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# CENTRAL AUDITORY DYSFUNCTION AS A HARBINGER OF ALZHEIMER'S DEMENTIA

**George A. Gates, MD, FACS[Emeritus Professor]**,
University of Washington, Department of Otolaryngology – Head & Surgery, Seattle, WA

**Melissa L. Anderson, MS[Biostatistician]**,
Group Health Research Institute, Seattle, WA

**Susan M. McCurry, PhD[Research Professor]**,
University of Washington, Department of Psychosocial and Community Health, Seattle, WA

**M. Patrick Feeney, PhD[Associate Professor]**, and
University of Washington, Department of Otolaryngology – Head & Neck Surgery, Seattle, WA

**Eric B. Larson, MD, MPH[Executive Director and Senior Investigator]**
Group Health Research Institute, Seattle, WA

## Abstract

**Objective—**Confirm that central auditory dysfunction may be a precursor to the onset of Alzheimer's Disease (AD)

**Design—**Cohort study

**Setting—**Research study center

**Participants—**274 volunteers from a dementia surveillance cohort were followed for up to 4 years after having complete audiometric assessment. 21 of the participants received a consensus diagnosis of AD after hearing testing.

**Intervention—**Three central auditory tests were performed: the Dichotic Sentence Identification, the Dichotic Digits, and the Synthetic Sentence Identification with Ipsilateral Competing Message.

**Main Outcome Measures—**A new diagnosis of Alzheimer's disease using the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria at a consensus conference

**Results—**The mean scores on each CAD test were significantly poorer in the incident dementia group. Cox proportional hazards models with age as the time-scale were used to estimate the hazard ratio for incident dementia based on CAD test results. After adjusting for educational level, the hazard ratio for incident dementia in people with severe CAD based on a Dichotic Sentence Identification in free report mode of <50% was 9.9 (95% C.I. 3.6, 26.7).

**Conclusions—**In these cases, CAD was a precursor to Alzheimer's dementia. We recommend evaluating older adults complaining of hearing difficulty with CAD tests. Those with severe CAD should receive a modified rehabilitation program and be considered for referral for neurologic evaluation.

Corresponding Author: George A. Gates, M.D., Virginia Merrill Bloedel Hearing Research Center, University of Washington, Box 357923, Seattle, WA 98195-7923, 830-336-4117 (Phone), ggates@u.washington.edu.

# Introduction

## Background

The growing prevalence and high virulence of Alzheimer's (AD) dementia has created a serious public health problem. Early detection of people with AD is a logical strategy for emerging treatments aimed at limiting the progression of the disorder. However, given the insidious onset of AD, it is difficult to distinguish the normal cognitive decline of aging from pathologic dysfunction in the early stages of AD. In this report we present data suggesting that central auditory dysfunction (CAD) may be an early manifestation of AD, and we make the case that use of CAD testing for older people with hearing complaints might have future utility in the earlier recognition of cognitive disorders such as AD.

CAD is suspected when people have difficulty understanding speech in the presence of background noise - a common problem for older adults. Most people with age-related CAD can converse reasonably well in quiet but do poorly in noise, the so-called cocktail party effect, which is also referred to by the terms "central presbycusis" and "age-related processing disorder".

CAD impedes communication and confounds conventional auditory rehabilitation in proportion to its severity. The pathophysiology of CAD is not fully understood but dichotic listening paradigms have been widely used to study interhemispheric interaction and callosal function. A number of studies such as the early work by Grady and colleagues [1;2] reported that AD patients' inability to divide attention in dichotic performance tasks was related to anterior temporal lobe atrophy and reduced glucose metabolism. More recent research has further implicated involvement of parietal and frontal areas which influence attention processing as well as a variety of executive function activities such as planning and initiation of activites.[3;4] Extracting auditory signals in noise or competing signals, as in CAD testing, requires substantial attentional and behavioral processing resources and we theorize that the neurodegeneration of the different cortical areas affected by dementia may affect CAD testing before other cognitive screening tests become abnormal.

CAD prevalence increases with age and is common in people diagnosed with AD. CAD is also more prevalent in older people with mild memory impairment compared to cognitively normal older people.[5] These findings suggest that CAD demonstrated by speech-in-noise testing or competing speech is a sign of subtle cognitive dysfunction. Given the dramatic world-wide increase in AD cases and the finding that many people have subtle cognitive dysfunction years before a diagnosis of AD is made[6], efforts aimed at early identification and at-risk status are appropriate. A logical question to ask is: do tests of CAD have a potential role in evaluating those elderly people with hearing complaints for possible cognitive decline? This question has direct clinical relevance because tests for CAD using competing speech are widely available, easy to administer in a short time, and are already in use for planning auditory rehabilitation.

In a previous study of the Framingham dementia cohort, *severe* CAD based on very low scores (<50% correct) on the Synthetic Sentence Identification with Ipsilateral Competing Message test was found to presage an incident dementia diagnosis by 3–12 years with a risk ratio of 9 –12.[7] The present study was conducted to confirm these findings in a different population and to determine if other competing speech tests are also associated with incipient dementia. Thus, we ascertained the presence and degree of CAD in a cohort of older individuals with and without mild memory impairment but no clinical diagnosis of dementia and followed their cognitive status for 4 years. Our hypotheses were:

- Older people with CAD would be more likely to experience the onset of dementia than people without CAD, controlling for age, and educational level.

- In older people with mild, amnestic, single-domain cognitive impairment - but no other manifestations of dementia - severe CAD would be more prevalent than in those with normal cognitive status
- Competing speech tests with a dichotic presentation (Dichotic Sentence Identification) would be more likely to be associated with an increased risk of dementia diagnosis in the follow-up period than tests involving dichotic digits (Dichotic Digits Test) or unilateral competing speech paradigms (Synthetic Sentence Identification with Ipsilateral Competing Message).

## Methods and Materials

### Participants

Participants were enrolled in the Adult Changes in Thought (ACT) study, a population-based longitudinal study of aging and dementia that began in 1994. The ACT study was designed to determine the incidence of Alzheimer's disease, other types of dementia and cognitive impairment, and to determine risk factors for these conditions. The details of the ACT study have been described previously.[8]

The present report is a longitudinal study of the 313 members of the ACT cohort who participated in hearing testing.[5] For the current analysis of incident dementia, 17 subjects with a dementia diagnosis at the time of hearing testing were excluded. In addition, 21 cognitively normal people who dropped out of the ACT study without a follow-up visit for cognitive assessment after the hearing testing were also excluded. These exclusions resulted in an analysis sample of 274 participants. At the time of hearing testing, 54 (20%) participants were judged as memory-impaired without dementia on the basis of a Cognitive Abilities Screening Instrument (CASI) total score ≤ 86, *or* a total CASI ≤ 90 with a CASI memory subscale score ≤ 10, *and* a team consensus diagnosis confirming no dementia was present. The ACT study does not assess subjects as having Mild Cognitive Impairment (MCI) but this memory-impaired group likely includes persons in this category. Details regarding group classification procedures can be found in Gates et al. (2008).

Informed consent was obtained for all participants using forms and procedures approved by the Human Studies Committee of the University of Washington and Institutional Review Board of the Group Health Cooperative.

### Cognitive Screening

The CASI consists of 25 items which cover nine cognitive domains (attention, mental manipulation, orientation, short-term memory, long-term memory, language ability, visual construction, list-generating fluency, and abstraction and judgment). Total scores range from 0 to 100, with higher scores indicating better cognitive performance. After the baseline exam, follow-up examinations which include CASI screening, are conducted biennially in the ACT study to identify incident cases of dementia and AD. Participants scoring 87 or higher on the CASI are considered dementia free.

All participants were administered the CASI at the ACT baseline exam and at each biennial evaluation. Persons scoring ≤86 on the CASI were referred for a standardized clinical and neuropsychological evaluation which was reviewed at a consensus diagnosis meeting attending by a geriatric physician, neurologist, research nurse, and neuropsychologist. Dementia diagnosis was based upon criteria in the 4$^{th}$ edition of the Diagnostic and Statistical Manual (DSM-IV). [9] Participants with dementia who met National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [10] criteria for possible or probable Alzheimer's

disease at the consensus conference were considered AD cases. The date of dementia onset is define by convention as the date halfway between the ACT study visit which triggers the dementia evaluation and the most recent prior ACT study visit.

## Hearing Testing

### Peripheral Auditory Tests

The status of the peripheral auditory system was assessed using standard clinical equipment and spaces. Conventional tympanometry, pure-tone behavioral thresholds and word recognition scores were obtained with equipment that met ANSI S3.6-1996 specifications. Additional details can be found in Gates et al. (2008).[5] Participants were required to have word recognition scores at a high but comfortable level in quiet of 72% correct or better to be included in the study.

### Auditory Evoked Potential (AEP) Test Battery

To control for the functional status of the ascending auditory pathways and primary auditory cortex, Auditory Brainstem Responses (ABR), Middle Latency Responses (MLR), and Late Latency Responses (LLR) were obtained using standard clinical paradigms that measured both amplitude and latency of the waveforms. (See Gates et al., 2008[5] for technical details and results). Because none of the AEP test results differed by cognitive status or incident dementia conversion, the data are not shown here.

### Central Auditory Processing Tests

The three behavioral central auditory tests were: 1) the Synthetic Sentence Identification test with ipsilateral competing message (SSI-ICM), 2) the Dichotic Sentence Identification test (DSI) in the free mode, and 3) the Dichotic Digits test (DDT). The sequence of test presentation was randomized to prevent an order effect. Recorded materials on compact disc used for the tests were obtained from Auditec of St. Louis. The poorer score across ears was used in the present analyses.

**Synthetic Sentence Identification test with Ipsilateral Competing Message (SSI-ICM)—**The SSI-ICM requires the listener to select which one of 10 nonsense sentences was presented against a background of an interesting narrative presented by the same talker in the same ear. A practice presentation of 1 to 3 lists was completed with a +10 dB signal-to-noise ratio (SNR). For the actual test the stimulus was at 0 dB SNR at the same presentation level. Up to 30 presentations may be necessary to reach an asymptote.[11;12] Only one list of 10 sentences was presented for participants scoring 90% or better, two lists if the score was 80% or better, otherwise three lists were presented. This strategy was used for both the training and the actual test. Since raw SSI-ICM scores are known to decrease with age and hearing level, we used a presentation level 50 dB above the mean pure-tone threshold (at .5 1.0 2.0 kHz) and insert earphones to enhance high-frequency audibility and avoid collapsing ear canals.[13] To obtain optimal performance from the participants, pauses between presentations were taken as needed for slow responders. Correct identification of 80% or more of presentations is considered normal.

**Dichotic Sentence Identification (DSI) test—**The DSI uses six of the same sentences as the SSI but presents one sentence to each ear simultaneously. The sentences were presented at 50 dB above the PTA in each ear and the participant was asked to select from a printed list which two sentences were heard. Fifer et al. (1983) showed that the test is resistant to the effects of sensorineural hearing loss until the degree of loss exceeds 50 dB HL. The DSI was administered as outlined by Jerger et al. (1994) in the free report mode. Five presentations were used if the score was 100%, otherwise, another five sentences per

ear, respectively, were administered (20 sentences in total). In adults the right ear scores are normally higher than the left ear scores, presumably due to age-related corpus callosum dysfunction.[14] Normal scores are 80% and above in adults.

**Dichotic Digits Test (DDT)—**The DDT is a widely used dichotic test to screen for central auditory dysfunction.[15] The DDT was given at 50 dB above the PTA for each ear. After practice sessions are completed, 25 sets of double-digit pairs were presented for a total of 50 digits per ear. The participant reported all digits heard for each presentation and a percent-correct score was calculated for each ear. If all numbers were recognized correctly, a score of 100% (50 × 2) was given. The participant reports all digits heard for each presentation and a percent-correct score was calculated for each ear. The DDT is relatively easy to administer, is not greatly affected by mild to moderate hearing loss [16], and is commonly abnormal in people with probable AD.[17] Normal scores for adults are 90% and above.[18]

## Statistical Methods

The behavioral CAD tests were scored on both the left and right ear of each study participant. For each CAD test, the current analysis used the poorer of the two scores from the left and right ears.

Mann-Whitney rank-sum tests were used to evaluate differences in the peripheral audiometric measures between participants with a dementia diagnosis during follow-up compared to those without a dementia diagnosis. Cox proportional hazards models with age as the time-scale were used to estimate the hazard ratio for incident all-cause dementia and AD associated with moderate or severe CAD. In analyses with AD as the outcome, follow-up time for participants with a dementia diagnosis of a type other than AD is censored at the dementia diagnosis date. Patients without a dementia diagnosis are censored at the date of their last ACT study visit. Regression models were adjusted for education level. STATA version 11 for Windows statistical software was used for data analysis (College Station, TX: StataCorp LP).

## Results

Table 1 shows the demographic characteristics of the study population. Thirty-seven percent were male, and nearly half (49%) were college graduates. The mean age was 80 years with a range of 71–96 years. Fifty-seven percent said they had a hearing problem but only 12 % had ever used a hearing aid. The word recognition score was normal (80% correct or better) in at least one ear for all participants, and between 72%-80% in the poorer ear in 7 (3%) participants.

Twenty-three participants had a positive consensus dementia diagnosis resulting from a follow-up ACT assessment 10 – 48 months (mean= 26.4 months) after the hearing testing. The mean time from hearing testing to dementia onset for the incident cases was 14 months. Of the 23 all-cause dementia diagnoses, 21 (91%) also met the NINCDS-ADRDA criteria for possible or probable AD. Eighteen of the incident dementia cases were from those with memory-impairment at the time of hearing testing, and five were from the cognitively normal group. These five subjects received their dementia diagnosis at 4, 9, 19, 21, and 24 months, respectively, after hearing testing.

Table 2 displays the mean scores for each of the three CAD tests and the percentage of participants with moderately abnormal (<80% correct) and severely abnormal (< 50% correct) results, stratified by dementia status during follow-up. On each hearing measure evaluated, the incident dementia group performed worse than the non-demented group, and

the differences were statistically significant. On average, the non-demented group scored approximately 75% correct across all three tests. The success across tests was more varied for the incident dementia group, with a mean score of 55% for the SSI-ICM, and 58% for the DDT. The incident dementia group scored particularly poorly on the DSI test, with a mean score of 37%. The proportion of participants scoring below the threshold for severe abnormality ranged between 8.8% (DDT) and 19.1% (SSI-ICM) among the non-demented participants. Among the incident dementia group nearly two-thirds (65%) scored in the severely abnormal range on the DSI test.

The results from the Cox proportional hazards models are summarized in Table 3. Since only 2 of the incident dementia cases were non-AD dementia, the regression results for all-cause dementia and AD dementia were similar. Only the results for the outcome of incident AD dementia are presented here. The adjusted hazard ratio for severe CAD (<50%) based on the DSI test was 9.9 (95% CI: 3.6–26.7). Moderate impairment (<80%) on the DSI test was also associated with increased risk of AD diagnosis, with an estimated hazard ratio of 6.8 (1.9, 24.1). Moderate impairment on the DDT was also associated with increased risk of AD, but a score of <50% was not a significant predictor. The SSI-ICM test results were not significant predictors at either level.

## Discussion

This is the second report showing an increased risk of a subsequent diagnosis of AD in older people with severe CAD. The present study showed that severe CAD as measured by the DSI in free report mode strongly and significantly predicted the risk of a subsequent diagnosis of AD up to 3 years later. The bulk of the incident dementia cases (80%) were in the original memory impaired group, based on the CASI test, and many of these may have had early dementia at the time of auditory testing if they had been evaluated. Nonetheless, the association of severe CAD and early dementia remains.

Given that over 1 million older people undergo auditory evaluation annually as part of the rehabilitation of age-related hearing loss, adding the DSI test to that evaluation would 1) be likely to establish or not establish the need for a modified aural rehabilitation program, 2) identify people at risk for cognitive dysfunction and 3) generate appropriate referrals at little extra cost or time.

Determining the presence of CAD using behavioral tests that employ dichotic competing speech paradigms has established value in selecting appropriate auditory rehabilitation measures for people with presbycusis.[19] In some cases, unilateral hearing aid fitting might be more appropriate than the customary binaural approach.[20] In addition, computer-based auditory training exercises are becoming widely available and may be useful in enhancing speech comprehension.[21]

The present study extends the utility of CAD testing in the detection of older people at-risk for cognitive decline. Those elderly people with very poor scores (<50%) on the dichotic competing speech tests but with normal or near-normal speech recognition in quiet may have cognitive decline as a factor. An area of future research would be a larger study to determine how frequent and what the longer term outcomes and eventually evaluate strategies aimed to target interventions on this population. We believe that today it is reasonable to consider such cases for referral for neurologic assessment.

If CAD indeed predicts the risk of a later dementia diagnosis, tests for CAD would have greater utility in the evaluation of elderly persons complaining of hearing difficulty than they do at present. CAD tests are currently used for people who are having difficulty with their hearing aids understanding speech in noise. If our results are again confirmed by future

studies, the case could be made for the widespread use of CAD tests to 1) a screen for both central auditory dysfunction as a cause of their complaints as well as 2) a risk factor for possible incipient dementia and, thus, an indication for neuropsychologic evaluation. While this approach would only identify a fraction of the total at-risk population, nonetheless this fraction could be evaluated for dementia sooner than the remainder of the population. Such a strategy would generate an enriched population for studies of new treatments designed to alter the course of the disease at an early stage.

## Strengths of study

The value of a prospective cohort approach is well-known. The auditory study was an addition to the original ACT study and benefited from the experience of the ACT scientists. Auditory testing was viewed by the cohort members as a popular addition to the study. The cohort members were familiar with the cognitive testing methods and easily adapted to the auditory test paradigms.

Early identification of people at risk for AD will become increasingly important especially if new, more effective treatments to delay the progression of AD are developed. Given that 1 million hearing aid evaluations of adults are done annually in the U.S. and that about 15% of these may have CAD, it is entirely plausible that central auditory testing could provide a useful screen for risk of preclinical AD. Additional study will be required to test that presumption.

## Weaknesses of study

The underlying premise of this study is that auditory testing might have utility as a screening test for dementia risk. The short span between hearing test and consensus in some cases argues that some participants, particularly those who failed consensus within 6 months of the auditory testing, may have been in an early, albeit undetected, stage of dementia at the time of their hearing test. However, none of these people were reported by their family members to be demented in terms of daily activities or worsened memory. Furthermore, the longer duration between test and consensus diagnosis for other subjects is consistent with our earlier findings. Because the transition between normalcy and dementia is usually envisioned as gradual, contemporary thinking suggests a transition zone between the two states. From that viewpoint, our CAD testing clearly labeled most of those who received a dementia diagnosis shortly after the auditory testing as being in such a transition. This is analogous to the now popular diagnostic state, Mild Cognitive Impairment. What is not known is whether CAD might be a good predictor of those persons with MCI who are more likely to progress. This is another important area where more research might be particularly valuable based on our results.

Another limitation of this study is the robustness of the results. The small sample size resulted in wide confidence intervals around estimated effect sizes. However, despite the wide confidence intervals, the results from this study support the findings from our prior study, and the consistency of the results across different study populations (ACT and Framingham) help to build the case for the observed associations.

Given that none of our subjects was diagnosed as demented at the time of hearing testing, the finding that CAD heralds a dementia diagnosis in a substantial number of cases has real-world implications. In our previous incident dementia cohort study, the SSI-ICM test was the only CAD test available. Comparison of the SSI-ICM, DDT, and DSI (Table 2) in the present study indicates that the DSI has the best predictive power for incident dementia among the three. In the present study, far greater effort was made to achieve maximum SSI-

ICM scores than was possible previously. It is possible but unproven that the modified SSI-ICM test paradigm[11] made the test "too easy".

The cut-point at which the CAD tests are imputed to be normal has traditionally been 80% or more correct. However, using that score as a cut-point in this and previous populations contributes to poor specificity of CAD testing in estimating the likelihood for subsequent dementia conversion. As in our previous report, a grossly abnormal score (<50% correct) in the presence of normal or near-normal word recognition scores improves the specificity greatly. Using the very low DSI score in people with normal or near-normal (above 72% correct) word recognition scores in quiet, the sensitivity (95% CI) of the low DSI score to detect incipient dementia is 65% (95% CI 44%, 86%) and the specificity is 88% (95% CI 84%, 92%), with a positive predictive value of 34% (95% CI 20%, 49%) and a negative predictive value of 97% (95% CI 94%, 99%). These findings illustrate the importance of considering the results of CAD testing in the elderly as merely indicators for further evaluation, rather than indicative of a definitive dementia diagnosis.

## Summary

We recommend that central auditory function be evaluated in senior citizens seeking assistance for hearing difficulty generally, and in those specifically complaining about difficulty hearing in noise. Patients who have a very-poor score (i.e. <50% correct) and are not known to be demented should be considered prime candidates for referral and evaluation of cognitive function. In the present study, the Dichotic Sentence Identification Test in free-report mode was the test most likely to uncover a latent cognitive defect. The DDT test using <80% correct as the cutpoint was also associated with a subsequent dementia diagnosis, though it was not as robust as the DSI at <50% correct criterion. The DDT is easier to complete than the DSI or SSI, so there were fewer people falling into the very low score category.

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## Table 1

Baseline demographic characteristics by performance on the DSI test

| | DSI < 50% N=44 | DSI ≥ 50% N=230 | Total N=274 |
|---|---|---|---|
| Gender, n (%) | | | |
| Female | 27 (61.4) | 145 (63.0) | 172 (62.8) |
| Male | 17 (38.6) | 85 (37.0) | 102 (37.2) |
| Age in years, mean (sd) | 83.3 (5.6) | 78.9 (4.8) | 79.6 (5.2) |
| Educational Level | | | |
| ≤High school | 18 (40.9) | 52 (22.7) | 70 (25.6) |
| Some college | 13 (29.6) | 56 (24.5) | 69 (25.3) |
| College graduate | 13 (29.6) | 121 (52.8) | 134 (49.1) |
| Hearing complaint | | | |
| No | 13 (29.6) | 105 (45.7) | 118 (43.1) |
| Yes | 31 (70.5) | 125 (54.4) | 156 (56.9) |
| Ever used a hearing aid | | | |
| No | 36 (81.8) | 206 (89.6) | 242 (88.3) |
| Yes | 8 (18.2) | 24 (10.4) | 32 (11.7) |
| Pure-tone average, mean (sd) | | | |
| Better ear | 27.8 (8.5) | 22.7 (8.7) | 23.5 (8.9) |
| Worse ear | 33.2 (8.5) | 26.9 (9.4) | 27.9 (9.5) |
| Word recognition score, worse ear | | | |
| < 80 | 42 (95.5) | 225 (97.8) | 267 (97.5) |
| ≥ 80 | 2 (4.6) | 5 (2.2) | 7 (2.6) |
| Cognitive Abilities Screening Instrument (CASI), baseline | 88.8 (5.4) | 95.6 (3.9) | 94.5 (4.9) |

## Table 2

Comparison of CAD tests by incident dementia during follow-up

| | Non-demented N=251 | Incident Dementia N=23 | |
|---|---|---|---|
| **Percent correct** | **Mean (sd)** | **Mean (sd)** | **P-value** |
| DSI * | 73 (24) | 37 (34) | <0.01 |
| DDT+ | 75 (16) | 58 (18) | <0.01 |
| SSI-ICM # | 74 (25) | 55 (29) | <0.01 |
| **Moderately abnormal test (<80% correct)** | **N (%)** | **n (%)** | **P-value** |
| DSI * | 112 (44.6) | 19 (82.6) | <0.01 |
| DDT+ | 127 (50.6) | 20 (87.0) | <0.01 |
| SSI-ICM # | 106 (42.2) | 17 (73.9) | <0.01 |
| **Severely abnormal test (<50% correct)** | **N (%)** | **n (%)** | **P-value** |
| DSI * | 29 (11.6) | 15 (65.2) | <0.01 |
| DDT+ | 22 (8.8) | 5 (21.7) | 0.046 |
| SSI-ICM # | 48 (19.1) | 10 (43.5) | <0.01 |

* Dichotic Sentence Identification (DSI), Free report mode; worse ear score

+ Dichotic Digits Test

# Synthetic Sentence Identification with Ipsilateral Competing Message

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**Table 3**

Hazard ratios (HR) for incident AD dementia in relation to low performance on the hearing tests

| | At Risk | Follow-up person-years | Events | Incidence* | Unadjusted | | Adjusted† | |
|---|---|---|---|---|---|---|---|---|
| **Severe CAD** | **N** | | **n** | | **HR** | **95% CI** | **HR** | **95% CI** |
| DSI | | | | | | | | |
| ≥ 50% correct | 230 | 600.9 | 7 | 11.6 | 1.0 | Reference | 1.0 | Reference |
| < 50% correct | 44 | 90.3 | 14 | 155.0 | 9.1 | 3.4, 24.5 | 9.9 | 3.6, 26.7 |
| DDT | | | | | | | | |
| ≥50% correct | 247 | 631.0 | 16 | 25.4 | 1.0 | Reference | 1.0 | Reference |
| < 50% correct | 27 | 60.2 | 5 | 83.1 | 2.1 | 0.7, 6.4 | 2.2 | 0.7, 7.0 |
| SSI-CCM | | | | | | | | |
| ≥50% correct | 216 | 558.7 | 12 | 21.5 | 1.0 | Reference | 1.0 | Reference |
| < 50% correct | 58 | 132.5 | 9 | 67.9 | 1.5 | 0.5, 4.4 | 2.1 | 0.7, 6.6 |
| **Moderate CAD** | | | | | | | | |
| DSI | | | | | | | | |
| ≥ 80% correct | 143 | 377.0 | 3 | 8.0 | 1.0 | Reference | 1.0 | Reference |
| < 80% correct | 131 | 314.2 | 18 | 57.3 | 5.7 | 1.7, 19.9 | 6.8 | 1.9, 24.1 |
| DDT | | | | | | | | |
| ≥80% correct | 127 | 338.1 | 2 | 5.9 | 1.0 | Reference | 1.0 | Reference |
| < 80% correct | 147 | 353.1 | 19 | 53.8 | 6.6 | 1.5, 28.9 | 7.0 | 1.6, 31.0 |
| SSI-CCM | | | | | | | | |
| ≥80% correct | 151 | 393.0 | 5 | 12.7 | 1.0 | Reference | 1.0 | Reference |
| < 80% correct | 123 | 298.2 | 16 | 53.7 | 2.3 | 0.8, 6.8 | 2.5 | 0.9, 7.5 |

Incidence per 1000 person-years

† Adjusted for education