significant (and in referent subjects (36 percent). The difference was death occurred in patients with dementia (42 percent) as compared with dementia-free referents. Sudden competing risk of noncardiac death was better among sub-

attributed to coronary disease) occurred among referent subjects with dementia, and 370 cardiac deaths (58 percent (55 percent attributed to coronary disease) occurred among subjects with dementia. However, biomarkers and Killip class did not differ according to the presence or absence of dementia. There were no differences between subjects with and without dementia in the frequency of hypertension, hyperlipidemia, diabetes, and smoking or in the treatment after myocardial infarction (early revascularization, thrombolysis, ace inhibitors, beta blockers, and aspirin).

Overall death and cardiac deaths

After a median of 7.0 years (range: 0.4–19.5) of follow-up, 837 deaths occurred among subjects with dementia and 698 among referent subjects. Overall survival was worse among subjects with dementia (e.g., at 10 years was 22 percent (95 percent CI: 20, 25) for cases compared with 39 percent (95 percent CI: 36, 43) for referent subjects) (p < 0.001). When cardiac conditions present anywhere on the death certificate were considered, 313 cardiac deaths (55 percent attributed to coronary disease) occurred among subjects with dementia, and 370 cardiac deaths (58 percent attributed to coronary disease) occurred among referent subjects.

Survival free of cardiac death after accounting for the competing risk of noncardiac death was better among subjects with dementia (p = 0.014). Dementia was associated with an 18 percent decrease in the risk of cardiac death after adjusting for age, sex, and accounting for competing causes of death (hazard ratio = 0.82, 95 percent CI: 0.70, 0.95; p = 0.010) as compared with dementia-free referents. Sudden death occurred in 130 patients with dementia (42 percent) and in 133 referent subjects (36 percent). The difference was not significant (p = 0.135).

**DISCUSSION**

The existence of a link between atherosclerosis and dementia has been suggested because both diseases share common risk factors, both established (8, 33) and novel (4, 7, 34), including markers of inflammation (35–39) and genetic risk factors (40, 41). The clinical relevance of this plausible biologic link would reside in the demonstration of an excess burden of clinical cardiovascular disease among subjects with dementia. This population-based study was undertaken to test the association between dementia and heart disease by use of two major clinical manifestations: myocardial infarction and cardiac death. In this geographically defined population, subjects with dementia exhibited no evidence of an increased risk of myocardial infarction or cardiac death compared with referents without dementia. To the contrary, an inverse association was observed for myocardial infarction and cardiac death following dementia.

**Myocardial infarction and dementia**

It has been hypothesized that, after a myocardial infarction, cognitive impairment can develop as a result of several factors including low cardiac output, cerebral hypoperfusion, and microembolization. Indeed, the Rotterdam Study found a significant association between cognitive impairment and prior myocardial infarction, and the Bronx Aging Study showed a significant association between myocardial infarction and dementia in elderly women (13, 14). By contrast, a cohort study and a case-control study failed to show an association between cognitive decline and prior myocardial infarction or coronary bypass grafting surgery (15, 42). Several methodological issues explain these discrepancies. In the Rotterdam Study, the difference in Mini-Mental State Examination scores between subjects with and without myocardial infarction was small, casting doubt on its clinical significance (13). In addition, the diagnosis of myocardial infarction was based only on electrocardiographic criteria; therefore, it is possible that some of the myocardial infarctions had been missed (e.g., non-Q-wave myocardial infarctions). Most importantly, this study used a cross-sectional design, which did not account for the time of onset of dementia (13). In the Bronx Aging Study, the time of detection of myocardial infarction was not specified (14). In the epidemiologic studies published so far, the subjects were prospectively enrolled; hence, they had to volunteer for cognitive assessment, likely resulting in selection bias.

The separation between myocardial infarction preceding or following the dementia is methodologically important (43). Because of the sampling on presence or absence of dementia, myocardial infarction preceding the dementia should be evaluated with a case-control analysis (dementia is the dependent variable), while myocardial infarction following dementia should be evaluated with a cohort analysis (dementia is the independent variable) as we did in the present study. The only study that analyzed the occurrence of myocardial infarction many years following the diagnosis of dementia, similarly to our study, did not detect an association (15).

After the onset of dementia, the risk of myocardial infarction was lower in the presence of dementia. This association was not affected by survival bias (subjects with dementia experiencing worse survival), as the analysis accounted for the competing risk of death.

It is conceivable that the diagnosis of validated myocardial infarction, which relies heavily on the patient’s

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**TABLE 2.** Cohort analysis for myocardial infarction following dementia, Rochester, Minnesota, 1985–1994

<table>
<thead>
<tr>
<th></th>
<th>No. of patients with dementia</th>
<th>No. of referent subjects</th>
<th>Hazard ratio*</th>
<th>95% confidence interval*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>35</td>
<td>64</td>
<td>0.54</td>
<td>0.36, 0.82</td>
<td>0.004</td>
</tr>
<tr>
<td>Death</td>
<td>837</td>
<td>698</td>
<td>1.67</td>
<td>0.71, 1.19</td>
<td>0.516</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>313</td>
<td>370</td>
<td>0.82</td>
<td>0.70, 0.95</td>
<td>0.010</td>
</tr>
</tbody>
</table>

* Adjusting for age at index year and sex.
complaint of cardiac pain, is more difficult to confirm among subjects with dementia. To this end, we observed a trend toward demented subjects with myocardial infarctions to report cardiac pain less often and to present with ST segment elevation more often than their dementia-free counterparts. This suggests that there may be particular difficulties in diagnosing myocardial infarction among patients with dementia, and that the lower risk of myocardial infarction may reflect underascertainment.

Cardiac death

As discussed above, subjects affected by dementia may have a different clinical presentation; therefore, they may be less likely to be diagnosed with a myocardial infarction. Thus, validated myocardial infarction may be an inadequate measure of the burden of cardiovascular disease in the setting of dementia. Therefore, it is of interest to examine whether subjects with dementia have any cardiovascular condition listed on the death certificate more often than dementia-free subjects.

Little is known about specific causes of death among subjects with dementia (44). Most of the previous studies considered only death from all causes; they often did not have a comparison group and thus used standardized mortality ratios (44). In the few studies investigating this matter, cardiovascular disease was the second most frequent cause of death after pneumonia (29, 45). However, relying on a single cause of death from the death certificate (underlying cause) likely increases the potential for misclassification, which may differ between subjects with and without dementia (27–29).

Thus, to minimize the effect of differential misclassification and to capture all forms of cardiovascular disease irrespective of their perceived causal link with death, we considered all entries in the death certificate. Given the shorter survival of patients with dementia compared with referents and to avoid overestimating the association of dementia with cardiac death, the analysis accounted for the competing risk from death of other causes. We observed that patients with dementia had a lower risk of cardiac death compared with referents.

Limitations and strengths

This study has some potential limitations. Because of the retrospective nature of the study, we lack information on other potential confounders. The diagnosis of dementia was retrospective, which may lead to misclassification bias. However, a neurologist with expertise in dementia confirmed the diagnosis while using rigorous criteria. Moreover, medical documentation was evaluated beyond the point at which dementia was diagnosed to document its progression and natural history. The study time frame antedated the 1996 consensus criteria for dementia with Lewy body (46); therefore, features of dementia with Lewy body outside of motor and cognitive domains were not recorded historically in the medical records. The limited number of endpoints does not enable robust analyses of subgroups based on the types of dementia.

Unmasking in data collection (exposure-suspicion bias) is unlikely because the data collection for myocardial infarction relied on standardized epidemiologic criteria (23) applied by abstractors unaware of the exposure (dementia) status. It is possible that patients who have a myocardial infarction before the dementia are at higher risk of death due to the myocardial infarction (or die earlier, before developing dementia) compared with patients without myocardial infarction. In the case-control study, because cases were selected on the basis of the disease, this differential survival bias may underestimate the association between cardiovascular disease and dementia.

While there may be difficulties in assigning the underlying cause of death, the use of cardiac death appearing anywhere on the death certificate increased its sensitivity. Moreover, the procedures for the completion of the death certificate in Rochester differ from those in most other places. The coroner or a pathologist, member of the staff of the Mayo Clinic, completes the death certificates of almost all county residents under the care of Mayo physicians, irrespective of whether or not an autopsy is performed. The entire medical record is reviewed before assigning the cause of death (23). The inverse association between dementia and cardiac death is hypothesis generating, and the investigation of the possible explanations should be the subject of future studies. Finally, myocardial infarction represents only one manifestation of clinical heart disease, and we cannot exclude that dementia may be associated with other clinical manifestations of atherosclerosis.

This study also has a number of strengths. First, it is population based, which minimizes the effect of referral bias and improves the generalizability of the results. Second, dementia cases, referents, and endpoints were all ascertained in the same population over the same period of time by use of rigorous criteria by abstractors who were unaware of the study hypothesis (18, 21, 23). Third, reliance on incident myocardial infarction is important to evaluate the association with myocardial infarction after the index year, because it reduced the risk of incidence-prevalence bias. Fourth, the matched design allows taking into consideration age and sex, which are two major confounders in this study. Finally, to the best of our knowledge, this is one of the few studies that use a method akin to follow-back approaches (47–51) to test this hypothesis, and thus it provides directions for future research.

In this population-based study, there was no evidence of a positive association between dementia and preceding myocardial infarction. In addition, compared with their dementia-free counterparts, subjects with dementia exhibited a decreased risk of myocardial infarction and cardiac death following dementia.

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REFERENCES