

Psoriasis Independently Increases Stroke Risk

BY BRUCE JANCIN
Denver Bureau

KYOTO, JAPAN — Severe psoriasis appears to be a potent risk factor for stroke independent of the traditional stroke risk factors, Dr. Rahat S. Azfar said at an international investigative dermatology meeting.

She presented a case-control study drawn from the U.K. General Practice Research Database (GPRD) in which she found severe psoriasis was associated with an excess stroke risk amounting to one additional stroke per 530 patients per year attributable to the immune-mediated skin disease, beyond background levels of traditional stroke risk factors.

"Given the prevalence of psoriasis worldwide, these numbers carry a potentially significant impact on public health," observed Dr. Azfar of the University of Pennsylvania, Philadelphia.

Psoriasis affects roughly 2.5% of the population worldwide, including an estimated 4.5 million U.S. adults.

She and her colleagues previously had shown psoriasis to be an independent risk factor for acute MI, also using the GPRD. But the relationship between psoriasis and stroke had never before been studied.

The GPRD is an extensive electronic medical record including more than 9 million U.K. patients under the care of general practitioners/family physicians in 450 primary care practices. Dr. Azfar reported on 129,143 patients with mild psoriasis in 1987-2002 and 496,666 contemporaneous controls without psoriasis, along with 3,603 patients with severe psoriasis and 14,330 separate controls. The mean follow-up was about 4 years.

As found in other studies, patients with severe psoriasis had higher rates of obesity and smoking than did controls, while rates of these and other traditional cardiovascular risk factors were similar in patients with mild psoriasis and in controls.

After adjustment for the major stroke risk factors—diabetes, hyperlipidemia, smoking, obesity, hypertension, age, and gender—patients with mild psoriasis were found to have a statistically significant 6% per year increased relative risk of stroke. In contrast, the stroke risk in patients with severe psoriasis was increased by 43% per year, compared with matched controls.

The attributable risk of stroke in patients with mild psoriasis was 2.4 strokes per 10,000 person-years, and with severe psoriasis it was 1.9 strokes per 1,000 person-years.

A caveat: Data audit suggested up to 15% of patients categorized in the GPRD as having mild psoriasis may actually have had moderate disease. If so, truly mild psoriasis may not be associated with any significant excess in strokes, Dr. Azfar said.

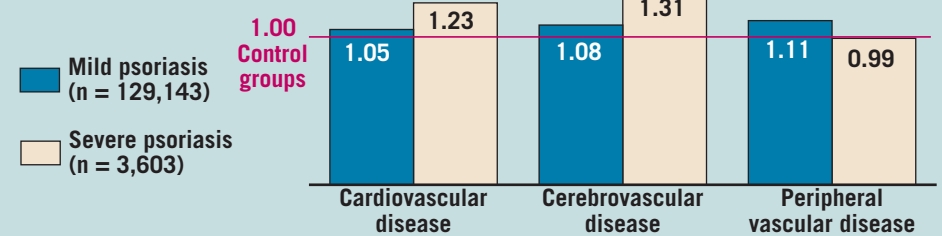
The hypothesis is that the link between psoriasis and stroke—and MI as well—lies in Th1/Th17-mediated systemic inflammation, a prominent shared feature, she explained at the meeting, sponsored by the European Society for Dermatological Research, the Japanese Society for Investiga-

tive Dermatology, and the Society for Investigative Dermatology.

To examine the possibility that the excess stroke risk seen in severe psoriasis was a function of toxicities of treatments for the disease rather than being intrinsic to severe psoriasis itself, the investigators reanalyzed the data

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Odds Ratios of Atherosclerotic Diseases In Psoriasis Patients at 4-Year Follow-Up



Notes: Odds ratios adjusted for traditional factors. There were 496,666 controls for mild psoriasis and 14,330 controls for severe psoriasis.

Source: Mr. Shin

ADVERTORIAL

The need is great.
The evidence is building.

IDENTIFY A CULPRIT IN CV RISK

What you do
today can have
immediate and
long-term impact

Hospital-based providers are in a unique position to help reduce the CV risk associated with undetected or uncontrolled diabetes.¹⁻⁵ Routine assessment of blood glucose (BG) levels, identification of high-risk patients using an A1C test, and referral of identified patients to the hospital diabetes team can help improve glycemic control.⁵⁻¹⁰

The need is great.

Continued from previous page

after excluding methotrexate users or restricting the analysis to patients treated with oral retinoids. It didn't have any significant impact upon the results. Neither did exclusion of psoriatic arthritis patients.

Elsewhere at the conference, Daniel B. Shin, Dr. Azfar's coinvestigator, presented an analysis of the rates of cardiovascular, cerebrovascular, and peripheral vascular disease in the same study population. The rationale for this additional analysis was that MI and stroke are acute thrombotic events, and it would be

informative to see if psoriasis is also associated with increased rates of chronic atherosclerotic diseases as reflected in the appropriate diagnostic codes, as well as procedure codes for coronary revascularization, carotid endarterectomy, and peripheral vascular intervention.

This indeed proved to be the case. As for stroke, the associated risks generally were greater with severe than with mild psoriasis, noted Mr. Shin, a medical student at the university. (See chart, page 14.)

The ongoing GPRD studies are partially funded by an unrestricted grant from Centocor. The investigators reported having no conflicts of interest. ■

'Bridging' With Enoxaparin Or Heparin Appears Risky

BY MARY ANN MOON
Contributing Writer

For patients with cardioembolic stroke, "bridging" therapy with either enoxaparin or heparin until long-term warfarin treatment takes effect raised the risk of serious bleeding, compared with immediately commencing warfarin, a study shows. In contrast, initiating warfarin shortly af-

ter cardioembolic stroke was found to be safe in this single-center retrospective review of 204 patients, according to Dr. Hen Hallevi of the University of Texas at Houston and associates (Arch. Neurol. 2008 July 14 [doi:10.1001/archneur.65.9.noc70105]).

Because this study was retrospective and nonrandomized, the results await validation; they should be viewed as "hypothesis-generating," and should be interpreted with caution, they noted.

Currently no consensus exists on when and how to institute long-term anticoagulation for secondary stroke prevention in these patients. "Bridging" with enoxaparin or heparin is common practice even though it is not endorsed in published guidelines, the investigators said.

Many clinicians also defer initiating warfarin for fear of precipitating a hypercoagulable state, which "may occur when warfarin is initiated without heparin and may lead to abnormal clotting and skin necrosis," they said. However, this is an uncommon occurrence in clinical practice, and is usually associated with protein C deficiency, they added.

In this study, all cases of cardioembolic stroke between April 2004 and July 2006 were reviewed. The decisions of whether to use bridging and, if so, whether to use enoxaparin or heparin were "based on clinical judgment and personal preference of the treating physician."

Thirty-five patients were given warfarin immediately, without any bridging. Forty-four received heparin bridging, and 29 received enoxaparin bridging. Another 8 patients received no anticoagulation therapy, and 88 received aspirin only.

The patients who received no anticoagulation or only aspirin fared poorly and were 12 times more likely to experience stroke progression than those in the other treatment groups.

Heparin bridging was significantly more likely to cause systemic bleeding, and enoxaparin bridging was significantly more likely to cause grade 2 parenchymal hematoma, compared with immediate warfarin.

There were no episodes of skin necrosis in the warfarin group, supporting the observation that this complication is very uncommon in clinical practice and that bridging specifically to prevent skin necrosis is unwarranted, Dr. Hallevi and his associates said.

Moreover, there was a clustering of cases of late, symptomatic hemorrhagic transformation "composing an alarming 10%" of the enoxaparin group, with no cases in the warfarin and heparin groups. This suggests a pathophysiologic link between enoxaparin and hemorrhagic transformation, they added.

"Warfarin treatment appears to be safe and can be started at any point during the hospital stay, along with deep vein thrombosis prophylaxis. [In contrast], bridging with a full dose of enoxaparin or heparin may carry a high risk of intracranial and systemic bleeding," the researchers said. ■

Hospital interventions to help reduce CV risk

ASSESS BG levels to help improve outcomes

Data supporting the impact of elevated BG on CV outcomes are compelling. In a review of 409 cardiac surgery patients, Gandhi et al found that a rise of only 20 mg/dL in mean postoperative BG level correlated with a 30% increase in adverse events, including death, up to 30 days postsurgery.¹¹

Krinsley found a relationship between levels of inpatient hyperglycemia considered acceptable and mortality.² In fact, at a BG level of 160 mg/dL, he observed an ~3-fold increase in mortality compared with 80 mg/dL.² In another study by Zerr et al, uncontrolled hyperglycemia was associated with an increased rate of postoperative deep sternal wound infections in 1585 cardiac surgery patients.¹²

These data underscore the need to assess BG levels to help identify inpatient hyperglycemia.

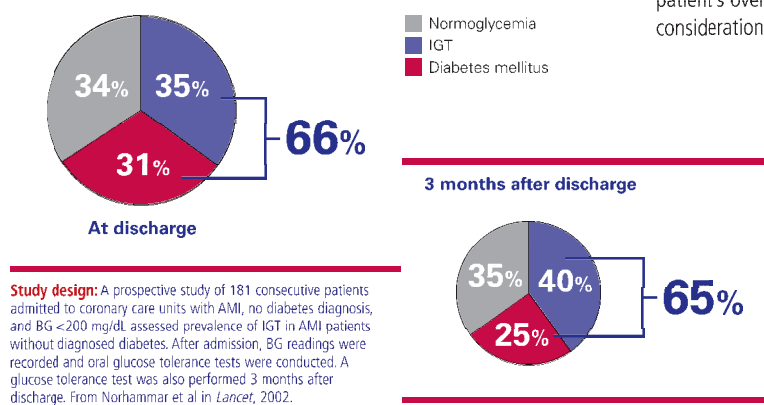
IDENTIFY high-risk patients using an A1C test

Despite improvements in disease management, 56% of patients with diabetes on prior antidiabetic therapy had uncontrolled A1C levels, according to NHANES data.¹³ This demonstrates the prevalence of poor glycemic control and the need to order A1C tests in hospitalized CV patients.¹⁰

In patients with acute myocardial infarction (AMI) and no prior diagnosis of diabetes, impaired glucose tolerance (IGT) and new-onset diabetes are common. The first pie graph shows that newly diagnosed diabetes or IGT was found in 2 out of 3 AMI patients.¹⁴

The second pie graph illustrates that 65% of these patients still met diagnostic criteria for diabetes or IGT 3 months postdischarge, when acute stress, left ventricular dysfunction, and inflammation should have subsided.¹⁴

PREVALENCE OF IGT AND NEWLY DETECTED DIABETES IN AMI PATIENTS¹⁴



SECOND IN A 3-PART SERIES ON DIABETES AND CARDIOVASCULAR CARE

Large epidemiologic studies correlate A1C control with CV outcomes

Data suggest that A1C elevations have a predictive relationship with negative CV outcomes. In a prospective 3-year study of 10,232 patients, each 1% increase in A1C was associated with a 20% to 30% increase in coronary and CV complications.¹⁵

Conversely, relative risk analysis in UKPDS showed that each 1% decrease in A1C significantly reduced CV disease events by up to 16%.¹⁶ A third epidemiologic, 6-year study of 2820 subjects confirmed that A1C testing was predictive of diabetes, whether used alone or together with fasting plasma glucose (FPG) results.¹⁷ Taken together, these studies highlight the value of A1C testing to help identify high-risk CV inpatients.^{16,17}

A1C—a practical approach

To diagnose outpatients with diabetes, the ADA and AACE urge consecutive testing of FPG over 2 days, with an oral glucose tolerance test to confirm results. Since this method requires second-day evaluation of patients who can drink fluids, it may be unrealistic for CV inpatients.^{8,9}

For these reasons, A1C testing offers a more practical way for CV care providers to identify previously undetected or uncontrolled diabetes in their inpatients.^{8,9,18}

A1C results also provide a snapshot of the patient's BG control over the past 2 to 3 months. This long-term view may be especially valuable in determining the patient's preadmission BG control.^{8,19}

As with any lab test, A1C results should be evaluated in the context of a patient's overall medical history and status. Refer patients with special considerations to the diabetes team.⁸

REFER high-risk patients to hospital diabetes team

For CV inpatients with newly diagnosed or poorly controlled diabetes, referral to a diabetes team for discharge planning may help improve patients' BG control at home.²⁰

On the horizon

Ongoing trials may further clarify the association between uncontrolled or undetected diabetes and CV risk. Results of some of these studies are expected in the next 2 years.²¹ Stay tuned.

References: 1. Haffner SM, Lehto S, Ronnema T, et al. *N Engl J Med*. 1998;339:229-234. 2. Krinsley JS. *Mayo Clin Proc*. 2003;78:1471-1478. 3. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853. 4. Bucerius J, Gummert JF, Walther T, et al. *Thorac Cardiovasc Surg*. 2003;51:11-16. 5. Nesto RW. *Rev Cardiovasc Med*. 2006;7(suppl 2):S18-S24. 6. Ishihara M, Inoue I, Kawagoe T, et al. *Eur Heart J*. 2006;27:2413-2419. 7. McAlister FA, Majumdar SR, Blitz S, et al. *Diabetes Care*. 2005;28:810-815. 8. American Diabetes Association. *Diabetes Care*. 2008;31(suppl 1):S12-S54. 9. American Association of Clinical Endocrinologists. *Endocr Pract*. 2007;13(suppl 1):3-68. 10. Aguilar D, Solomon SD, Kober L, et al. *Circulation*. 2004;110:1572-1578. 11. Gandhi GY, Nuttall GA, Abel MD, et al. *Mayo Clin Proc*. 2005;80:862-866. 12. Zerr KJ, Furnary AP, Grunkemeier GL, et al. *Ann Thorac Surg*. 1997;63:356-361. 13. Malik S, Lopez V, Chen R, et al. *Diabetes Res Clin Pract*. 2007;77:126-133. 14. Norhammar A, Tenerz A, Nilsson G, et al. *Lancet*. 2002;359:2140-2144. 15. Khaw K-T, Wareham N, Bingham S, et al. *Ann Intern Med*. 2004;141:413-420. 16. Stratton IM, Adler AI, Neil HAW, et al. *BMJ*. 2000;321:405-412. 17. Droumaguet C, Balkau B, Simon D, et al. *Diabetes Care*. 2006;29:1619-1625. 18. American College of Cardiology/American Heart Association Task Force. *J Am Coll Cardiol*. 2004;44:671-719. 19. Lab Tests Online. A1C. <http://www.labtestsonline.org/understanding/analytes/a1ctest.html>. Accessed February 4, 2008. 20. DCCT/EDIC Study Research Group. *N Engl J Med*. 2005;353:2643-2653. 21. ClinicalTrials.gov Web site. <http://clinicaltrials.gov/ct2/show/NCT00032487?term=VADT&rank=1>. Accessed December 4, 2007.