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The increasing incidence of anticoagulant-associated intracerebral hemorrhage

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Abstract—*Objective:* To define temporal trends in the incidence of anticoagulant-associated intracerebral hemorrhage (AAICH) during the 1990s and relate them to rates of cardioembolic ischemic stroke. *Methods:* We identified all patients hospitalized with first-ever intracerebral hemorrhage (ICH) in greater Cincinnati during 1988, from July 1993 through June 1994, and during 1999. AAICH was defined as ICH in patients receiving warfarin or heparin. Patients from the same region hospitalized with first-ever ischemic stroke of cardioembolic mechanism were identified during 1993/1994 and 1999. Incidence rates were calculated and adjusted to the 2000 US population. Estimates of warfarin distribution in the United States were obtained for the years 1988 through 2004. *Results:* AAICH occurred in 9 of 184 ICH cases (5%) in 1988, 23 of 267 cases (9%) in 1993/1994, and 54 of 311 cases (17%) in 1999 ($p < 0.001$). The annual incidence of AAICH per 100,000 persons was 0.8 (95% CI 0.3 to 1.3) in 1988, 1.9 (1.1 to 2.7) in 1993/1994, and 4.4 (3.2 to 5.5) in 1999 ($p < 0.001$ for trend). Among persons aged ≥80, the AAICH rate increased from 2.5 (0 to 7.4) in 1988 to 45.9 (25.6 to 66.2) in 1999 ($p < 0.001$ for trend). Incidence rates of cardioembolic ischemic stroke were similar in 1993/1994 and 1999 (31.1 vs 30.4, $p = 0.65$). Warfarin distribution in the United States quadrupled on a per-capita basis between 1988 and 1999. *Conclusions:* The incidence of anticoagulant-associated intracerebral hemorrhage quintupled in our population during the 1990s. The majority of this change can be explained by increasing warfarin use. Anticoagulant-associated intracerebral hemorrhage now occurs at a frequency comparable to subarachnoid hemorrhage.

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Community use of warfarin anticoagulation for stroke prevention in patients with atrial fibrillation became more common following publication of pivotal clinical trials in the 1990s.[1-8] The risk-benefit ratio of warfarin treatment for atrial fibrillation is good among certain high-risk subgroups, including patients with prior thromboembolism, but is narrower when used for primary prevention among elderly subjects, where benefits may be offset by increased bleeding.[9,10] Although intracranial bleeding is the most feared complication of warfarin use, anticoagulant-associated intracerebral hemorrhage (AAICH) has not been well studied in population-based settings. Intracerebral hemorrhage (ICH) is conservatively estimated to occur in 67,000 persons in the United States annually; precise estimates of the incidence and demographic characteristics of AAICH are not available.[11] We hypothesized that AAICH is increasing in frequency, and therefore studied the incidence of AAICH in three groups assembled from the same population before and after publication of important clinical trials of warfarin use for stroke prevention. To assess the potential benefit of warfarin in preventing ischemic stroke, we also determined incidence rates for patients hospitalized with ischemic stroke of cardioembolic mechanism during two of these periods.

Methods. This study includes three groups of patients with ICH and two groups of patients with ischemic stroke derived from the five-county Greater Cincinnati/Northern Kentucky (GCNK) area. Group 1 was assembled from January 1988 through December 1988, included only patients with ICH and subarachnoid hemorrhage, and has been the subject of previous reports.[12,13] Cases were identified by review of primary and secondary International Classification of Diseases-9 (ICD-9) codes 430, 431, 432.9, 436, 437.3, and 747.81 at all regional hospitals and a review of coroner's cases.[13] Group 2 was assembled from July 1993 through June 1994 and Group 3 was assembled from January 1999 through December 1999 during comprehensive epidemiologic stroke studies performed during those years (the Greater Cincinnati/Northern Kentucky Stroke Study or GCNKSS).[11,14] The GCNKSS involved ascertainment of both hemorrhagic and ischemic stroke events. In 1993/1994, study nurses screened the medical records of all inpatients with primary or secondary stroke-related ICD-9 discharge diagnoses (430–438) from all acute-care hospitals in the study region. Patients with stroke not found by inpatient screening were ascertained by monitoring all stroke-related visits to hospital emergency departments (with the exception of Cincinnati Children's Hospital) and screening of coroner's cases. In 1999, the ICD-9 codes screened were changed to 430–436 for inpatient as-

Table 1 *Annual incidence rates for intracerebral hemorrhage (ICH), anticoagulant-associated intracerebral hemorrhage (AAICH), and ischemic stroke in the Greater Cincinnati/Northern Kentucky area**

	1988	1993–1994	1999
All ischemic stroke	NA	140.0 (133.2–146.8)	142.6 (135.8–149.3)
Cardioembolic ischemic stroke	NA	31.1 (27.9–34.3)	30.4 (27.3–33.5)
Cardioembolic ischemic stroke due to atrial fibrillation	NA	22.0 (19.3–24.7)	20.6 (18.1–23.2)
All ICH	16.5 (14.1–18.9)	22.1 (19.4–24.8)	24.6 (21.8–27.4)
AAICH	0.8 (0.3–1.3)	1.9 (1.1–2.7)	4.4 (3.2–5.5)

Parentheses indicate 95% confidence intervals.

* Age-, sex-, and race-adjusted to the 2000 US population, expressed per 100,000 persons.

NA = not available.

certainment because codes 437 and 438 produced an extremely low yield for the 1993/1994 data.[15]

The 1993/1994 and 1999 epidemiologic studies also included monitoring of university and public health clinics as well as a sampling scheme of private outpatient physician offices and nursing homes.[11] To provide consistency with data from 1988, strokes ascertained in the outpatient setting were not included in incidence calculations. Residents of the five-county GCNK region seek care almost exclusively at one of the participating metropolitan hospitals included in each study period.[13] Patients living outside of the five counties of interest were excluded by zip code of residence.

In all periods, nurses performed chart abstraction for all potential cases. These abstracts were then reviewed in detail by study physicians. Physicians assigned a stroke category and mechanism to each event based upon all available information, using criteria previously reported.[11,16] Intracerebral hemorrhage was defined as the nontraumatic, abrupt onset of severe headache, altered level of consciousness, or focal neurologic deficit associated with a focal collection of blood within the brain parenchyma on neuroimaging or at autopsy.[17] Exclusion criteria for ICH applied to all cohorts were traumatic ICH and hemorrhage associated with brain tumor, encephalitis, recent endarterectomy, or thrombolytic treatment of ischemic stroke. Among patients with ICH, prior ischemic stroke was not exclusionary unless the ICH was judged to be the hemorrhagic conversion of a recent (<2 week old) infarct.

AAICH was defined as ICH while patients were receiving warfarin or heparin. Among warfarin users no lower limits of prothrombin time (PT) or international normalized ratio (INR) values were set because a previous study has suggested that among these patients INR values <2 confer similar ICH risk to values of 2 to 3.[18] Warfarin or heparin use was determined from chart review. The first available INR value upon medical presentation was recorded.

Subtyping of ischemic stroke cases was performed using criteria adapted from the Classification of Cerebrovascular Diseases III and epidemiologic studies in Rochester, MN.[16,17,19-21] Ischemic stroke subtypes were cardioembolic, large vessel, small vessel (lacunar), other, and stoke of undetermined cause. In cases meeting criteria for >1 cause, study physicians made a final judgment about the most likely cause, except when cases met criteria for both large vessel and cardioembolic stroke, which were classified as large-vessel.[16] Conditions allowing designation of an ischemic stroke as cardioembolic in mechanism included myocardial infarction within 6 weeks of stroke onset, mitral valve stenosis, artificial heart valve, atrial fibrillation or atrial flutter by history or EKG, thrombus in the atrium or ventricle or on the aortic or mitral valve, left ventricular aneurysm, akinetic left ventricular wall segment, and sick sinus syndrome.

Incidence rates were calculated for first-ever ICH, first-ever AAICH, first-ever ischemic stroke, first-ever ischemic stroke with a cardioembolic mechanism, and first-ever cardioembolic stroke attributed to atrial fibrillation. For the calculation of incidence rates, the entire population of the five GCNK counties was considered at risk. Denominator age-, race-, and sex-specific population estimates for each study year were obtained from published census data.[22] For the 1988 cohort, population estimates from 1990 were used. Overall incidence rates were age-, race-, and sex-adjusted to the 2000 US population. To statistically compare incidence rates Poisson regressions were performed with Proc Genmod (SAS 9.1) using year as the independent variable and adjusting for age, race, and sex with the five-county GCNK populations as the offset. When three incidence rates were available a p value for trend was obtained using year as a continuous variable. When two incidence rates were available a pairwise comparison was obtained with 1999 as reference and year as a categorical variable. The institutional review board for each participating hospital system approved each study.

To correlate changes in stroke incidence with warfarin use, we obtained records of warfarin distribution in the United States from 1988 to 2004 from the MIDAS database maintained by IMS Health Inc. (personal communication, IMS Health Inc., IMS MIDAS database, data extracted November 2005).[23] The data are expressed as counting units and represent shipments of warfarin from wholesalers to clinical points of care (pharmacies, clinics, and hospitals). IMS Health collects data on approximately 98% of wholesaler warehouse shipments and figures are adjusted to reflect non-covered warehouses. Sales for products purchased by retail pharmacies directly from the manufacturer are collected from 100 manufacturers. These data are unprojected (personal communication, IMS Health, August 2006). While counting units are not equivalent to prescriptions or the number of warfarin users, they represent a reasonable proxy for drug sales volume.

To account for population growth between 1988 and 2004, values are expressed as warfarin counting units per 100,000 persons in the United States for each year. For 1988, 1993/1994, and 1999 the values for warfarin counting units per 100,000 persons were divided by the AAICH incidence rates to produce warfarin counting units per AAICH. These data were used to extrapolate an AAICH incidence rate for 2004. A lower estimate was produced by assuming the value of warfarin counting units per AAICH remained stable between 1999 and 2004. Total warfarin counting units (per 100,000 persons) was then divided by this number. An upper estimate was produced by using the average annual percent change in warfarin counting units per AAICH from 1988 to 1999 and applying this value to the interval from 1999 to 2004.

Results. AAICH occurred in 9 of 184 ICH cases (5%) in 1988, 23 of 267 ICH cases (9%) in 1993/1994, and 54 of 311 ICH cases (17%) in 1999 ($p < 0.001$). Records of brain imaging or autopsy were available for 181/184 cases in 1988, 262/267 cases in 1993/4, and 309/311 cases in 1999. Warfarin accounted for 21 of 23 AAICH cases (91%) in 1993/1994 and 53 of 54 AAICH cases (98%) in 1999. INR values were available for 46 of 53 AAICH patients taking warfarin in 1999. INR intensity was <2 for 15 patients (33%), 2 to 3 for 12 patients (26%), 3 to 4 for 8 patients (17%), and >4 for 11 patients (24%).

For each period incidence rates for all ICH, AAICH, all ischemic stroke, all cardioembolic ischemic stroke, and cardioembolic ischemic stroke attributed to atrial fibrillation are presented in table 1. Incidence rates for all ICH, AAICH and ischemic stroke attributed to atrial fibrillation

Table 2 *Age-stratified annual stroke incidence rates in the Greater Cincinnati/Northern Kentucky area**

	1988	1993–1994	1999
All ICH			
Overall	16.5 (14.1–18.9)	22.1 (19.4–24.8)	24.6 (21.8–27.4)
Age 0–49	2.2 (1.3–3.2)	3.2 (2.1–4.3)	5.0 (3.6–6.5)
Age 50–69	26.4 (19.6–33.2)	41.0 (32.7–49.4)	39.0 (31.1–47.0)
Age 70–79	76.0 (55.4–96.6)	103.4 (80.1–126.6)	99.6 (77.0–122.3)
Age 80+	140.5 (102.0–178.9)	156.6 (118.2–195.0)	207.0 (164.6–249.4)
AAICH			
Overall	0.8 (0.3–1.3)	1.9 (1.1–2.7)	4.4 (3.2–5.5)
Age 0–49	0.2 (0–0.5)	0.1 (0–0.3)	0.3 (0–0.7)
Age 50–69	0.9 (0–2.2)	3.7 (1.1–6.3)	5.5 (2.5–8.6)
Age 70–79	5.7 (0.1–11.4)	12.3 (4.2–20.4)	24.3 (12.9–35.6)
Age 80+	2.5 (0–7.4)	13.0 (1.5–24.6)	45.9 (25.6–66.2)
Ischemic stroke caused by atrial fibrillation			
Overall	NA	22.0 (19.3–24.7)	20.6 (18.1–23.2)
Age 0–49	NA	0.3 (0–0.7)	0.1 (0–0.3)
Age 50–69	NA	20.0 (14.1–25.9)	15.5 (10.5–20.6)
Age 70–79	NA	117.1 (92.9–142.8)	95.1 (72.9–117.3)
Age 80+	NA	298.7 (245.4–351.9)	324.8 (272.1–377.4)

Parentheses indicate 95% confidence intervals.

* Overall rates are age-, sex-, and race-adjusted to the 2000 US population. Age-specific rates are sex- and race-adjusted to the 2000 US population. All rates are expressed per 100,000 persons.

ICH = intracerebral hemorrhage; AAICH = anticoagulant-associated intracerebral hemorrhage; NA = not available.

in 1988, 1993/1994, and 1999 are stratified by age in table 2. The age-, sex-, and race-adjusted incidence of all ICH per 100,000 persons increased from 16.5 (95% CI 14.1 to 18.9) in 1988 to 24.6 (21.8 to 27.4) in 1999 ($p < 0.001$ for trend), driven by a change between 1988 and 1993/1994 ($p < 0.001$) but not between 1993/1994 and 1999 ($p = 0.24$). The incidence of AAICH increased from 0.8 (0.3 to 1.3) in 1988 to 4.4 (3.2 to 5.5) in 1999 ($p < 0.001$ for trend). AAICH rates changed most dramatically in persons age ≥80 years, rising from 2.5 (0 to 7.4) in 1988 to 45.9 (25.6 to 66.2) in 1999 ($p < 0.001$ for trend). Between 1993/1994 and 1999 there was no change in the incidence of first-ever cardioembolic ischemic stroke of any cause (31.1 vs 30.4, $p = 0.65$) or first-ever cardioembolic ischemic stroke attributed to atrial fibrillation (22.0 vs 20.6, $p = 0.44$). Among persons age ≥80 the incidence of stroke attributed to atrial fibrillation increased from 298.7 to 324.8 cases per 100,000 persons ($p = 0.47$). The mean age of persons ≥80 years with ischemic stroke attributed to atrial fibrillation did not change between 1993/1994 and 1999 (86.0 years vs 86.4 years, $p = 0.51$), indicating that incidence rates were not altered by an increase in mean age in this open-ended age stratum.

Data from the MIDAS database are shown in the figure. The distribution of warfarin in the United States increased from 114,248 counting units per 100,000 persons in 1988 to 499,813 counting units per 100,000 persons in 2004. The value warfarin counting units per AAICH decreased from 142,810 in 1988 to 97,197 in 1999, suggesting that AAICH incidence increased at a faster rate than warfarin distribu-

tion. The extrapolated AAICH incidence in our area for 2004 was 5.1 to 6.5 cases per 100,000 persons.

To determine how many cases of ICH may have been missed in 1988 because of coding methodology, we applied the ICD-9 codes used in 1988 to ICH cases ascertained in
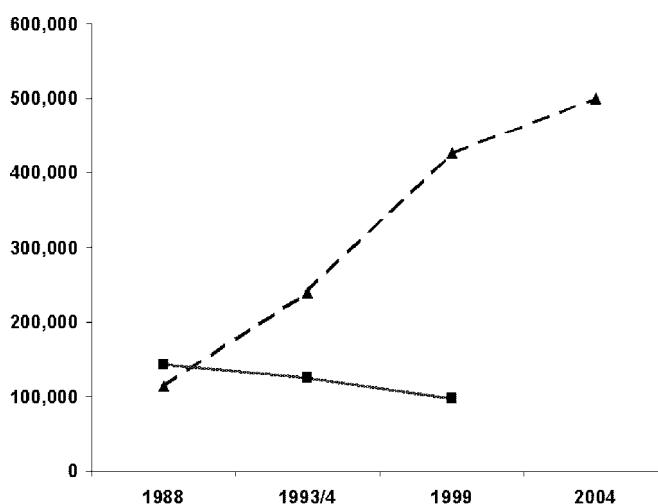

Figure. Warfarin counting units and anticoagulant-associated intracerebral hemorrhage over time. The x-axis is time. The y-axis represents warfarin counting units per 100,000 persons (dashed line with triangles) and warfarin counting unit per anticoagulant-associated intracerebral hemorrhage (solid line with squares).

1993/1994 and 1999. Using only those codes applied in 1988, in 1993/1994 we would have missed 21 of 267 total ICHs (8%) and 1/23 AAICHs (4%). For 1999 we would have missed 23/311 total ICHs (7%) and 6/54 AAICHs (11%). Thus, we estimate that our data from 1988 underestimate the true number of ICH cases and AAICH cases for that year by 5 to 10%.

Discussion. This study provides the first estimates of AAICH incidence rates and documents that AAICH incidence quintupled in our region during the 1990s. Previous reports suggested a growing number of anticoagulant-associated hemorrhages in the last two decades but the magnitude of the problem has not been defined on a population scale.[24,25] To place the burden of AAICH in context, its overall incidence is now only slightly less than subarachnoid hemorrhage, which occurs at a rate of 6.6 cases per 100,000 persons in our metropolitan area.[26]

Data from the MIDAS database show that the distribution of warfarin to points of care nearly quadrupled on a per capita basis between 1988 and 1999 (figure). Warfarin use for the prevention of ischemic stroke in patients with atrial fibrillation increased dramatically following publication of the Stroke Prevention in Atrial Fibrillation (SPAF) trials, European Atrial Fibrillation Trial, and other studies in the 1990s.[1-9] An analysis of the Cardiovascular Health Study found that warfarin use among patients with atrial fibrillation rose from 13% to 50% between 1990 and 1996, while a study of participants in the National Ambulatory Medical Care Survey documented an increase from 28% to 41% between 1991 and 2000, including an increase from 14% to 48% among patients age ≥80.[1,2] The downward trend for "warfarin counting units per AAICH" over time (figure) suggests that rates of AAICH increased more rapidly than the distribution of warfarin. This may be due to a disproportionate increase in warfarin use among elderly persons who have higher bleeding risks.

Warfarin is the predominant cause of AAICH and atrial fibrillation is the most common reason for warfarin use. We found only a small, nonsignificant drop in the incidence of first-ever ischemic stroke caused by atrial fibrillation between 1993/1994 and 1999. This contrasts with a report from Olmsted County, MN, in which rates of first-ever ischemic stroke among patients with atrial fibrillation remained relatively stable between 1980 and 1994 but declined between 1995 and 2000.[8] A recent study of a large sample of Medicare recipients also documented a decline in ischemic stroke rates among persons with atrial fibrillation between 1992 and 2002 (from 46.7 per 1,000 patient years to 19.5 per 1,000 patient years).[27] Additionally, the prevalence of atrial fibrillation in the United States appears to be increasing over time independent of age.[27-29] Given this fact, rates of cardioembolic stroke might have been expected to increase, and therefore we believe that our static incidence rates likely represent benefit from warfarin use in prevention of ischemic stroke. Differences in study methodologies make it difficult to further reconcile our conflicting results.

The benefit of warfarin for patients with atrial fibrillation is unequivocal among certain high risk subgroups without strong contraindications to anticoagulation, most notably patients with prior thromboembolism. In the setting of primary prevention for patients with atrial fibrillation, women age ≥75 and hypertensive men age ≥75 are at relatively high risk for ischemic stroke on aspirin therapy, but these patients also have higher bleeding risks from warfarin.[10,30] A recent meta-analysis of atrial fibrillation treatment trials found that among patients age ≥75 years, treatment with warfarin instead of aspirin reduced the annual rate of ischemic stroke from 5.9% to 3.7% but increased the annual rate of serious bleeding from 1.5% to 3.2%.[10] Management of warfarin anticoagulation in elderly patients is made more difficult by drug interactions and the need for scrupulous dose adjustment to maintain the desired INR value of 2 to 3.[31] While INR values above 3 produce greater risk of AAICH, in our population fewer than half of AAICHs were associated with supratherapeutic anticoagulation.[32] Thus, stricter INR regulation among patients using warfarin would only partially attenuate the rise in AAICH incidence. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study, designed to compare aspirin and warfarin therapy among patients with atrial fibrillation age ≥75 years, has completed recruitment and may further clarify the risk-benefit ratio for warfarin among the elderly.[33] In our population incidence rates for ischemic stroke attributed to atrial fibrillation among persons age ≥80 years increased in a nonsignificant manner between 1993/1994 and 1999, while point estimates for AAICH incidence increased more than tenfold between 1988 and 1999, heightening concern about bleeding and the risk-benefit ratio of warfarin in this elderly group.

In addition to its use for atrial fibrillation, warfarin is used for secondary stroke prevention in patients with alternative stroke mechanisms (or unknown mechanism), for primary prevention in patients with mechanical heart valves, for prevention and treatment of deep venous thrombosis, and for other thrombotic disorders. The effectiveness of warfarin in the setting of mechanical heart valves and deep venous thrombosis is clear but its use for stroke prevention among patients without a definite cardioembolic mechanism or hypercoagulable state has scant support and is likely to increase bleeding risk.[34-38]

Patients with AAICH are known to have worse outcomes than other patients with ICH.[39-41] Current treatment for AAICH includes supportive care and reversal of coagulopathy with vitamin K and either fresh-frozen plasma or prothrombin complex concentrates.[42] Little data exist comparing the efficacy of these agents. Given the number of AAICHs now occurring annually clinical treatment trials in this

area are warranted. Alternative anticoagulants are being developed and tested, including inhibitors of thrombin and factors IXa and Xa, but thus far none has proven clearly safer or more effective than warfarin.[43]

Our study has several limitations. We did not include persons with ICH who did not present to a hospital or have a postmortem examination because such cases were not ascertained in 1988, but these instances are rare (only two ICH cases were ascertained among outpatients in 1999). We studied only hospitalized, first-ever cases of cardioembolic ischemic stroke. Warfarin provides significant secondary risk reduction for patients with minor ischemic stroke and atrial fibrillation.[6] In our 1993/1994 epidemiologic study we did not routinely document the mechanism of recurrent ischemic strokes and so we cannot produce accurate incidence rates for recurrent cardioembolic infarcts. Our rates may therefore underestimate the benefit of increasing warfarin use.

The modest increase in ICH incidence over time is partly attributable to the increase in AAICH. Race specific rates also show a relatively large increase in ICH incidence among African Americans between 1988 and 1993/1994 (data not shown), suggesting that some ICH cases among African Americans were missed in 1988, and that the increase in all ICH between 1988 and 1993/1994 is partly artifact. Our review suggests that the ICD-9 codes used in 1988 resulted in 5 to 10% of cases being missed relative to later years. We do not believe this discrepancy invalidates our findings. Even if the incidence of AAICH for African Americans was equal to that for whites in 1988, the overall incidence of AAICH in that year would only rise from 0.8 to 0.9 cases per 100,000 persons. Furthermore, the increase in AAICH incidence was greater in the second period of our study (1993/1994 to 1999) than the first. Approximately 2/3 of the increase in point estimates of ICH among persons age ≥80 between 1988 and 1999 is accounted for by the rise in AAICH. When AAICH cases are removed, the change in ICH incidence in this age group becomes nonsignificant.

To our knowledge, counting units have not been previously used to estimate trends in national drug use outside of retail settings. Nonetheless, the information presented from the MIDAS database is consistent with the observed increase in AAICH incidence as well as other studies showing increased warfarin use among patients with atrial fibrillation. Finally, the Greater Cincinnati/Northern Kentucky region is representative of the United States with regard to median age, percent African American, median household income, education level, and percent of population below the poverty level.[15] It is possible that in some respects the GCNK population does not follow national trends in AAICH incidence or warfarin use. However, previous estimates from our epidemiologic stroke studies have proven consistent with data from other sources.[11]

Warfarin is highly effective for the prevention of ischemic stroke in appropriately selected patients with atrial fibrillation, and the risk-benefit ratio favors anticoagulation in many patients.[9,44] Our findings should not discourage warfarin use when appropriate, but rather spur research into safer alternatives to warfarin, improved risk stratification for elderly patients, and better treatments for patients with hemorrhagic complications.

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NEW FELLOWSHIP CREATED IN PARKINSON RESEARCH

The AAN Foundation and the Parkinson's Disease Foundation have partnered to create a new clinical research training fellowship, The Parkinson's Disease Foundation/AAN Foundation Clinician Scientist Development Award. The two-year award will provide $75,000 per year to support training in clinical research in Parkinson disease. Applications are due February 1, 2007. For information, visit www.neurofoundation.org/pcrtf.

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