The article by Prandoni and colleagues (1) showed that residual venous thrombosis as a predictive factor for recurrent venous thromboembolism. The high incidence of persistent abnormalities on venous ultrasonography after 3 months of anticoagulation for initial deep venous thrombosis (DVT) has been previously noted (2, 3), but the reasons for this lack of resolution remain unclear. Because the authors did not report any specific data on international normalized ratios (INRs) or the length of time that the INRs remained in the therapeutic range during the initial course of anticoagulation, it is possible that such treatment variables might explain the high incidence of residual abnormalities noted on follow-up ultrasonography. Caprini and associates (4) reported that patients with incomplete DVT resolution after 6 months of warfarin treatment had median INRs that were significantly lower than the INRs of patients who demonstrated complete thrombus resolution. We believe that strict maintenance of the INR within the therapeutic range might increase the rate of complete DVT resolution and thereby lessen the subsequent risk for recurrent thromboembolism.

James L. Sebastian, MD
Dario M. Torre, MD, MPH
Medical College of Wisconsin
Milwaukee, WI 53226

References

TO THE EDITOR: The article by Prandoni and colleagues (1) showed an association between residual venous thrombosis and recurrent venous thromboembolism. As demonstrated in several studies, DVT appears to be multifactorial (2). Therefore, the authors’ classification of patients is confusing. They divided patients into three main categories: thrombophilia, secondary thrombosis, and idiopathic thrombosis. This does not take into consideration the fact that in thrombophilia, a triggering event (for example, secondary thrombosis) often contributes to the disease (3). Furthermore, 15% of Prandoni and colleagues’ patients were not tested for thrombophilia. It would be useful for the medical community and ongoing or future studies to adopt a consensus classification for the description of the subpopulations; this would allow us to extrapolate results from one study to another.

The authors demonstrated an association between residual thrombosis and recurrence, but they also nicely showed that the rate of venous sequelae decreased over time, from 60% at 6 months to less than 30% at 36 months. On the other hand, the rate of recurrence also decreased with time, mainly after the first 24 months following the acute event. These observations, together with the fact that most recurrences affect the contralateral leg (without sequelae), suggest that residual thrombosis itself is probably not a major cause of thrombosis. Prandoni and colleagues suggested that their results are widely generalizable, but the interesting association they reported should first be confirmed in other studies. Finally, sequelae were assessed only by venous compression, but pulsed Doppler echocardiography for reflux was not done. It would be of interest to demonstrate that complete or partial obstruction of a vein is worse than major reflux, which induces stasis. However, this last evaluation is probably not as easy and reproducible as vein compression.

Joseph Emmerich, MD, PhD
Jean-Noël Fiessinger, MD
Hôpital Européen Georges Pompidou
75908 Paris Cedex 15

References

TO THE EDITOR: In the article by Prandoni and colleagues (1), veins were considered recanalized if they measured 3.0 mm or less in diameter during a 6-year period. However, in a previous study of 1017 patients, it was very unusual to observe a diameter less than 5 mm in cases of DVT (2), and 5 mm was proposed as the minimum threshold value for diagnosis of thrombus (2). Meissner and associates (3) studied patients with unilateral thrombosis and found that segments with residual disease were 0.07 to 0.28 cm smaller than those on the contralateral disease-free side. In addition, the diameter index (ipsilateral–contralateral diameter) was significantly lower in patients with unilateral thrombosis than in normal patients. At the end of 6 months, recanalized segments did not differ significantly from those on the contralateral side, and diameter indices in patients with unilateral thrombosis and in normal patients were indistinguishable (3). I propose that the acceptable minimum threshold for the quantitative definition of residual DVT be 5 mm. Diameter index may play a role in assessing unilateral residual thrombus.

Vijay Rapput, MBBS
Robert Wood Johnson Medical School
Camden, NJ 08103

References

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IN RESPONSE: Regarding the comments of Drs. Sebastian and Torre, we would like to state that all of our patients received an initial course of therapeutic dosages of low-molecular-weight heparin followed by vitamin K antagonists, monitored intensively to maintain the INR between 2.0 and 3.0. However, despite specialized anticoagulation clinics and optimal, dedicated physician care, subtherapeutic INRs are encountered approximately 20% of the time. Currently, we are not aware of any routinely used strategy to improve the percentage of time spent in the therapeutic range and counteract the potential detrimental effect of subtherapeutic INRs.

We agree with Drs. Emmerich and Fiessinger that the assessment of venous reflux is much less reproducible than compression ultrasonography. We also agree that our results need confirmation before implementation in daily routine, since prognostic associations do not necessarily translate into causal relationships. However, it should be noted that our results are fully consistent with the recent results of a study by another group (1). The observation that patients with residual venous thrombosis are as likely to develop ipsilateral as contralateral venous thrombosis suggests that residual venous thrombosis is not the cause in itself but is merely a marker (as a result of underlying hypercoagulability?) for subsequent venous thromboembolism. Indeed, it would be ideal to widely adopt a consensus classification for the description of the various subpopulations in venous thrombosis, but we view this as a difficult task to achieve because of the ongoing evolution of insights in etiology and pathogenesis.

To Dr. Rajput, we would like to reiterate that our study did not evaluate the compressed vein diameters at presentation of the acute episode but reported on the presence of residual thrombosis after months of anticoagulation and its association with subsequent recurrent venous thromboembolism.

Paolo Prandoni, MD, PhD
University of Padua
35128 Padua, Italy

Anthonie W.A. Lensing, MD, PhD
University of Amsterdam
Amsterdam, the Netherlands

Martin H. Prins, MD, PhD
University of Maastricht
Maastricht, the Netherlands

Reference

Use of β-Blockers in Patients with Reactive Airway Disease

TO THE EDITOR: We are very concerned about the conclusions of Salpeter and colleagues’ meta-analysis on cardioselective β-blockers in patients with reactive airway disease (1). With reactive airway disease, the immediate drop in FEV1 may not indicate the risk to patients taking β-blocking medications. In the 10 continued treatment studies, only 141 participants received β-blockers for 3 days to 4 weeks. Individuals with mild to moderate asthma may tolerate β-blockade well between asthma triggers. Long-term studies (≥1 year) must be performed to examine the frequency of asthma exacerbations and steroid burst, as well as hospitalization and death rates, before the true safety of β-blockade can be ascertained. Most persons with reactive airway disease can tolerate a substantial degree of airway obstruction until challenged with exercise, a viral respiratory infection, or an allergen exposure. We disagree with Dr. Epstein’s editorial (2), which states that Salpeter and colleagues’ meta-analysis proves the safety of β-blockade in persons with mild to moderate asthma. Salpeter and colleagues’ findings do suggest that many persons with mild to moderate asthma can receive β-blockade for a relatively short time, but the question of safety over the long term has not been answered.

David J. Shulan, MD
Michael Katlan, MD
Certified Allergy & Asthma Consultants
Albany, NY 12211

Mollie Lavsky-Shulan, MD
Stratton Veterans Affairs Medical Center
Albany, NY 12208

References

IN RESPONSE: We agree that further study of the long-term effects of β-blockers in patients with reactive airway disease is needed. Our study demonstrated the safety of cardioselective β-blockers in patients with mild to moderate reactive airway disease who were followed for up to 4 weeks. We believe that this study paves the way for larger, long-term trials to be done. In the meta-analysis, patients who received a single dose or continued treatment with a cardioselective β-blocker had an increased FEV1 response to β-agonists compared with placebo. Furthermore, in the continued treatment trials, steroid use, asthma exacerbations, and hospitalizations did not increase.

We remind readers that the evidence for the benefit of β-blockers in conditions such as acute myocardial infarction, coronary artery disease, diabetes mellitus, and congestive heart failure, as well as in the perioperative period, is convincing and strong. Our analysis, which pooled results from 29 randomized, controlled trials, indicated that β-blocker use should not be withheld from patients with a history of reactive airway disease. We hope our study will encourage more widespread use of cardioselective β-blockers in patients who could benefit from them.

Shelley R. Salpeter, MD
Thomas M. Ormiston, MD
Santa Clara Valley Medical Center
San Jose, CA 95128
Breast Cancer in Men

TO THE EDITOR: As a male survivor of breast cancer, I read the article by Giordano and colleagues (1) with great interest. I would appreciate their comments on three issues. First, in institutions experienced in sentinel node biopsy (meaning they have demonstrated excellent correlation between sentinel node biopsy and axillary node dissection), should patients routinely be offered sentinel node biopsy as an alternative to dissection? Second, should patients with tumors less than 1 cm in diameter and negative nodes undergo positron emission tomography, bone marrow aspiration, or both to look for micrometastases before forgoing adjuvant cytotoxic chemotherapy? Third, does 5 years of tamoxifen therapy influence the risk for prostate cancer?

Robert H. Jackson, MD
Louisiana State University Health Sciences Center—Shreveport
Shreveport, LA 71130-3932

Reference

IN RESPONSE: We appreciate Dr. Jackson’s interest in our article and will address his questions with pleasure. First, with regard to the role of sentinel lymph node biopsy in men, limited data are available. Several case reports of sentinel node biopsies performed in men have been published (1). However, the correlation between sentinel node biopsy and standard axillary dissection has not been established in men. We recognize that the rarity of male breast cancer makes the collection of a sufficient number of cases difficult, and thus it may not be possible to conclusively answer this question. Given that we would not expect a difference in the accuracy of this procedure by sex, sentinel node biopsy is a reasonable, although unproven, approach.

In answer to the second question, we would not recommend positron emission tomography or bone marrow aspiration as tools to decide whether a patient with early-stage disease should undergo adjuvant therapy. We do not routinely use these tests to determine whether women will benefit from adjuvant chemotherapy and are aware of no data to support their routine use in men with breast cancer.

The third question inquires about the relationship between adjuvant tamoxifen and the risk for prostate cancer. Tamoxifen is a selective estrogen receptor modulator (SERM) that has both estrogenic and antiestrogenic properties and appears to have some activity against prostate cancer. Tamoxifen and raloxifene (another SERM) have been shown to induce apoptosis in human prostate cancer cell lines (2, 3). However, in clinical trials, tamoxifen has had only limited activity in treating metastatic androgen-independent prostate cancer. Whether tamoxifen is effective as a chemopreventive agent for prostate cancer is unclear. In a rat model, tamoxifen prevented cancer of the seminal vesicle and prostate (4). Because of the promising results in animal models, a phase II clinical trial using another SERM (GTx-006) for chemoprevention of prostate cancer is under way (5). We will have to await the results of this and other clinical trials and epidemiologic studies to definitively answer this question.

Sharon H. Giordano, MD
Aman U. Buzdar, MD
Gabriel N. Hortobagyi, MD
University of Texas M.D. Anderson Cancer Center
Houston, TX 77030

References

Advancing the War on Malaria

TO THE EDITOR: Jennifer Fisher Wilson’s article “Advancing the War on Malaria” (1) comprehensively reviews current understanding of the disease. We agree with her that “science often fails to deliver to the poor even existing, simple solutions.” This is certainly the case in sub-Saharan Africa. However, Ms. Wilson understated the role of insecticide-treated nets (ITNs). Evidence for the effectiveness of ITNs has been accumulating for two decades. A Cochrane review concluded that ITNs reduce overall mortality by 20% in Africa and that among 1000 children younger than 5 years of age who are protected, 6 lives can be saved per year (2). Described as one of the most effective child-survival strategies ever devised, matched only by measles vaccine and oral rehydration fluids (3), ITNs, like vaccines, offer both personal protection to the individual user and a community-wide “mass” effect.

With the efficacy of ITNs in Africa firmly established, we agree with Ms. Wilson that the challenge is to find systems for delivering these valuable tools to the most needy. Strategies used by ministries, agencies, and projects in recent years have been diverse, resulting in a wealth of evidence and lessons learned. Among its many achievements, the World Health Organization’s Roll Back Malaria partnership developed an initiative called Scaling-Up Insecticide-Treated Netting Programmes in Africa: A Strategic Framework for Coordinated National Action (4). The framework addresses the need for an effective, affordable, and sustainable strategy that combines public provision of targeted subsidies to maximize public health benefits with support and stimulation of the commercial market. It is unrealistic to believe that the resource level required to sustain effective coverage for all those in need can be maintained by philanthropy alone. It makes sense to exploit and develop local production and commercial distribution of ITNs. Policy decisions leading to both effectiveness and sustainability need to be evidence-based. There is an urgent need for the operational research that will provide such evidence.

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Treatment of Severe Pulmonary Hypertension with Inhaled Iloprost

TO THE EDITOR: We report successful treatment of severe pulmonary hypertension with inhaled aerosolized iloprost in a patient with Gaucher disease, a lysosomal storage disorder (1–4). A 39-year-old woman with underlying adult Gaucher disease was admitted to our hospital with exertional dyspnea that markedly limited her physical activity (New York Heart Association class III). She had received a diagnosis of type I Gaucher disease at the age of 12 years and had been treated with enzyme replacement therapy (imiglucerase).

On presentation, she was able to walk 500 m in 6 minutes. During cycle spiroergometry with a working rate of 60 W, she reached a peak oxygen uptake (VO₂) of 15.1 mL/kg per minute. During cycle spiroergometry with a working rate of 60 W, she had been treated with enzyme replacement therapy (imiglucerase). She had received a diagnosis of type I Gaucher disease at the age of 12 years and had been treated with enzyme replacement therapy (imiglucerase).

After 6 weeks of iloprost treatment and to 1 after 9 months of treatment. Distance in the 6-minute walk improved to 600 m after 6 weeks of therapy and 650 m after 9 months of therapy. Peak VO₂ increased to 17.1 mL/kg per minute with a working rate of 80 W after 6 weeks and to 19.1 mL/kg per minute after 3 months. After 6 months, peak VO₂ reached 20.8 mL/kg per minute at a working rate of 100 W. In addition, brain natriuretic peptide levels normalized after 6 months. On the basis of these results, we suggest that inhaled iloprost should be considered for treatment of pulmonary hypertension associated with Gaucher disease.

H.H. Leuchte, MD
R.A. Bauwinger
J. Behr, MD
University of Munich, Grosshadern
81377 Munich, Germany

References

CORRECTION

Correction: The Ankle Brachial Index Is Associated with Leg Functioning and Physical Activity

In an article on the association of the ankle brachial index with leg functioning and physical activity (1), Table 2 contained errors. In the column titled “β-Regression Coefficient (95% CI),” the values for the reference groups are listed as 1.0 but should have been listed as zero. The 1.0 value is correct as printed in the column titled “Odds Ratios (95% CIs).”

Reference
TO THE EDITOR: We read the paper by Krantz and colleagues (1) about torsades de pointes in patients treated with methadone. In our hospital, four HIV-infected patients receiving methadone therapy presented with episodes of syncope. All of them had a prolongation of the corrected QT interval (QTc) (<0.45 seconds) and several episodes of torsades de pointes. All of these patients were men, and the mean age was 35 years. When the syncope occurred, two patients had AIDS and three were taking antiretroviral therapy with reverse transcriptase inhibitors. The mean daily methadone dose was 365 mg (range, 275 to 500 mg), and the mean QTc interval was 0.59 seconds (range, 0.51 to 0.64 seconds). Three patients had mild echocardiographic abnormalities, namely ventricular dilatation and hypokinetic areas; two had ionic disorders (potassium level, 2.9 mmol/L; ionized calcium level, 0.95 mmol/L [3.8 mg/dL]); and three were simultaneously taking potentially arrhythmogenic drugs (clarithromycin, foscarnet, and cotrimoxazole). Furthermore, we cannot rule out the possibility that these patients were adult carriers of a silent genetic anomaly. We were able to reduce the methadone dose in three of four patients and, of interest, observed a shortening of the QT interval. The resulting mean QTc interval was 0.47 second (range, 0.38 to 0.57 second).

The long QT syndrome related to viral cardiomyopathies or autonomous neuropathies has been described in HIV-infected patients (2, 3) but is usually related to drugs (macrolides, quinolones, clindamycin, trimethoprim–sulfamethoxazole, fluconazole, foscarnet, and pentamidine). Methadone affects several variables of cardiac function and has a negative inotropic and chronotropic effect in vitro (4). Antiretroviral therapy increases drug interactions by the inhibition and induction of cytochrome P450, and higher doses of methadone are used when the drug is given with non-nucleoside reverse transcriptase inhibitors.

Although all of our patients had nonpharmacologic factors that may potentially prolong the QT interval, the sequence of events suggests that methadone caused the prolongation and provided the substrate for torsades de pointes.

Montserrat Sala, MD
Ignasi Anguera, MD
Manuel Cervantes, MD
Institut Universitari Parc Taulí, Hospital de Sabadell
08208 Sabadell, Barcelona, Spain

References

Acute Renal Failure and Myocarditis Associated with Intravenous Immunoglobulin Therapy

TO THE EDITOR: Background: Intravenous immunoglobulin (IVIG) is a widely used treatment for various autoimmune disorders. Acute renal failure, although rare, is a known complication of this therapy; in most reports, it has occurred after administration of IVIG preparations containing sucrose as a stabilizing agent. We report a case of acute renal failure in a patient receiving a nonsucrose preparation of IVIG.

Case Report: A 59-year-old woman with a history of hypertension and chronic idiopathic thrombocytopenic purpura presented with persistent severe thrombocytopenia that was resistant to standard medical therapy. She was taking danazol, metoprolol, ramipril, calcium carbonate, and alendronate. On the day of admission, she received IVIG, 110 g, with 2% glucose and glycine as stabilizers (Polygam S/D, American Red Cross, Reston, Virginia). On day 2, after she received 50 g of IVIG, her blood pressure transiently increased to 180/100 mm Hg. Later that day, she developed a sharp, constant epigastric pain at rest, which was associated with nausea and vomiting. The pain increased in severity to 7 on a scale of 1 to 10 by the next morning. Her blood pressure remained elevated at 160/100
mm Hg, and other vital signs were stable. Findings on physical examination were unremarkable except for bilateral purpura of the lower extremities. Laboratory data showed a platelet count of 55 × 10^9 cells/L (baseline value 3 weeks earlier was 6 × 10^9 cells/L), elevated blood urea nitrogen level (from 6.8 mmol/L to 13.6 mmol/L [19 mg/dL to 38 mg/dL]), and increased serum creatinine concentration (from 115 μmol/L at baseline to 195 μmol/L [1.3 mg/dL to 2.2 mg/dL]). Cardiac enzyme levels were also elevated: Creatine kinase level was 569 U/L (normal range, 20 to 170 U/L), creatine kinase–MB isoenzyme level was 22.5 μg/L, and troponin I level was 51 μg/L (normal range, <0.1 μg/L). Electrocardiography showed T-wave inversion in anterolateral and inferior leads with no ST-segment elevation. Cardiac catheterization showed normal coronary arteries and low-normal left ventricular systolic function, suggestive of acute myocarditis. The patient remained hemodynamically stable during her subsequent days in the hospital, and her symptoms gradually resolved. Troponin I level decreased to 3.1 μg/L by the 7th day. The patient’s renal function deteriorated after cardiac catheterization; serum creatinine concentration peaked at 265 μmol/L (3.0 mg/dL) on day 4 and gradually decreased to 212 μmol/L (2.4 mg/dL) at discharge on day 7. Results of renal ultrasonography were normal. Three months later, her serum creatinine concentration was 115 μmol/L (1.3 mg/dL).

Discussion: The association of polyvalent IVIG with acute renal failure is well described. It is thought that intravenous sucrose, which cannot be hydrolyzed, is filtered at the glomerulus, causing osmotic nephrosis (that is, sucrose nephropathy). Renal function deteriorates after approximately 3 days of therapy, and 84% of patients recover after IVIG is discontinued (1). Acute renal failure has also been reported in 4 patients receiving IVIG preparations containing maltose and in 3 patients receiving IVIG with glucose and glycine as stabilizers (2). This raises the possibility that IVIG itself, rather than the stabilizers, may be responsible for acute renal failure. Of note, a recent report showed no association between the amount of sucrose in IVIG and development of acute renal failure (3).

To our knowledge, the only previously reported cardiac complication associated with IVIG was acute myocardial infarction in a patient with preexisting three-vessel coronary artery disease (4). In this patient, it was speculated that an increase in platelet count and blood viscosity had caused a prothrombotic state that led to acute myocardial infarction. Although the temporal relationship between administration of IVIG and development of myocarditis in our patient seems convincing, the mechanism remains unclear. Until there is further evidence supporting an association between IVIG and myocarditis, it would be prudent to closely monitor patients receiving IVIG for acute renal failure and acute myocardial ischemia or myocarditis.

Irme Akhtar, MD
Bahar Bastani, MD
Saint Louis University School of Medicine
St. Louis, MO 63110

References