

COMMENTS AND RESPONSES

Biological Significance of Anti-Cyclic Citrullinated Peptide Antibody in Rheumatoid Arthritis

TO THE EDITOR: We read with great interest the thorough meta-analysis and review by Nishimura and colleagues (1) on the diagnostic accuracy of anti-cyclic citrullinated peptide (CCP) antibody in rheumatoid arthritis (RA). The authors conclude that although anti-CCP antibodies are more specific than rheumatoid factor, their sensitivity is only 67%. However, we believe that anti-CCP may in fact define a biologically distinct subset of RA, and therefore a simple assessment of its sensitivity for RA in general may be misleading. Emerging data show that the presence of anti-CCP antibodies interacts with genetic risk factors, such as the shared epitope in the human leukocyte antigen locus (2); environmental risk factors, such as smoking (3, 4); and response to treatment (5). Therefore, anti-CCP positivity may not be as important for diagnosing RA as for being the first of a new generation of biomarkers that allow us to redefine RA according to biological and genetic categories rather than purely phenotypic ones. Such a transition has already begun in oncology, where lymphomas have been reclassified according to biomarker status rather than histology, leading to better definition of prognosis and treatment responses (6). Thus, in the future, we should be thinking not about the sensitivity and specificity of CCP for RA, but rather about anti-CCP-positive versus anti-CCP-negative RA.

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Potential Financial Conflicts of Interest: Drs. Roubenoff and Beckman are employees of Biogen Idec.

References

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2. Irigoyen P, Lee AT, Wener MH, Li W, Kern M, Batliwalla F, et al. Regulation of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis: contrasting effects of HLA-DR3 and the shared epitope alleles. *Arthritis Rheum.* 2005;52:3813-8. [PMID: 16320316]
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5. Mikuls TR, O'Dell JR, Stoner JA, Parrish LA, Arend WP, Norris JM, et al. Association of rheumatoid arthritis treatment response and disease duration with declines in serum levels of IgM rheumatoid factor and anti-cyclic citrullinated peptide antibody. *Arthritis Rheum.* 2004;50:3776-82. [PMID: 15593224]

6. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. ; Lymphoma/Leukemia Molecular Profiling Project. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346:1937-47. [PMID: 12075054]

TO THE EDITOR: I read the article by Nishimura and colleagues (1) with great interest. The use of anti-CCP testing makes RA diagnosis more accurate, which allows earlier detection in an attempt to avoid joint damage. However, the study has 3 potential pitfalls. First, up to 20% of new patients with RA are seronegative in the first year, when early diagnosis is essential to prevent erosive joint disease. It would have been helpful to see the anti-CCP data during the first, vitally important year of disease. Other modalities, such as magnetic resonance imaging and ultrasonography, play a role in the early detection of RA. Second, false-positive results do occur with the anti-CCP test because of cross-reactivity to citrullinated proteins found in inflamed joints. I have several patients with gout or lupus who have tested false-positive for anti-CCP, which has delayed a correct diagnosis in some cases. Finally, most physicians, including rheumatologists, do not differentiate between first- and second-generation anti-CCP assays and use whichever is clinically available to them. As mentioned, selection of the anti-CCP assay is important because of potential false-positive results. Many of the studies excluded in the meta-analysis used such assays. In conclusion, don't give up completely on the use of rheumatoid factor in diagnosing RA. Often, the use of both a rheumatoid factor test and an anti-CCP test can be clues that lead to accurate assessment of RA. In addition, I encourage consultation with a rheumatologist to make an early diagnosis and initiate aggressive treatment.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med.* 2007;146:797-808. [PMID: 17548411]

IN RESPONSE: Dr. Roubenoff and colleagues and Dr. Arkfeld raise interesting points in their letters. We admit that early diagnosis of RA requires a combination of anti-CCP testing and other new biological markers or diagnostic imaging tests. However, currently available studies for these are too limited to conduct meta-analysis quantitatively. The aim of our study was to clarify the diagnostic value of anti-CCP testing from studies conducted so far.

We appreciate the opinion expressed by Dr. Roubenoff and colleagues and agree that anti-CCP-positive and -negative RA may

be different subsets of RA and that levels of other biological markers, such as shared epitopes, play important roles in diagnosis. However, from the currently available evidence, we believe that the sensitivity and specificity of anti-CCP testing is still crucial for diagnosing RA. First, whereas anti-CCP is widely used for diagnosing RA, tests for new genetic markers, such as shared epitopes, are still not used routinely in daily practice. Second, the number of studies evaluating shared epitopes and anti-CCP is still low, and the clinical importance of this combination needs further evaluation. As far as we know, only Berglin and colleagues (1) have reported the sensitivity and specificity for the combination of shared epitope and anti-CCP testing. They reported that the sensitivity of the combination of anti-CCP and shared epitope testing was only 28% and the specificity was only 64%. We admit that the presence of anti-CCP antibodies interacts with genetic risk factors, such as shared epitopes in the human leukocyte antigen locus (2). However, data in the same study showed that anti-CCP was 50.9% positive for shared epitope-negative patients in the North American Rheumatoid Arthritis Consortium cohort, and that study has no information for specificity. To conduct a systemic review for the diagnostic value of anti-CCP and other new biological marker levels, we need more studies.

We thank Dr. Arkfeld for identifying 3 points that need clarification. First, for the early diagnosis of RA, we already evaluated and reported that the sensitivities and specificities showed the same tendencies (3). Second, we reported that, although the specificity of anti-CCP is 95%, the specificity of anti-CCP or rheumatoid factor is actually 83% because of the low specificity of rheumatoid factor for other rheumatic diseases. Therefore, if we include positive results of either rheumatoid factor or anti-CCP as the positive criteria for RA, we would observe potentially 17 positive results out of 100 in the population without RA and have more false-positive results. Therefore, we discussed measuring both anti-CCP and rheumatoid factor, in case there are any patients with high previous probability of RA or patients in rheumatology clinics, to avoid missing potentially treatable patient. Interpretation of these tests requires the prudent judgment of other clinical information. Third, although the current commercially available anti-CCP is usually a second-generation test, old studies used first-generation anti-CCP, which has lower sensitivity than rheumatoid factor.

The second-generation anti-CCP was developed to improve these sensitivities (4). We excluded the studies not by the generation of anti-CCP but by the availability of information needed to calculate likelihood ratios, sensitivity, and specificity. Studies that did not report the specificity provide no information about the false-positive results that Dr. Arkfeld asked about.

To further evaluate the points indicated in these 2 letters, we need more evidence.

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β -Blockers and Progression of Coronary Atherosclerosis

TO THE EDITOR: In their recent meta-analysis, Sipahi and colleagues (1) propose a mechanism of decreased atherosclerosis progression attributed to β -blockers. Why do we not see this when β -blockers are used in the treatment of hypertension? Prospective studies have shown no decreased incidence of myocardial infarction (MI) and stroke in patients treated with β -blockers versus placebo. How can this mechanism of decreased atherosclerosis progression be active in a patient who has had MI treated with β -blockers and not in a patient with hypertension treated with β -blockers? I think this contradiction demonstrates a fatal flaw in the conclusion reached by the meta-analysis.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Sipahi I, Tuzcu EM, Wolski KE, Nicholls SJ, Schoenhagen P, Hu B, et al. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med*. 2007;147:10-8. [PMID: 17606956]

IN RESPONSE: Dr. Dunaway's statement that "[p]rospective studies have shown no decreased incidence of myocardial infarction (MI) and stroke in patients treated with β -blockers versus placebo" is not true. The meta-analyses by Lindholm and colleagues (1) and Bradley and colleagues (2), involving more than 20 000 patients with hypertension, showed that β -blockers statistically significantly reduced the incidence of stroke by 19% compared with placebo (95% CI for relative risk, 0.71 to 0.93). Although a non-statistically significant reduction in incidence of MI occurred in these meta-analyses (CI for relative risk, 0.83 to 1.05), β -blockers statistically significantly reduced the incidence of MI by 28% to 41% in patients with a history of MI (3, 4). Recently, it has been recommended that β -blockers not be preferred over other antihypertensives as first-line agents in primary prevention. However, we stated that "... our analysis involved only patients with established coronary artery disease. Therefore, no conclusion about the effects of β -blocker use can be drawn for primary prevention (for example, hypertensive patients without coro-

nary artery disease).” This statement limits the implications of our study to secondary prevention.

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Potential Financial Conflicts of Interest: Dr. Sipahi has received an educational grant from Pfizer and lecture honoraria from AstraZeneca. Dr. Nissen has received research support from AstraZeneca, Eli Lilly, Pfizer, Takeda, Sankyo, and Sanofi-Aventis. Dr. Sipahi has also consulted for many pharmaceutical companies without financial compensation. All honoraria, consulting fees, or other payments from any for-profit entity are paid directly to charity so that no income or tax deduction is received.

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Can't We Improve on Advance Directives?

TO THE EDITOR: In his perspective on advance directives, Perkins (1) states what many physicians have known or suspected for a long time: Advance directives are of little or no benefit in many, if not most, end-of-life situations. This is undoubtedly why so few physicians draft advance directives for themselves.

I agree that we should not completely discard advance directives, because they do have value in at least 2 situations. The first is the patient who, because of advanced age or very poor health, is absolutely certain that he or she is ready to die a natural death when the time comes. These patients can clearly specify in writing that they want “do not resuscitate” status in the event of cardiac or respiratory arrest. They can then make this known to their family and friends.

The second situation is the patient who does not trust a certain family member to make medical decisions for them. This family member may be in the “next-of-kin” hierarchy and could gain legal power to make medical decisions for the patient if the patient becomes incompetent to make them. Patients in this situation should draft a durable power of attorney for health care that clearly excludes untrustworthy family members from the decision-making process.

Perhaps the greatest danger of current advance directives is that patients may unknowingly sign away their right to basic treatments, such as nutrition and hydration, in the event of serious illness complicated by incompetence. It could be argued that cases involving withdrawal of nutrition and hydration are so complex that they should not be covered by advance directives.

Patients are sometimes led to believe that if they don't sign an advance directive, they might be leaving the “burden” of difficult

medical decisions to their family. But isn't this one of a family's ultimate responsibilities? How many articles on death and dying issues have ended with the conclusion that the solution lies in “more and better use of advance directives”? The time has come for physicians (and the media) to stop exaggerating the benefits of advance directives.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Perkins HS. Controlling death: the false promise of advance directives. *Ann Intern Med*. 2007;147:51-7. [PMID: 17606961]

TO THE EDITOR: I share Perkins's hope for improvement in advance care planning (1), and I would like to share an observation from a primary care practice of more than 30 years. During this time, I have offered advance directives to all my patients and discussed the broad concept with them. Although few have completed the advance directive, essentially all patients have expressed the wish to forgo life support in a situation that looks hopeless (one patient was willing to say only that she wanted her family to make decisions if she were unable). I have noted this wish in my patients' records and have found that notation helpful in subsequent end-of-life discussions with families. On the basis of this observation, I think the greatest flaw in the concept of advance directives may be the underlying assumption that, unless otherwise indicated, people want to be kept alive in such conditions as a persistent vegetative state. It might make more sense to continue to make advance directives available to everyone, but to shift the burden of necessary documentation to those rare individuals who want to continue care that seems futile to their medical providers.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Perkins HS. Controlling death: the false promise of advance directives. *Ann Intern Med*. 2007;147:51-7. [PMID: 17606961]

TO THE EDITOR: “Every system is perfectly designed to produce the outcomes it achieves.” The article by Perkins (1) underscores this point. Whereas many patients believe that completing an advance directive improves the chance that their choices will be respected (2), the tragic events of this story demonstrate that health systems are often unprepared to recognize and honor a patient's preferences even when they are specifically stated.

The failure in the story of Mr. Jones is not because of a flawed advance directive but because the primary physician did not establish a support structure, such as hospice, to keep Mr. Jones comfortable at home and did not include his daughter in the planning. Because such support was lacking, it is not surprising that Mrs. Jones brought Mr. Jones to the hospital for management of his dyspnea. At that

point, the hospital failed to provide the resources, such as an ethics consultation or a palliative care team, to address the daughter's concern and honor the patient's clear wishes. The end result was that Mr. Jones was hospitalized against his wishes for expensive medical care that he specifically did not want.

A recent report by the Citizens Health Care Working Group (3) highlighted concerns with the quality of care at the end of life. The report noted that more than 50% of Americans wish to die at home, but only 15% are able to do so. It also noted that 25% of our health care dollars are spent in the last year of life and that care doesn't always improve quality or length of life (3), as is demonstrated in Mr. Jones's story.

End-of-life planning needs to 1) ensure that patients and families clearly understand the health condition, 2) design a plan around the patient's beliefs and values, 3) store the plan in a rapidly retrievable format throughout the health system, and 4) have systemwide commitment in honoring the plan.

Completing an advanced directive without these components in place is similar to having a patient sign a consent form for surgery without arranging operating room time, support staff, and a surgeon to perform the procedure—then being surprised and upset when the procedure does not happen, despite the appropriately signed and discussed consent form in the record. Is the problem a flawed consent form? When a more systematic approach to advance care planning is taken, a high degree of success is achieved (4, 5).

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Potential Financial Conflicts of Interest: Gundersen Lutheran Medical Foundation sponsors the Respecting Choices program, and Dr. Hammes receives a portion of his salary for work in that program.

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1. Perkins HS. Controlling death: the false promise of advance directives. *Ann Intern Med.* 2007;147:51-7. [PMID: 17606961]
2. Perkins HS, Cortez JD, Hazuda HP. Advance care planning: does patient gender make a difference? *Am J Med Sci.* 2004;327:25-32. [PMID: 14722393]
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IN RESPONSE: These letters represent a wide range of views about the usefulness of advance directives. Dr. Simcic's skepticism is similar to mine. Dr. Carter gives advance directives modest support, using them for now but hoping for better approaches in the future. Drs. Brasic and Hammes believe strongly that the current system of advance directives prevents overly aggressive treatment of dying patients, saves resources, and promotes comfort.

The view of Drs. Brasic and Hammes, whose end-of-life work I admire, differs most from my own. I believe their enthusiasm for advance directives rests on 2 faulty assumptions. The first is that

future illness is sufficiently predictable to permit useful advance instructions about care. Two studies indicate otherwise (1, 2). One study found that, despite receiving detailed patient-specific prognoses, physicians typically wrote do-not-resuscitate orders no sooner than 2 days before patients died, suggesting that "hopelessness" becomes apparent only late in a patient's course (1). The other study involved frequent functional assessments of elderly patients before they died (2). Functional decline followed 5 patterns, each accounting for about 20% of deaths: treatable but eventually terminal disease, such as cancer (slow decline over months, then a rapid decline to death); organ system failure, such as heart failure (waxing and waning function with frequent rescues until an eventual, unpredictable death); chronic frailty, such as dementia (low and slowly diminishing function with an unpredictable death); sudden death; and "unclassifiable" (2).

Today's patients, who often are suffering from multiple diseases simultaneously, might follow any of several possible patterns. The attendant unpredictability severely limits the usefulness of advance directives in planning care.

The second faulty assumption is that people behave logically and consistently. As my own studies suggest, few patients who believe that advance directives can promote their care wishes actually sign them (3). Furthermore, many signers do not grasp the implications of their advance directives (which may, therefore, inaccurately reflect their wishes in the event of a crisis), many proxies do not understand patients' wishes (4) or act on them faithfully, and many physicians do not incorporate those wishes into treatment.

I used to believe strongly in the predictive powers of medicine and in the rationality of patients, so I advocated vigorously for advance directives. Yet repeated disappointments have tempered my enthusiasm (5). I now believe that advance directives have only a limited role in prompting and structuring advance care planning and that their effect must not be exaggerated. I also believe there must be a better way to prepare patients, families, and health professionals for the arduous, unpredictable trials of end-of-life care. Health professionals must take the lead in finding that better way.

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Potential Financial Conflicts of Interest: None disclosed.

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2. Lunney JR, Lynn J, Foley DJ, Lipson S, Guralnik JM. Patterns of functional decline at the end of life. *JAMA.* 2003;289:2387-92. [PMID: 12746362]
3. Perkins HS, Geppert CM, Gonzales A, Cortez JD, Hazuda HP. Cross-cultural similarities and differences in attitudes about advance care planning. *J Gen Intern Med.* 2002;17:48-57. [PMID: 11903775]
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CLINICAL OBSERVATION

Anaphylactic Shock with Multiorgan Failure in a Cyclist after Intravenous Administration of Actovegin

Background: Actovegin (Nycomed Pharma, Zurich, Switzerland) is a calf-blood extract free of proteins and filtrated to remove prions. It is marketed in some countries for the treatment of cerebrovascular and metabolic disorders, peripheral flow disorders, burns, and wounds (1–4) and is used by some athletes to improve blood oxygenation without raising hematocrit, purportedly by promoting glucose and oxygen uptake by cells (5, 6). Actovegin has been banned by the International Olympics Committee since 2000.

Objective: To report a case of anaphylaxis with use of Actovegin.

Case Report: A 22-year-old man who was an amateur cyclist with no significant medical history self-injected intravenous Actovegin, 5 mL, over 5 minutes the night before a competition. He had administered the drug 1 year earlier with no consequences. Ten minutes later, the patient developed fever with rigors, abdominal pain, and vomiting. Three hours later, after taking anti-inflammatory medication with no effect, the patient presented to the emergency department. He was conscious and oriented, with a blood pressure of 100/60 mm Hg, heart rate of 87 beats/min, temperature of 37.9 °C, and normal oxygen saturation. His physical examination was normal except for epigastric and right upper quadrant pain with hepatomegaly on palpation. Initial blood analysis showed a blood urea nitrogen level of 19.3 mmol/L, creatinine level of 106.76 μ mol/L (1.4 mg/dL), alanine aminotransferase (ALT) level of 566 U/L, aspartate aminotransferase (AST) level of 335 U/L, lactate dehydrogenase (LDH) level of 6.46 μ kat/L, and bilirubin level of 15.74 μ mol/L (0.92 mg/dL). Hemoglobin level was 138 g/L, leukocyte count was 2.1×10^9 cells/L, and platelet count was 133×10^9 cells/L. His electrocardiogram and chest radiograph were normal. During his stay in the emergency department, his blood pressure decreased to 77/50 mm Hg and liver test values increased to 824 U/L ALT, 564 U/L AST, and 13.62 μ kat/L LDH.

The patient was transferred to the intensive care unit, where he was sleepy but still conscious. He remained hypotensive despite a fluid challenge and required dopamine, 10 μ g per kg of body weight per minute, to maintain his blood pressure. He received nasal oxygen at 2 L/min. His arterial blood gas values were pH, 7.42; PCO₂, 30 mm Hg; PO₂, 164 mm Hg; and HCO₃, 20 mmol/L. On arrival at the intensive care unit, his blood analysis showed a glucose level of 8.55 mmol/L (154 mg/dL), creatinine level of 109.8 μ mol/L (1.44 mg/dL), ALT level of 796 U/L, AST level of 633 U/L, LDH level of 11.00 μ kat/L, lactic acid level of 2.44 mmol/L, prothrombin activity of 47%, activated cephalin time of 62 seconds, international normalized ratio of 1.6, and fibrinogen level of 4.38 μ mol/L. The rest of the blood analysis, including amylase, creatinine phosphokinase, and ammonia, were normal. A urine toxicology screening was negative.

The patient was given an empirical antibiotic for a temperature of 38 °C. Thoracic–abdominal computed tomography showed enlargement of the inferior vena cava with increase of the suprahepatic veins. A follow-up abdominal ultrasonography showed hepatomegaly and moderate ascites but no Budd–Chiari syndrome. Indirect and direct antiglobulin testing (Coombs test) were normal.

Over time, the patient's hepatic profile and coagulopathy normalized, and dopamine therapy was titrated downward and discontinued.

After 2 days of supportive treatment, the patient was discharged from the intensive care unit to the general ward with a diagnosis of anaphylactic shock after intravenous administration of Actovegin, hypoxic hepatitis, and prerenal acute renal failure.

Discussion: Although this case is no more than a hypersensitivity reaction type I (anaphylactic shock), it highlights the life-threatening adverse effects that may accompany administration of performance-enhancing (“doping”) substances. The particular drug in this case was Actovegin, a substance with few indications that is marketed in a few countries. It was allegedly used by some cyclists in the 2000 Tour de France because it has properties similar to those of erythropoietin without raising hematocrit. Life-threatening anaphylaxis revealed that this individual had been doping, but most cases remain unknown. We think the medical community should be aware of the problem, especially because these substances are prescribed by physicians and very few articles describe these cases in the scientific literature (7, 8).

Conclusion: Intravenous Actovegin can cause life-threatening anaphylaxis.

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Potential Financial Conflicts of Interest: None disclosed.

References

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CORRECTIONS

Correction: In the Clinic: Dyslipidemia

In the recent *In the Clinic* issue on Dyslipidemia (1), an error was printed on page ITC9-9. In the box under “Patients with 10-year risk 10–20%,” the first bullet point should have read, “If LDL cholesterol > 130 mg/dL . . .” not “10 mg/dL,” as originally stated.

Reference

1. Kopin LA, Pearson TA. In the clinic: dyslipidemia. *Ann Intern Med.* 2007;147:ITC9-1-16.

Correction: In the Clinic: Migraine

In the recent In the Clinic issue on Migraine (1), Table 4 contained an error. The mechanism of action for amitriptyline should say “Inhibits norepinephrine”; the side effects for methysergide should say “No longer available in the United States.” Text at the bottom of the page should say, “Valproate and topiramate are the only anticonvulsants approved by the U.S. Food and Drug Administration for migraine prevention.”

Reference

1. Wilson JF. In the clinic: migraine. *Ann Intern Med.* 2007;147:ITC11-1-16.

Correction: Risk for Fatal Pulmonary Embolism after Discontinuing Anticoagulation

In a recent Summary for Patients on risk for fatal pulmonary embolism after discontinuing anticoagulation (1), the final sentence of “What are the implications of the study?” should have read, “The rates of recurrent pulmonary embolism are *higher* if the patient stops anticoagulation, but the physician must also consider the possibility of death from bleeding as a result of getting too much anticoagulation.” The original sentence read, “The rates of recurrent pulmonary embolism are *lower* if the patient stops anticoagulation, but the physician must also consider the possibility of death from bleeding as a result of getting too much anticoagulation.”

Reference

1. Summaries for patients: risk for fatal pulmonary embolism after discontinuing anticoagulation. *Ann Intern Med.* 2007;147:I-38.

Congratulations to Rachel Mercer, winner of the 2007 *Annals* Personae prize. Ms. Mercer’s photograph was published on the cover of the 5 February 2008 issue (vol. 148, no. 3) and is reprinted below.



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