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EDITORIAL

An Afternoon in Iraq

It was almost 4:00 pm in the afternoon. The Iraqi afternoons, just like the mornings, were relentlessly hot and humid, with temperatures reaching almost 120°F. My medics and I, having completed our daily chores of stocking our medications and cleaning our facility, sat silently in front of the fan, waiting for patients to show up at the aid station, when suddenly there was a huge explosion. I almost fell off the edge of my chair. The walls of the aid station almost caved in and the roof barely stood supported on its beams. My heart was pounding faster than I could count. I had no idea what was happening. One of my medics came racing around the corner yelling, “Sir, it’s mortars, put on your Kevlar and vest, seek cover!” For a moment I sat frozen to my chair thinking, mortars! Cannot be! It took another huge explosion to bring me back to reality and in a matter of seconds I had put on my vest and Kevlar and was seeking cover flat on the floor in a cement room.

It seemed like an eternity until finally it quieted down. There must have been 6 to 7 mortars launched our way. I was hoping that the mortars would land far away from our patrol base. I could hear myself praying that no one was hurt. Alas! My worst fears came true. An up-armored Humvee (high mobility multipurpose wheeled vehicle) speedily rolled by the aid station, the driver yelling that there was a casualty. The young soldier, barely in his early twenties, had been hit by shrapnel (small jagged metal fragments) dispensed with high velocity, shearing easily through flesh as the mortar hit the ground. He was conscious and yelling in agony. Fear of his unknown injury had given him a ghostly look.

We immediately hoisted him onto a litter, and I found myself directing the medics on what to do to stop any bleeding and save his life. It was like running a code during my senior residency year, the difference being that we had limited resources. We had just finished stabilizing his wounds, given him antibiotics and enough morphine to lessen his pain but keep him alert, when the medic helicopter arrived and whisked him away to a combat support hospital in Baghdad. I knew we had saved his life, and he would make it.

A few hours passed by and what had just happened seemed so unreal, a bad dream, a terrible nightmare. I sat with my face in my hands analyzing what had just occurred. A young man had been seriously injured, and there was no reason why. We had been bombarded by deadly mortars, and I could not make any sense of the situation. Was this what the world had succumbed to? Was there a value to life in this part of the world? One thing that I came to appreciate was the meaning of bravery and camaraderie. Some of these soldiers have been in this part of world more than twice, 12 long months at a time. They fully understand the risk involved and how easily one can lose his or her life at any time, yet they continue to serve their country and fellow soldiers faithfully and without any hesitation.

Later that evening, one of my medics and I toured the entire base, talking with the soldiers about their feelings and their emotions about the event that had occurred that afternoon. The soldiers showed mixed feelings on the situation; lots of anger, some fear, but a sense to carry on. We also sat down with the injured soldier’s immediate team, discussing what had occurred and what we had done medically for him. They felt reassured that he was going to make it.

As for my medics and me, we continue to spend another and yet another day in Iraq threatened by daily and deadly attacks. We try to laugh and share our time, hoping that every day will be a mortar-free day and that our deployment will come to an end soon. Every night before I go to bed, I pray for the safety and sanity of all our soldiers. As I drift away, I often find myself pondering if all this bloodshed and loss of life is worth any cause.

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US ARMY, CPT MC
Post-stenting Antithrombotic Drug Therapy in Patients with Atrial Fibrillation

From 1980 to 2000, the age-adjusted incidence of atrial fibrillation among adults in the United States climbed 12.6%, an observation attributed in part to increased obesity among Americans. When the rise was considered along with population growth occurring over that period, researchers estimated that 3.2 million adults had atrial fibrillation in 1980, compared with 5.1 million adults in 2000. Even if the age-adjusted incidence holds steady at the 2000 rate, as many as 12.1 million adults could have atrial fibrillation in 2050; if the rate continues to escalate, some 15.9 million adults could be afflicted.

Given findings like these, physicians can expect to be treating more patients with atrial fibrillation and associated coronary artery disease. An increasingly common management quandary is what to do when a patient with atrial fibrillation and a high risk of stroke presents with an acute coronary syndrome or requires a percutaneous coronary intervention, particularly with implantation of a drug-eluting coronary artery stent. How can the necessary antiplatelet drugs best be administered to patients with atrial fibrillation and a high risk of stroke, when they already take warfarin and maintain an international normalized ratio (INR) of 2-3?

The European Society of Cardiology guidelines for percutaneous coronary intervention suggest that patients undergoing elective procedures be given a combination of aspirin and clopidogrel for 4 weeks following placement of a bare metal stent; aspirin therapy then continues for life. For patients given a drug-eluting stent, the recommendation is that aspirin and clopidogrel be administered for 6-12 months, because of the risk of late stent thrombosis. Similarly, 9-12 months of post-stenting maintenance therapy with aspirin and clopidogrel is advised for patients presenting with non-ST-segment elevation acute coronary syndrome, and the recommendation is increasingly applied to patients presenting with ST-elevation myocardial infarction.

As a recent case series illustrates, no coordinated strategy exists for the prevention of stroke or thromboembolic events in patients with atrial fibrillation who are candidates for primary or elective percutaneous coronary intervention. The maintenance regimens prescribed after the procedure often vary in both composition and duration. While a combination of aspirin and clopidogrel was used in most cases—71.4%—there was little consistency in the recommended period of use. Treatment with aspirin, clopidogrel, and warfarin was uncommon; a finding attributed to general fear of hemorrhage with this triple-therapy regimen. Undoubtedly, management of these patients must maintain a delicate equilibrium between stroke prevention in the high-risk atrial fibrillation patient; the bleeding risks posed by drug therapy; the risk of thrombosis with stenting; recurrent cardiac ischemia; and the expected benefits from the percutaneous coronary intervention procedure.

Recently, the American College of Cardiology, American Heart Association, and European Society of Cardiology published joint guidelines for the management of patients with atrial fibrillation. These state that after percutaneous coronary intervention, “low-dose aspirin (<100 mg/day) and/or clopidogrel (75 mg/day) may be administered concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding.” A recommended post-procedure maintenance regimen is clopidogrel, 75 mg/day, and a warfarin dosage that maintains an INR of 2-3. Clopidogrel administration is advised for at least 1 month after implantation of a bare metal stent; for at least 3 months after insertion of a sirolimus-eluting stent; for at least 6 months after placement of a paclitaxel-eluting stent; and in selected cases, for 1 year or more. Once clopidogrel is discontinued, patients who have not suffered a subsequent coronary event can continue warfarin as monotherapy.

As noted, these recommendations offer no definitive course of action for patients at greater risk of bleeding. In addition, they do not distinguish between patients undergoing percutaneous coronary intervention for acute coronary syndrome and those scheduled for elective procedures. After reviewing the evidence from a number of studies in various settings, we have developed our own management approach, which takes into account both the perceived risk of bleeding and the presence—or absence—of acute coronary syndrome in patients with atrial fibrillation (Table).
Among our many considerations was the finding that aspirin provides no additive benefit in reducing ischemic stroke or other vascular events in patients with atrial fibrillation who are taking anticoagulants, but it does substantially increase bleeding risk. While oral anticoagulation is a useful treatment option in acute coronary syndrome and may be an alternative to aspirin in that situation, treatment with aspirin and clopidogrel is a poor strategy for prevention of ischemic stroke in high-risk patients with atrial fibrillation. In patients recovering from acute coronary syndrome per se, aspirin monotherapy may be marginally less effective than aspirin plus warfarin (INR maintained at 2-3) in preventing nonfatal myocardial infarction, nonfatal thromboembolic stroke, and all-cause death, but there is a 2-fold increase in risk of major bleeds associated with the combination.

The heightened danger of hemorrhage with aspirin plus warfarin and the relative lack of additional benefit led us to recommend warfarin and clopidogrel when an anticoagulant and a platelet aggregation inhibitor need to be used in combination. Furthermore, the main benefit of aspirin administered after myocardial infarction is seen early on, within the first 35 days, and longer treatment offers minimal benefit with respect to mortality.

Our recommendations have not been subject to formal investigation. Clearly, the optimal approach to managing patients who develop acute coronary syndrome in tandem with atrial fibrillation will not be identified without addi-

<table>
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<th>Stroke Risk</th>
<th>Usual Strategy Recommended</th>
<th>Perceived Risk of Bleeding</th>
<th>Presents with Acute Coronary Syndrome</th>
<th>Suggested Regimen following Percutaneous Coronary Intervention*</th>
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<td>Low</td>
<td>Aspirin</td>
<td>Low</td>
<td>No</td>
<td>Bare metal stent: aspirin plus clopidogrel for 4 weeks; then aspirin. Drug-eluting stent: aspirin plus clopidogrel for 6-12 months; then aspirin. Use bare metal stent if possible. Bare metal stent: triple therapy with warfarin, aspirin plus clopidogrel for 2-4 weeks; then change to warfarin plus clopidogrel for up to month 12, then warfarin alone. Drug-eluting stent: triple therapy with warfarin, aspirin and clopidogrel for 3-6 (or more) months; then warfarin plus clopidogrel for up to month 12; then warfarin alone. Bare metal stent or drug-eluting stent: triple therapy with warfarin, aspirin, and clopidogrel for 3-6 (or more) months, then warfarin plus clopidogrel for up to month 12; then warfarin alone. Use bare metal stent if possible. Bare metal stent: triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks; then change to warfarin alone. Drug-eluting stent: triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks, then warfarin plus clopidogrel for up to month 12, then warfarin alone. Bare metal stent or drug-eluting stent: triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks, then warfarin plus clopidogrel for up to month 12; then warfarin alone.</td>
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<td>High</td>
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<td>Bare metal stent or drug-eluting stent: triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks, then warfarin plus clopidogrel for up to month 12; then warfarin alone.</td>
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<tr>
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<td></td>
<td>Low</td>
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<td>*Dosages: aspirin, 75 mg/day; clopidogrel, 75 mg/day. Warfarin dosage adjusted to target international normalized ratio of 2-2.5. †Particular attention paid to the following risk factors: age older than 75 years; concurrent treatment with antiplatelet drugs or nonsteroidal anti-inflammatory drugs; concurrent treatment with multiple drugs (polypharmacy); uncontrolled hypertension; history of bleeding (for example, peptic ulcer or cerebral hemorrhage); and history of poorly-controlled anticoagulation therapy.</td>
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</table>
tional data, although the development of large randomized trials is unlikely. Instead, further data from large registries would be very helpful in determining the risks and benefits of different antithrombotic strategies in these high-risk patients.

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References


Complementary Medicine for Treating or Preventing Influenza or Influenza-like Illness

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ABSTRACT

The objective of this review was to assess the evidence for the effectiveness of complementary and alternative therapies for preventing or treating influenza or influenza-like illness, including avian influenza. Systematic literature searches were conducted in 5 databases until June 2006; other data sources included bibliographies of located articles, manufacturers of commercially available preparations, and experts in the field. Randomized clinical trials, controlled against placebo or active comparator, were included. Decisions on inclusion, data extraction, and methodological quality assessment were performed independently by 2 reviewers. Fourteen randomized controlled trials testing 7 preparations were included. For Oscillococcinum, *P. quinquefolium* extract, *Sambucus nigra*, and the herbal combination Kan Jang, 2 or more trials reporting some encouraging data were identified. In conclusion, the effectiveness of any complementary and alternative therapy for treating or preventing seasonal influenza is not established beyond reasonable doubt. Current evidence from randomized controlled trials is sparse and limited by small sample sizes, low methodological quality, or clinically irrelevant effect sizes. For avian influenza, no data are currently available. These results strengthen conventional approaches for seasonal influenza. © 2007 Elsevier Inc.

KEYWORDS: Complementary medicine; Influenza; Influenza-like illness

Influenza is an acute respiratory illness caused by infection with influenza type A or B viruses. Uncomplicated influenza is generally resolved over a 2- to 5-day period, although cough and malaise can persist for weeks. Among the most vulnerable population, annual influenza epidemics are associated with increased morbidity and hospitalization rates, and excess mortality.1,2 Treatments of influenza include drugs for alleviating symptoms and antiviral drugs. Seasonal epidemics can be controlled by vaccination of high-risk populations. Since the first cases of human infection with the avian influenza A (H5N1) virus were reported in Hong Kong in 1997, more than 200 laboratory-confirmed human cases of H5N1 avian influenza were reported to the World Health Organization. These reports originated from 9 countries with a case fatality rate of over 50%. A mutant or reassortant virus capable of efficient human-to-human transmission could trigger another influenza pandemic. There have been reports of resistance to antiviral drugs. Vaccines against H5N1 are still at the developmental stage of phase I clinical trials. In this situation, some may look beyond the conventional treatment and consider complementary and alternative medicines. It has been suggested that osteopathic manipulative treatment,3 homeopathy,4 and herbal medicine5 may be beneficial in the management of a possible influenza pandemic. An Internet search has identified numerous websites promoting complementary and alternative medicine for avian influenza. A number of such therapies have been used traditionally for influenza-like illness. However, whether they are supported by clinical evidence is unknown. We therefore conducted this systematic review to critically assess the available evidence for complementary and alternative therapies for treating or preventing influenza or influenza-like illness, including avian influenza.
METHODS

Searching

The following electronic databases were searched from their respective inceptions to June 2006: MEDLINE, EMBASE, Cochrane Library, CINAHL, and AMED. The search strategy included MESH and free text terms: Complementary medicine or Complementary therap* or Alternative medicine or Alternative therap* or influenza or flu, as well as names of individual therapies. No language restrictions were imposed. Attempts were made to identify additional studies by searching the reference lists of identified trials and reviews. Manufacturers of commercial products and experts in the field were contacted and asked to contribute published and unpublished material.

Selection

We included randomized controlled trials testing any complementary and alternative therapy in subjects of either sex or any age. Subjects in treatment trials had to be clinically diagnosed with influenza or influenza-like illness; for prevention trials subjects were required to be healthy. Trials had to be placebo-controlled or controlled against active antiviral medication. Trials of upper respiratory tract infection or common cold without subgroup analyses of patients with influenza or influenza-like illness were excluded. Trials in which randomization could not be ascertained from the report were also excluded. Trials that assessed the immune responses to influenza vaccination as the only outcome measures were excluded. All clinically relevant outcomes including adverse events were assessed. We were particularly interested in the duration and severity of symptoms, frequency and severity of influenza-associated complications in treatment trials, and frequency and severity of influenza cases in prevention trials. All titles and abstracts identified through the literature searches were scanned to decide whether a full-text article needed to be obtained (RG, MHP). The retrieved full-text articles were then reviewed by 2 authors (RG, MHP) to make independent decisions on inclusion or exclusion. Discrepancies were resolved by discussion between the 2 reviewers (RG, MHP) and, if needed, by consulting the third author (EE).

Validity Assessment

Methodological quality of the included trials was assessed using the Jadad score. We also evaluated other items in the following 4 areas: selection, performance, attrition, and detection. Each item was scored as “yes,” “no,” or “don’t know.” Two reviewers (RG, MP) independently assessed the validity of each trial. Discrepancies were resolved by discussion between the 2 reviewers and, if needed, by consulting the third author (EE).

Data Extraction and Analysis

Data on study design, population, intervention, outcomes, and adverse events were extracted from included trials by one reviewer (RG) and independently verified by a second reviewer (MHP) based on the data in the original article using a specific data extraction sheet. Additional data, reported in published reviews or meta-analysis, were also extracted and used. For studies in which the statistical significance or effect sizes were not clearly reported and in which sufficient primary data were available, effect sizes of main outcomes and their 95% confidence intervals (CI) were calculated using Cochrane collaboration’s Review Manager Software (RevMan 4.2; Copenhagen, Denmark: The Nordic Cochrane Centre). Results from dichotomous data were calculated as risk ratio (RR; proportion of the responders in the test group divided by the proportion of the responders in the control group). Results for continuous data were calculated as mean difference (MD), or weighted MD if pooled. Pooling the results was performed when the original data were suitable for combination. Heterogeneity of the combined studies was assessed using RevMan 4.2. The methods used in our review and the trial selection criteria were all predefined. For 2 studies we decided to calculate the Peto odds ratio (Peto OR) instead of RR because the number of events was low.

RESULTS

The literature search identified 2603 references. Full-text articles of 103 potentially relevant references were obtained for further evaluation. One additional unpublished randomized controlled trial, which was included in a Cochrane review, was obtained from the author of the review. No further unpublished randomized controlled trials were identified. A total of 29 controlled trials were identified, of which 15 were subsequently excluded for the following reasons: not reported as randomized (n = 2); no subgroup analyses of influenza patients in trials of influenza and common cold or upper respiratory tract infection (n = 4); and immune responses to influenza vaccination as the only outcome measures (n = 9). Fourteen randomized controlled trials described in 12 articles met the inclusion criteria and were included in our review (Fig-
Key characteristics of the included trials are summarized in Tables 1 and 2 (available online). Methodological quality of these trials is shown in Table 3 and details of the preparations used are listed in Table 4.

**Sambucus nigra.** Two trials tested a commercial brand of *S. nigra* extract (Sambucol, Razei Bar Ltd, Jerusalem, Israel). This syrup contains 38% standardized extract. Significant inter-group differences were reported for the proportion of patients whose symptoms were resolved within 3 days (RR 2.6; 95% confidence interval [CI], 1.1-5.9; n = 40). Of the 27 patients who completed the study, 25 had laboratory confirmation of influenza A or B infection. Another trial reported that Sambucol reduced the duration of symptom resolution by 4 days (MD -4.0; 95% CI, -5.0 to -3.0; n = 60). All patients had laboratory confirmation of either influenza A or B virus infection.

**Echinacea purpurea.** One trial tested 2 different doses of *E. purpurea* extract (450 mg and 900 mg) and reported that the higher dose (900 mg) was superior to placebo for the severity of symptoms at days 3 and 4 (symptoms score: MD 1.7; 95% CI, 2.3 to 1.1; n = 120) and at days 8 to 10 (MD -2.9; 95% CI, -3.6 to -1.1; n = 120). A nonsignificant trend was observed for the lower dose (450 mg) of *E. purpurea* extract (Table 1 available online).

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**Table 3**  
Methodological Quality of All Included Trials

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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>D</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Zakay-Rones et al, 2004</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

**Number of RCTs scored “Y”**

| 6 | 6 | 7 | 10 | 10 | 4 | 9 | 11 | 1 | 1 | 1 | 1 | 1 |

**Y** = Yes; **N** = No; **D** = Don’t know.

- A. Is randomization performed using an appropriate method?
- B. Was the treatment allocation concealed?
- C. Were the groups similar at baseline regarding the most important prognostic indicators?
- D. Was the patient blinded?
- E. Was the care provider blinded?
- F. Was the withdrawal/dropout rate unlikely to cause bias?
- G. Was the outcome assessor blinded?
- H. Was there a predefined primary outcome measure and the result reported?
Oscillococcinum. Oscillococcinum (Boiron; Sainte-Foy-lès-Lyon, France) is a homeopathic remedy made from duck liver and heart (Table 4). Four randomized trials tested the effect of Oscillococcinum for influenza-like illness.25-27,30 Responder rates for complete symptom resolution within 48 hours were reported in 2 randomized controlled trials.27,30 Pooling of the results showed a significant intergroup difference (RR 1.5; 95% CI, 1.1-2.1; n = 850). No statistical heterogeneity was detected (chi-squared 0.59, P = .44). Combining the results for the duration of symptom resolution suggested a significant but small beneficial effect of Oscillococcinum compared with placebo (WMD days: 0.3; 95% CI, −0.5 to −0.1; n = 850; chi-squared = 0.00, P = 1.00).

Active Comparator Controlled Trials
Three randomized controlled trials described in 2 articles were controlled against amantadine.28,34

Kan Jang. Kan Jang (Svenska Örtmedicinska Institutet, Göteborg, Sweden) is a combination of 2 standardized herbal extracts in tablet form (Table 4). We identified 2 randomized controlled trials reported in one article assessing its effects for treating influenza.28 Influenza virus infection (A1, A3) was confirmed in a randomly selected sample of 40 patients from each trial. The proportion of patients developing secondary infection-induced complications were reported in both trials and the combined result showed a significant intergroup difference favoring the test intervention (RR 0.5; 95% CI, 0.3-0.6; n = 606). No statistical heterogeneity was detected (chi-squared = 0.01, P = .92). The second trial also suggested a reduction in sick leave by 2.6 days (MD 2.6, 95% CI, 5.0 to 3.0; n = 66). Significant inter-group differences were reported for symptom severity.

Gan Mao Jiao Nan. Gan Mao Jiao Nan is a mixture of Chinese herbal medicines in capsule form. One trial assessed its effects in 213 patients with clinically diagnosed influenza and 738 healthy subjects.34 Responder rate for symptoms resolved within 48 hours were significantly greater among patients treated with Gan Mao Jiao Nan compared with amantadine (RR 5.19; 95% CI, 3.8-7.0).

PREVENTION
Placebo-controlled Trials
Panax quinquefolium (North American Ginseng). Two randomized trials reported in one article tested a proprietary extract of P. quinquefolium (CVT-E002) for preventing influenza in institutionalized elderly adults (Table 2, online).29 Patients received CVT-E002 (200 mg, twice daily)
or placebo for 8 or 12 weeks. The primary outcome was the number of cases of laboratory-confirmed influenza. Intergroup differences were not statistically significant in either of the studies. However, the combined result (n = 198) showed a significant inter-group difference favoring the test group (Peto OR 0.2; 95% CI, 0.1-0.9).

Oscillococcinum. One trial tested the preventative effect of Oscillococcinum in 1573 healthy subjects (Table 2, online).24 The primary outcome was the incidence of influenza-like illness. No statistically significant intergroup difference was found (RR 0.9; 95% CI, 0.7-1.1, P = .38).

Mucococcinum. One trial tested the homeopathic remedy mucococcinum, made from a variety of inactivated bacterial and viral strains (Table 4, online).31 The number of influenza symptoms, physician’s assessment, and 7 individual symptoms were evaluated. No significant intergroup differences were reported for the number of symptoms. Positive results were reported for physician’s assessment and symptoms. Original data were insufficient to estimate an effect size and 95% CI.

Active Comparator Controlled Trials
Gan Mao Jiao Nan was assessed for its preventative effects and compared against amantadine.34 The number of influenza cases that developed during the 7-day study period was the primary outcome. The number of cases in the test group was significantly lower than that in the control group (RR 0.5; 95% CI, 0.4-0.6; n = 738).

Adverse Events
There was no mention of adverse events in 7 of the 14 included randomized trials. Three reported that no adverse events were observed. Three trials reported such events in some detail. A high incidence of adverse events was reported in one trial of P. quinquefolium,29 although there was no difference compared with placebo. Half of these incidents were gastrointestinal symptoms and most of them were mild or moderate in severity. A small percentage of serious adverse events were judged to be unrelated to the study medication. In another trial,24 a significantly higher frequency of adverse events was reported in the test group (Oscillococcinum) compared with placebo (RR 4.6; 95% CI, 2.7-7.6). Another trial of Oscillococcinum reported 5 incidents, but failed to clarify from which group.30 Adverse effects were not monitored in the other 3 randomized trials of Oscillococcinum.25-27

DISCUSSION
We found no compelling evidence from randomized controlled trials supporting the use of any complementary and alternative therapy for treating or preventing influenza or influenza-like illness. Although some encouraging results were reported for Oscillococcinum, P. quinquefolium extract, Sambucus nigra, and the herbal combination Kan Jang, these findings are limited both in quantity and quality. North American ginseng (P. quinquefolium) extract produced a marginal preventative effect by reducing the number of cases of laboratory-confirmed influenza in elderly patients. These findings are based on the combined result from 2 studies.29 Eighty-five percent of these participants had been vaccinated against influenza, and it was not clear whether those who developed influenza were among those vaccinated. We, therefore, cannot be certain whether the apparent preventative effect is purely due to the intervention. Further research in this patient group or another age group is required. S. nigra extract, Sambucol, was found to reduce the duration of symptoms in patients with laboratory-confirmed influenza virus infection. However, both randomized controlled trials,32,33 which were financially supported by the manufacturer of the product, were of limited sample size and conducted in younger patients (≤56 years of age) rather than older, more vulnerable, patient populations. Larger independent trials are therefore needed to confirm these results. Specific strains of influenza virus should be evaluated in separate trials. Another herbal product, Kan Jang, appears to reduce the rate of influenza complications. This result was based on 2 small trials.28 Both were non-blinded and therefore open to bias. In addition to these limitations, the first trial reported few details on outcomes, results, and statistical analyses. The homeopathic remedy, Oscillococcinum, was found to reduce the time to symptom resolution by about a quarter of a day based on combined data from 2 randomized controlled trials.27,30 Although statistically significant, this result is of debatable clinical relevance. In the other 2 randomized trials25,26 of Oscillococcinum, significant improvements were reported for several symptoms, but these positive results may have been selectively reported. An earlier trial reported significant intergroup differences for 3 of the 5 symptoms, but not for the other 2 symptoms.25 In a later study conducted by the same group,26 only the results from the former 3 symptoms were reported. Large effect sizes for both treatment and prevention were reported in one trial testing Gan Mao Jiao Nan against amantadine.34 However, important details are missing, such as inclusion criteria, patients’ demographic descriptions, and baseline data.

Further limitations relate to the concealment of allocation sequences, which was reported in only 6 of 14 trials, appropriate randomization methods, which also were reported in only 6 of 14 trials, and details of withdrawal and dropouts. This potential selection and attrition bias may thus have distorted the results.37,38 Influenza virus infection was confirmed by laboratory test in 4 trials and partly confirmed (by random sampling) in another 2 trials. In other trials, influenza was only diagnosed clinically. Additionally, there is a lack of standardization or independent validation of the agent being tested.

Most of the included trials do not seem to have monitored adverse events, as this was reported in only 7 of 14 trials. Herbal medicines may be linked to serious adverse events, and herb-drug interaction may have serious clinical
consequences. Homeopathic remedies are generally regarded as safe due to the extensive dilution of the products. It is worth noting that one trial reported significantly higher incidents of adverse events from a homeopathic remedy compared with placebo. Interestingly, another trial studied the same product and reported only 5 adverse events, including those in the placebo group.

Many complementary therapies have been suggested for avian influenza. We did not find any randomized trials testing complementary and alternative therapies for avian influenza. Generalization from data on seasonal influenza to avian influenza is not appropriate.

Limitations of our review pertain to the potential incompleteness of the reviewed evidence. The disturbing effects arising from publication bias and location bias are well documented. For this analysis, we searched databases arising from publication bias and location bias are well documented. The distorting effects of incomplete evidence from randomized controlled trials is sparse in avian influenza. No data are currently available. These results strengthen conventional approaches for seasonal influenza.

References


<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size, Age (Years) (Diagnosis)</th>
<th>Intervention and Daily Dose</th>
<th>Treatment Duration/Follow-up (Days)</th>
<th>Main Outcomes and Results RR or MD (95% CI)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casanova, 1984&lt;sup&gt;25&lt;/sup&gt;</td>
<td>DB, PC Parallel</td>
<td>100 T/C mean 42/41 (ILI)</td>
<td>Oscillococcinum (n = 50), 4 doses (standard dosage, detail not reported) in over 2 days at 6-h intervals</td>
<td>Placebo (n = 50)</td>
<td>2/8, Global assessment of therapeutic effects by patient, RR 0.32 (0.18-0.59)&lt;sup&gt;†&lt;/sup&gt;; Significant inter-group differences reported for fever, chill and aches. No significant differences reported for rhinitis and bronchial congestion</td>
<td>Not reported</td>
</tr>
<tr>
<td>Casanova and Gerard, 1992&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Blinding not reported, PC</td>
<td>300 T/C mean 44/38 (ILI)</td>
<td>Oscillococcinum (n = 150), a dose of globules each time (detail of dosage not reported), twice daily</td>
<td>Placebo (n = 150)</td>
<td>3 ~ 4/4, Temperature at day 4, MD −0.5 (−0.67 to −0.33)&lt;sup&gt;†&lt;/sup&gt;; Significant inter-group differences reported for fever, chill and aches.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ferley et al, 1989&lt;sup&gt;27&lt;/sup&gt;</td>
<td>DB, PC Parallel</td>
<td>478 ±12 (ILI)</td>
<td>Oscillococcinum (n = 237), 5 doses in total (200 granules per dose), taken one at the admission then the following mornings and evenings in 2 days</td>
<td>Placebo (n = 241)</td>
<td>3/7, Recovery rate within 48 h (resolution of fever and all cardinal symptoms), RR 1.67 (1.1-2.7)&lt;sup&gt;†&lt;/sup&gt;; Duration of symptom resolution (days) MD −0.26 (−0.64-0.12)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Not reported</td>
</tr>
<tr>
<td>Papp et al, 1998&lt;sup&gt;30&lt;/sup&gt;</td>
<td>DB, PC Parallel</td>
<td>372 Range 12-60 (ILI)</td>
<td>Oscillococcinum (n = 188), 3 doses daily (1 dose consisted of 200 globules); concomitant medication taking in 14% patients</td>
<td>Placebo (n = 184), concomitant medication in 9% patients</td>
<td>3/7-10, Responder rate for full recovery within 48 h (all symptoms resolved), RR 1.25 (0.77-2.03)&lt;sup&gt;†&lt;/sup&gt; and partial recovery within 48 h, RR 1.28 (0.96-1.69)&lt;sup&gt;†&lt;/sup&gt;; total improvement rate within 48 h, RR 1.27 (1.03-1.56)&lt;sup&gt;†&lt;/sup&gt;; Duration of symptom resolution (days) MD −0.26 (−0.52-0.00)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>5 events (nature not clear)</td>
</tr>
<tr>
<td>Zakay-Rones et al, 1995&lt;sup&gt;33&lt;/sup&gt;</td>
<td>DB, PC Parallel</td>
<td>40 Range 5-56 (influenza B, lab confirmed)</td>
<td>Sambucus nigra (Sambucol), (n = 20) 2 ~ 4 tablespoons daily</td>
<td>Placebo (n = 20)</td>
<td>3/6, Recovery rate within 3 days (all symptoms resolved), RR 2.60 (1.14-5.93)&lt;sup&gt;†&lt;/sup&gt; and partial recovery rate (symptoms improved) RR 3.73 (1.39-10.04)&lt;sup&gt;†&lt;/sup&gt; Days with fever: MD −0.97 (−1.93 to −0.01)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Not monitored, but tolerability was tested in 35 healthy subjects before the trial</td>
</tr>
<tr>
<td>Zakay-Rones et al, 2004&lt;sup&gt;32&lt;/sup&gt;</td>
<td>DB, PC Parallel</td>
<td>60 Range 18-54 (influenza A &amp; B, lab confirmed)</td>
<td>Sambucus nigra (Sambucol), (n = 30), 60 mL daily, rescue medications (paracetamol or Otriven nasal spray) were allowed</td>
<td>Placebo (n = 30), rescue medications same as in the test group</td>
<td>5/8, Duration of symptom resolution (days) MD −4.00 (−5.01 to −2.99)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>None</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size, Age (Years) (Diagnosis)</td>
<td>Intervention and Daily Dose</td>
<td>Treatment Duration/ Follow-up (Days)</td>
<td>Main Outcomes and Results RR or MD (95% CI)</td>
<td>Adverse Events</td>
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<td>Bräunig et al, 1992&lt;sup&gt;25&lt;/sup&gt;</td>
<td>DB, PC Parallel</td>
<td>180, Not reported (ILI)</td>
<td>Echinacea purpureae radix extract: 1) HD 900 mg daily (n = 60) 2) LD 450 mg daily (n = 60)</td>
<td>10</td>
<td>Symptoms score at day 3-4: HD vs. placebo, MD −1.7 (−2.26 to −1.14)&lt;sup&gt;†&lt;/sup&gt;, LD vs. placebo, −0.3 (−0.95-0.35)&lt;sup&gt;†&lt;/sup&gt;; at day 8-10: HD vs. placebo, −2.90 (−3.61 to −1.14)&lt;sup&gt;†&lt;/sup&gt;, LD vs. placebo, −0.1 (−0.83-0.63)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Not reported</td>
</tr>
<tr>
<td>Active comparator controlled trials</td>
<td>Open Parallel</td>
<td>540 Range 19-63 (influenza A, lab confirmed in random sample)</td>
<td>Kan Jang, 600 mg daily, plus paracetamol if body temperature &gt;39°C (n = 71)</td>
<td>3 to 5</td>
<td>Frequency of influenza complications, RR 0.46 (0.32-0.65)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Not reported</td>
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<tr>
<td>Kulichenko et al, 2003a&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Open Parallel</td>
<td>66 Range 20-63 (influenza A, lab confirmed in random sample)</td>
<td>Kan Jang, 900 mg daily, paracetamol was prescribed if body temperature &gt;39°C (n = 35)</td>
<td>5</td>
<td>Duration of sick leave (days): MD −2.60 (−2.85 to −2.35)&lt;sup&gt;†&lt;/sup&gt; Frequency of influenza complications, RR 0.44 (0.26-0.76)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Not reported</td>
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<tr>
<td>Kulichenko et al, 2003b&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Open Parallel</td>
<td>Not reported (ILI)</td>
<td>GMJN (CHM) capsules 10.5 g daily (n = 202)</td>
<td>7</td>
<td>Recovery rate within 48 h (symptoms resolution), RR 5.19 (3.84-7.02)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>None in treatment group, gastrointestinal complaints were reported in the control group without details.</td>
</tr>
<tr>
<td>Xue and Dong, 1999&lt;sup&gt;14&lt;/sup&gt;</td>
<td>DB, Parallel</td>
<td>432 Not reported (ILI)</td>
<td>GMJN (CHM) capsules 10.5 g daily (n = 202)</td>
<td>7</td>
<td>Recovery rate within 48 h (symptoms resolution), RR 5.19 (3.84-7.02)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>None in treatment group, gastrointestinal complaints were reported in the control group without details.</td>
</tr>
</tbody>
</table>

CAM = complementary and alternative medicine; RR = risk ratio; CI = confidence interval; MD = mean difference; DB = double-blind; PC = placebo controlled; ILI = influenza-like illness; HD = higher dose; LD = lower dose; /d = per day; T/C = treatment group/control group; GMJN = Gan Mao Jiao Nan; CHM = Chinese herbal medicine.

*Details of the preparations can be found in Table 4.
†Results (effect sizes and 95% CI) were calculated by the reviewers.
‡Data were obtained from published reviews.
Table 2  Randomized Clinical trials of Complementary and Alternative Therapies for Preventing Influenza or Influenza-like Illness*

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size, Age (Years)</th>
<th>Influenza Vaccination</th>
<th>Intervention Test*</th>
<th>Duration (Weeks)</th>
<th>Main Outcomes and Results, RR or MD (95% CI)</th>
<th>Adverse Events</th>
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<td>Placebo-controlled trials</td>
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<tr>
<td>Attena et al, 1995</td>
<td>DB, PC</td>
<td>1595/1573, No other details</td>
<td>Not reported</td>
<td>Oscillococcinum, 4 doses in total, 1 weekly for 3 weeks, then 1 month later (n = 783)</td>
<td>Placebo (n = 790)</td>
<td>6†</td>
<td>Cases of ILI during experimental period: RR 0.89 (0.71-1.13)‡</td>
</tr>
<tr>
<td>McElhaney et al, 2004a</td>
<td>DB, PC</td>
<td>89, Mean &gt;80</td>
<td>&gt;85%</td>
<td>Panax quinquefolium (CVT-E002), 400 mg daily (n = 40)</td>
<td>Placebo (n = 49)</td>
<td>8</td>
<td>Laboratory confirmed cases of influenza: Peto OR 0.12 (0.01-2.20)‡</td>
</tr>
<tr>
<td>McElhaney et al, 2004b</td>
<td>DB, PC</td>
<td>109, Mean &gt;80</td>
<td>&gt;85%</td>
<td>Panax quinquefolium (CVT-E002), 400 mg daily (n = 57)</td>
<td>Placebo (n = 52)</td>
<td>12</td>
<td>Laboratory confirmed cases of influenza: Peto OR 0.27 (0.03-2.37)‡</td>
</tr>
<tr>
<td>Rottey et al, 1995</td>
<td>DB, PC</td>
<td>501, T/C mean 39/37</td>
<td>Not reported</td>
<td>Mucococcinum 200 K, 1 pill weekly (n = 251)</td>
<td>Placebo (n = 250)</td>
<td>12</td>
<td>Number of symptoms</td>
</tr>
<tr>
<td>Active comparator controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Xue and Dong, 1999</td>
<td>DB, PC</td>
<td>738, Age not reported</td>
<td>Unclear</td>
<td>GMJN (CHM) capsules 10.5 g/d (n = 395)</td>
<td>Amantadine (210 mg/d) (n = 343)</td>
<td>1</td>
<td>Number of cases of ILI: RR 0.48 (0.38-0.61)‡</td>
</tr>
</tbody>
</table>

DB = double-blind; PC = placebo controlled; /d = per day; CHM = Chinese herbal medicine; T/C = treatment group/control group; RR = risk ratio; 95% CI = 95% confidence interval; ILI = influenza-like illness; MD = mean difference.*Details of the herbal preparations can be found in the Appendix.
†Duration of the treatment is not clearly reported in original reference.
‡Results (effect sizes and 95% CI) were calculated by the reviewers.
We have entered a new era of medicine in which both the interest of scientific rigor and pressure from health care purchasers demand increased adoption of empirically based standards of care. Certain therapeutic areas have seen rapid transformation from a model in which care is based on a clinician’s intuition to one based on therapies and standards backed by substantial clinical evidence. The condition of non–ST-elevation acute coronary syndromes, a leading cause of death in industrialized nations, provides an excellent example of this transformation and a potential model for other areas of disease treatment. This article discusses the cycle of quality (the conceptual basis for quality improvement in non–ST-elevation acute coronary syndromes), the approach taken by the American College of Cardiology and the American Heart Association in developing their clinical practice guidelines, the use of performance indicators in clinical practice, and the ever-increasing evidence that adherence to practice guidelines and attention to performance measures result in improved patient outcomes. © 2007 Elsevier Inc. All rights reserved.

**KEYWORDS:** Acute coronary syndromes; Clinical trials; Outcomes; Patient care; Quality improvement

We are entering a new period of accountability in medicine, fueled by forces both internal and external to the field. Within the profession, rigorous scientific inquiry is promoting the adoption of empirically based standardized algorithms of care. Yet, perhaps more revolutionarily, government and major health care purchasers are increasingly demanding information on providers’ quality of care and linking these data to financial and nonfinancial incentives. The condition of non–ST-elevation acute coronary syndromes provides an excellent example of the rapid transformation of a therapeutic approach from a system of care largely based on intuition supported by biological rationale to a discipline increasingly based on empirical evidence from proven diagnostic technologies and therapies. Very recently, this evidence has become definitive enough to permit development of consensus-driven clinical practice guidelines and quality measures that can define whether a practice is providing care consistent with its peers. Public reporting of these performance measures, as well as recent efforts tying provider payment to performance-based measures, has further enhanced the importance of acute coronary syndromes as a test bed for broader issues of quality in medicine.

**DEFINITION AND CLINICAL EPIDEMIOLOGY OF THE CONDITION**

Non–ST-elevation acute coronary syndromes are defined by the presence of symptoms consistent with myocardial ischemia in an accelerating pattern or occurring newly at rest without ST-segment elevation on the electrocardiogram. This electrocardiographic distinction is critical, because the presence of ST-segment elevation denotes an emergency in which acute reperfusion of the suspected coronary occlusion should be accomplished as effectively and efficiently as possible. Acute coronary syndromes, including both non-ST elevation and ST elevation, are one of the most common causes of death. Each year, more than 1.5 million patients are admitted to emergency departments in the United States and more than 400,000 people die of cardiovascular causes outside of the hospi-
tal. Of those admitted, the majority have non–ST-elevation acute coronary syndromes, and epidemiology indicates that the number of cases will continue to grow in the future. In economically developed countries, despite advances in prevention, increased life expectancy and the aging of the “baby boom” generation will ensure a steady stream of elderly populace at high risk for acute coronary syndromes. Meanwhile, in developing countries, economic successes in preventing premature death caused by starvation and infectious disease, as well as the “westernization” of diet, sedentary lifestyles, and smoking habits, are leading to acute coronary syndromes becoming the predominant cause of death.

Despite the massive number of people afflicted with non–ST-elevation acute coronary syndromes, until approximately a decade ago, only a modest number of small clinical trials that could guide diagnosis and therapy with modern evidence had been completed. Since then, more than 200,000 patients have been entered into randomized controlled trials evaluating therapies and strategies, and many of these studies have been coupled with evaluation of biomarkers in stratifying prognosis or treatment effect. This broad base of evidence provides clinical guideposts that have been incorporated into evidence-based guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA).

This delay in the generation of evidence-based recommendations (compared with that for ST-elevation myocardial infarction) has contributed significantly to a lag in focus on measuring and improving quality of care for patients with non–ST-elevation acute coronary syndromes. In addition, the more diverse patient population, together with the uncertainty of diagnosis at hospital arrival—often requiring recognition of non–ST-elevation coronary syndromes solely on the basis of subjective symptoms of chest pain in the absence of any electrocardiographic findings or elevated cardiac markers—has hindered rapid risk-stratification processes and application of early therapies that vary on the basis of the patient’s risk status. Nevertheless, efforts are ongoing to overcome these barriers and enhance evidence-based care for patients with non–ST-elevation acute coronary syndromes. These efforts have led to measurable improvements in outcomes.

**THE CYCLE OF QUALITY**

The conceptual basis for improving quality that stimulated much of the activity is shown in Figure 1. When a medical...
problem has such profound societal implications, it is proper to make an intense investment in science that will lead to numerous biological, behavioral, material, and structural targets for diagnosis and therapy of the condition. Indeed, in the field of non–ST-elevation acute coronary syndromes, research has been rewarded by multiple new diagnostic tests and therapeutic approaches. However, these approaches cannot be validated without adequate clinical trials based on the principles listed in Table 1. These trials should measure tangible outcomes important to patients and enroll enough clinical outcomes to detect modest treatment effects. They also should strive to enroll populations who reflect patients who will be treated in practice, including elderly patients and those with likely comorbidities, and studies should be carried out in a setting typical of community care. When these trials reach definitive conclusions, their results can be translated into clinical practice guidelines. The definitive elements from clinical practice guidelines can be translated into performance measures, providing a numerator and denominator for actually measuring whether a practitioner, hospital, clinic, or health system is adhering to proven standards of diagnosis and treatment. Throughout the cycle, gaps in knowledge can be identified as important dilemmas arise from situations commonly encountered by practitioners and their patients. The cycle also must be monitored to ensure that adoption of new care practices is associated with corresponding declines in morbidity and mortality.

Three fundamental infrastructure elements are central to this cycle of quality construct: First, a robust informatics platform with standard nomenclature and data standards is necessary. Second, a professionally driven education and reporting system must be present to provide timely and credible performance feedback. Finally, the quality improvement process should be driven by strong local clinician champions and aided by financial and nonfinancial incentives to provide higher quality of care.

### APPROACH TO CLINICAL PRACTICE GUIDELINES

In 1994, the Agency for Health Care Policy and Research commissioned the first set of national clinical practice guidelines for non–ST-elevation acute coronary syndromes (at that time called “unstable angina”). The report noted the paucity of large-scale randomized clinical trials data, but it established an approach to nomenclature that paved the way for major clinical trials. Shortly thereafter, the government decided to discontinue direct oversight of clinical practice guidelines efforts, and this effort was assumed by professional societies.

Development of clinical practice guidelines in North America occurs through a process implemented by a joint committee of the ACC and AHA. The guidelines committee is dominated by cardiovascular specialists but includes representatives from general medical groups; guidelines are vetted through multiple organizations before final publication. The system organizes each issue by weight of evidence and class of recommendation. Weight of Evidence A includes single large clinical trials or multiple smaller clinical trials with consistent results, Weight of Evidence B includes well-conducted observational studies or small clinical trials, and Weight of Evidence C derives from expert opinion. Class I recommendations are those that should be done in eligible patients, Class IIa recommendations are reasonable options for care, Class IIb denotes that the practice is not believed to be helpful, and Class III recommendations mean that the practice is likely to be detrimental to the patient.

Table 2 shows the therapies that achieve level of evidence A or B with a Class I recommendation. Despite the large number of recent clinical trials, the number of proven diagnostic and therapeutic approaches is smaller than commonly believed. Of course, the guidelines document contains considerable detail about multiple issues for which desirable evidence does not exist. Figure 2 shows a flow diagram for key decisions in high-risk patients with non–ST-elevation acute coronary syndromes. The surest way to achieve the largest effect is to ensure that basic components of care occur reliably, including prompt measurement of clinical, electrocardiographic, and biomarker measures of risk, and administration of aspirin, clopidogrel, thrombin inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors, glycoprotein IIb/IIIa receptor antagonists, and statins to appropriate patients. Clinical trials indicate an advantage of early angiography in high-risk patients (identified through positive myocardial markers, hemodynamic compromise, or marked ST segment changes on electrocardiogram).

### APPROACH TO PERFORMANCE INDICATORS

As evidence accumulates rapidly, it becomes possible to define practices meeting the definition of necessary or cru-
cial care. Necessary care is defined as care that would result in harm to a patient if omitted or in significant health benefits if enacted. The arbiter of this definition is the professional provider group with the knowledge base to assess therapeutic impact. When viewed from this perspective, only a small number of clinical practice guideline recommendations have the level of certainty required to make the list of necessary or crucial care. The powerful

Table 2 Class I, Level A or B Recommendations for Selected Therapies Based on American College of Cardiology and the American Heart Association Guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of patients with definite acute coronary syndromes and ST-segment elevation for immediate reperfusion therapy</td>
</tr>
<tr>
<td>Immediate, continued antiplatelet therapy with aspirin; add clopidogrel as soon as possible, continue for ≥ 1 mo (indefinitely if aspirin not tolerated)</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa inhibition (plus aspirin and heparin) if continued ischemia or other high-risk features</td>
</tr>
<tr>
<td>Subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin (plus aspirin and/or clopidogrel)</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa antagonist (plus aspirin and heparin) if catheterization and percutaneous coronary intervention planned</td>
</tr>
<tr>
<td>Early invasive strategy for recurrent angina/ischemia: (1) at rest, (2) with low level of activities despite intensive anti-ischemic therapy, or (3) with heart failure symptoms, S3 gallop, pulmonary edema, worsening rales, or new/worse mitral regurgitation, elevated troponins; new ST-segment depression; high-risk findings on noninvasive stress testing; left ventricular systolic dysfunction (eg, ejection fraction &lt; 40% on noninvasive test); hemodynamic instability; sustained ventricular tachycardia; percutaneous coronary interventions &lt; 6 mo; prior bypass surgery.</td>
</tr>
<tr>
<td>Percutaneous coronary intervention for multivessel disease with suitable anatomy, normal left ventricular function, and no diabetes mellitus</td>
</tr>
<tr>
<td>Bypass surgery for significant left main disease, 3-vessel disease, or 2-vessel disease with significant proximal left anterior descending and either left ventricular dysfunction or ischemia during noninvasive testing.</td>
</tr>
<tr>
<td>Lipid-lowering agents (HMG-CoA reductase inhibitor) and diet if low-density lipoprotein level &gt; 130 mg/dL</td>
</tr>
<tr>
<td>Hypertension control to &lt; 130/85 mm Hg</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors for patients with heart failure, ejection fraction &lt; 40%, hypertension, or diabetes mellitus</td>
</tr>
</tbody>
</table>

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.


Figure 2 The Duke Algorithm for key decisions in patients with acute coronary syndromes. ACS = acute coronary syndromes; CABG = coronary artery bypass graft; cath = cardiac catheterization; DTB = door-to-balloon; GP = glycoprotein; IABP = intra-aortic balloon pump; LBBB = lower bundle branch block; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.
influence of differential reimbursement on the behavior of providers and hospitals demands that careful attention be paid to selecting performance measures only when they are proven correct.

As with Clinical Practice Guidelines, the AHA/ACC effort has developed a detailed process plan for developing performance measures. The approach begins by assembling an ecumenical committee with expertise in clinical and quantitative aspects of medicine, and with explicit consideration of conflicts of interest. The committee begins by identifying the population of interest, realizing that “gaming” the numerator or denominator in a performance measure can be a major problem. Then, relevant dimensions of care are defined for the population of interest. The literature is surveyed with particular attention to quantitative systematic overviews of evidence. Here, the clinical practice guidelines system provides a template that allows rapid identification of measures from the Level of Evidence A, Grade I or Grade III recommendations. Beyond a definitive recommendation, however, measures must be susceptible to clear identification of both the numerator (proper execution of the action) and denominator (population for whom the action was indicated). A formal mechanism is then used to distill a penultimate list of measures. Given the list of possible measures, a feasibility period ensues in which the operating characteristics of measures are quantified in practice. This period is critical to prevent enactment of inappropriate incentives for practitioners or hospitals. Finally, the measures are put into practice and, especially during the early period of use, continually refined to ensure that they are truly measuring a construct that is widely accepted as beneficial.

EVIDENCE FOR GAPS IN THE QUALITY OF CARE FOR PATIENTS WITH NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

Despite unequivocal evidence for efficacy from randomized controlled trials and compelling demonstration of the relationship between performance on process of quality of care indicators and outcomes, several recent studies have shown significant gaps in adherence to guideline-based therapies. In fact, many recommended therapies continue to be underused in patients without any documented contraindications. Non–ST-elevation acute coronary syndromes care is consistently less adherent than that seen with ST-elevation myocardial infarction, perhaps indicating in part a failure to appropriately recognize the severity of this condition. In one study, up to two thirds of patients with non–ST-elevation acute coronary syndromes failed to receive 1 or more therapies indicated for their condition as recommended by national guidelines. Other studies found that those at highest risk and with the most potential for benefit from therapy also tend to be, paradoxically, those least likely to receive it. Clinically, studies have consistently demonstrated disparities in care based on age, race, gender, and socioeconomic factors.

EVIDENCE THAT BETTER QUALITY LEADS TO BETTER OUTCOMES

Until recently, clinicians often argued that the massive tome of clinical practice guidelines, combined with a small list of definitive recommendations from clinical practice guidelines and performance measures, had little chance of influencing overall outcomes because so many medical decisions fall far short of the level of evidence required. The use of “cookbook medicine” without consideration of the many elements of clinical judgment was thought by some to be dangerous for overall patient outcome. This skepticism was the direct result of a lack of data demonstrating a relationship between evidence-based care and outcomes in the general population receiving care in a community setting. However, an increasing number of studies report a direct relationship between successful implementation of performance measures and reductions in mortality and morbidity.

By using data from the Cooperative Cardiovascular Project, Chen et al showed that hospitals with the best adherence to evidence-based medicine had the lowest mortality. Eagle et al reported that hospitals in the Michigan region displayed a variable degree of adherence to clinical practice guidelines. When outcomes were measured as a function of adherence, there was a direct relationship. The link between care and outcomes also has been shown for patients with non–ST-elevation acute coronary syndromes. By using data on approximately 47,000 high-risk patients from the national Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines Quality Improvement Initiative, Peterson and colleagues found a strong association between hospitals’ levels of adherence to guideline-based therapies and their in-hospital mortality.

THE FUTURE

The future of improving clinical quality in acute coronary syndromes has great promise. Our clinical research enterprise is maturing, leading to more rapid translation of bench discoveries into studies in humans and, ultimately, into definitive clinical trials. Professional societies have begun embracing the vital need to update and disseminate clinical practice guidelines. In addition, software and Web-based acute coronary syndromes registries now aggregate national performance information and provide timely feedback to caregivers. A similar technologic revolution at the local level also is empowering clinicians with computerized order decision and decision support tools as a means of ensuring consistent high-quality, standardized care. Finally, patients, clinicians, and administrators alike have been engaged in the quality improvement process through public reporting and pay-for-performance strategies. As the cycle of quality becomes more organized through these processes and policies, patient care and ultimately outcomes should improve in this critical area of medicine.
References


Rheumatoid Arthritis: Diagnosis and Management

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ABSTRACT

Accurate diagnosis of rheumatoid arthritis may be difficult early in its course and demands high clinical suspicion, astute examination, and appropriate investigations. Early use of disease-modifying antirheumatic drugs and biologics has improved outcomes but requires close monitoring of disease course and adverse events. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Diagnosis; Review; Rheumatoid arthritis; Therapy

Rheumatoid arthritis is a chronic, systemic, inflammatory autoimmune disorder causing symmetrical polyarthritis of large and small joints, typically presenting between the ages of 30 and 50 years. The most common inflammatory arthritis, it afflicts an estimated 25 men and 54 woman per 100,000 population and is responsible for 250,000 hospitalizations and 9 million physician visits in the US each year.

The etiology of rheumatoid arthritis is not fully understood but involves a complex interplay of environmental and genetic factors. Genetics also play a role in disease severity. A triggering event, possibly autoimmune or infectious, initiates joint inflammation. Complex interactions among multiple immune cell types and their cytokines, proteinases, and growth factors mediate joint destruction and systemic complications.

DIAGNOSIS

The diagnosis of rheumatoid arthritis is primarily clinical. The typical presentation is polyarticular, with pain, stiffness, and swelling of multiple joints in a bilateral, symmetric pattern. A minority of patients present with oligoarticular asymmetric involvement. The onset is usually insidious, with joint symptoms emerging over weeks-months and often accompanied by anorexia, weakness, or fatigue. Patients usually note morning stiffness lasting more than an hour. Commonly involved joints are the wrists, proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints, with distal interphalangeal joints and spinal joints usually spared.

Typical examination findings include swelling, bogginess, tenderness and warmth of, with atrophy of muscles near, the involved joints. Weakness is out of proportion to tenderness.

Rarely, patients may present with single joint involvement or with severe systemic symptoms of fever, weight loss, lymphadenopathy, and multiple organ involvement such as lung or heart.

Infection-related reactive arthropathies, seronegative spondyloarthropathies, and other connective tissue diseases may have symptoms in common with rheumatoid arthritis, as may an array of endocrine and other disorders. These must be excluded in the initial diagnostic evaluation. Table 1 lists some common diseases that should be considered in the differential diagnosis.

There is no single test that confirms rheumatoid arthritis. Initial laboratory tests should include a complete blood cell count with differential, rheumatoid factor, and erythrocyte sedimentation rate or C-reactive protein. Rarely, joint aspiration also may be required, especially with monoarticular presentations, to rule out infectious or crystal-induced arthritis. Baseline renal and hepatic function tests are recommended to guide medication choices. Anticyclic citrullinated peptide antibody carries high specificity and positive predictive value but is present in fewer than 60% of rheu-
rho-matoid arthritis patients. Tests to rule out other disorders in the differential diagnosis (Table 1) should be performed as clinically indicated.

The American College of Rheumatology criteria (Table 2) are helpful in formally diagnosing and following rheumatoid arthritis patients in research trials. In the clinical setting, a definitive diagnosis using these criteria is not possible in all the cases; they should be used only in combination with all other available information in an individual case.

**KEY POINTS: DIAGNOSIS AND INITIAL MANAGEMENT DECISIONS**

There are 2 questions for the primary care physician when evaluating a patient with arthritis: Is the diagnosis of rheumatoid arthritis likely? Does the patient need early treatment or referral to a rheumatologist, or both? Findings making rheumatoid arthritis the likely diagnosis and prompting initiation of treatment are:

- Joint swelling (and pain) of 3 or more joints
- Metacarpal or metatarsal joint involvement (a positive squeeze test, ie, significant pain when squeezed across these joints)
- Morning stiffness lasting more than 30 minutes
- Elevated erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor

Referral to a rheumatologist is indicated if the diagnosis is unclear, more than 5 joints or large joints are involved with accompanying significant subjective symptoms, or laboratory abnormalities are present.

**Table 1** Diseases that Can Mimic Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Common Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other connective tissue syndromes</td>
<td>Systemic lupus erythematosus,</td>
</tr>
<tr>
<td></td>
<td>Systemic vasculitides,</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>Sarcoidosis, Still’s disease, Infective</td>
</tr>
<tr>
<td></td>
<td>endocarditis, Rheumatic fever</td>
</tr>
<tr>
<td>Spondyloarthropathies</td>
<td>Psoriatic arthritis, Reactive arthritis</td>
</tr>
<tr>
<td>Infectious arthritis</td>
<td>Viral arthritides (esp. Parvo virus),</td>
</tr>
<tr>
<td></td>
<td>Bacterial arthritis, Gonococcal arthritis</td>
</tr>
<tr>
<td>Crystal-induced arthritis</td>
<td>Polyarticular gout</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Thyroid disorders</td>
</tr>
<tr>
<td>Soft-tissue syndromes and</td>
<td>Fibromyalgia, Polyarticular</td>
</tr>
<tr>
<td>Degenerative disorders</td>
<td>osteoarthritis</td>
</tr>
<tr>
<td>Deposition disorders</td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Malignancy (paraneoplastic</td>
<td>Lung cancer, Multiple myeloma</td>
</tr>
<tr>
<td>syndromes)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Classification Criteria for Rheumatoid Arthritis*

- Morning stiffness (lasting ≥ 1 hour)†
- Arthritis of 3 or more joint areas (areas are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints)†
- Arthritis of hand joints (proximal interphalangeal or metacarpophalangeal joints)†
- Symmetric arthritis, by area†
- Subcutaneous rheumatoid nodules
- Positive rheumatoid factor
- Radiographic changes (hand and wrist, showing erosion of joints or unequivocal demineralization around joints)

†Present for ≦6 weeks.

**TREATMENT**

A comprehensive approach to managing rheumatoid arthritis consists of patient education, physical/occupational therapy, and drug treatment. Patients should be educated about the disease and referred to these ancillary specialists to maintain joint function and delay disability. Drug treatment generally involves a 3-pronged approach: nonsteroidal anti-inflammatory drugs and low-dose oral or intra-articular glucocorticoids; disease-modifying antirheumatic drugs; and consideration of biologic response modifiers/biologics. Nonsteroidal anti-inflammatory drugs reduce joint pain and swelling, but do not alter the disease course and should not be used alone.3 Steroids (prednisone 10 mg daily or equivalent) relieve symptoms and may slow joint damage,3 they should be prescribed at a low dose for short duration, primarily as “bridge” therapy, and with daily calcium (1500 mg) and vitamin D (400-800 IU) oral supplements to limit bone demineralization.3

All patients with rheumatoid arthritis should be evaluated for disease-modifying antirheumatic drugs treatment.3 Early use slows disease progression and improves overall long-term prognosis.3 Although there is consensus among rheumatologists that rheumatoid arthritis should be treated early and aggressively, a number of issues (choice of initial therapy, timing and patient criteria for initiation of combination therapy, or use of biologics) remain under evaluation.

The following is an approach consistent with the available evidence. Patients with mild disease (typically <5 joints involved and mild subjective symptoms) and normal radiographic findings can receive hydroxychloroquine, sulfasalazine, minocycline, or possibly methotrexate. Methotrexate remains the initial treatment of choice in moderate-severe disease (typically >5 joints or large joint involvement with significant subjective symptoms) or radiographic changes of bone loss/erosion. The target dose (15 mg/week) should be reached within 6-8 weeks if tolerated. When response is inadequate, lefunomide, azathioprine, or combination therapy (methotrexate plus another agent) may be considered. Combinations of disease-modi-
fying antirheumatic drugs may be more effective than single-drug regimens. Women of childbearing age should use adequate contraception when taking certain (teratogenic) disease-modifying antirheumatic drugs (Table 3).

Biologics, the latest generation of antirheumatic drugs, have novel molecular mechanisms that target cytokines, signaling molecules and cells involved in inflammation and joint destruction. These include the tumor necrosis factor antagonists: adalimumab, etanercept, and infliximab (first line agents); the Interleukin-1 antagonist, anakinra; the anti-B cell antibody, rituximab; and the down-regulator of T-cell co-stimulation, abatacept. All biologics are associated with an increased risk of infection (bacterial, viral, and fungal) and tuberculosis reactivation. Table 3 lists disease-modifying antirheumatic drugs and biologic dosing regimens, times to onset of benefit, adverse effects, and safety monitoring.

It is important to note that there is disagreement among rheumatologists about the choice of initial therapy. There is evidence that combination of methotrexate and a biologic agent is the most effective current therapy but the short- and long-term risks, as well as the cost-effectiveness of biologic agents, are not well defined. Due to these unanswered questions, common rheumatology practice is to begin methotrexate alone as initial therapy.

Chronic treatment of rheumatoid arthritis is a continuous process, and periodic patient re-assessment is paramount. Patients should be evaluated every 2-3 months for control of

---

**Table 3  Rheumatoid Arthritis Treatment: Disease-Modifying Antirheumatic Drugs and Biologic Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of Effect</th>
<th>Adverse Events</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>500-1000 mg (weight based) at 0, 2 and 4 weeks then every 4 weeks</td>
<td>2-12 weeks</td>
<td>ISR, infections, hypersensitivity, COPD exacerbation</td>
<td>Monitor for TB, other infections; CBC, chemistry and LFTs at baseline and with each infusion</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg sc biweekly</td>
<td>2-12 weeks</td>
<td>ISR, infections, TBr; demyelinating disorders (rare)</td>
<td>TB, fungal, other infections; CBC and LFTs at baseline and then every 2-3 months</td>
</tr>
<tr>
<td>Anakinra</td>
<td>100 mg sc daily</td>
<td>4-12 weeks</td>
<td>ISR, leucopenia, infections, hypersensitivity</td>
<td>CBC at baseline and every 3 months</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50-150 mg po daily</td>
<td>2-3 months</td>
<td>GI intolerance, cytokopena, hepatitis, infections</td>
<td>CBC, LFTs every 2-4 weeks initially, then every 2-3 months</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.5-5 mg po daily</td>
<td>2-3 months</td>
<td>GI intolerance, cytokopena, infections, hypertension, renal disease</td>
<td>Cr every 2 weeks at initiation, then monthly: consider CBC, LFTs, and K⁺</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg sc twice/ week or 50 mg sc weekly</td>
<td>2-12 weeks</td>
<td>ISR, infections, TBr; demyelinating disorders (rare)</td>
<td>TB, fungal, other infections; CBC and LFTs at baseline and then every 2-3 months</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200-400 mg po daily</td>
<td>2-6 months</td>
<td>GI intolerance, Retinal toxicity, infection, TBr; demyelinating disorders (rare)</td>
<td>Fundoscopy every 12 months: TB, fungal, other infections; CBC and LFTs at baseline and then every 2-3 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 mg/kg at weeks 0, 2 and 4, then every 8 weeks</td>
<td>2-12 weeks</td>
<td>GI intolerance, skin rash, hepatitis, cytokopena; highly teratogenic</td>
<td>Hepatitis B and C serology in high-risk patients: CBC, Cr and LFTs mostly x6, then every 1-2 months; reduce dose or stop if LFTs elevate</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>20 mg daily</td>
<td>4-12 weeks</td>
<td>GI intolerance, oral ulcers, alopecia, hepatitis, pneumonitis, cytokpena, rash; teratogenic</td>
<td>Fundoscopy every 6 months: TB, fungal, other infections; CBC and LFTs at baseline and then every 2-3 months</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15-25 mg orally, sc or IM weekly</td>
<td>1-2 months</td>
<td>GI intolerance, oral ulcers, alopecia, hepatitis, pneumonia, cytokpena, rash; teratogenic</td>
<td>CBC, Cr and LFTs mostly x6, then every 1-2 months; adjust dose or stop if LFTs elevate</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg twice daily 1000 mg at 0 and 15 days</td>
<td>1-3 months</td>
<td>Dizziness, skin pigmentation, infection risk, new and reactivation viral infections; respiratory difficulty, cytokpena</td>
<td>none</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1000 mg at 0 and 15 days</td>
<td>2-12 weeks</td>
<td>GI intolerance, oral ulcers, cytokpena, rash</td>
<td>Monitor for TB, other infections; CBC, chemistry and LFTs at baseline and 2-3 months</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>2-3 gm daily</td>
<td>1-3 months</td>
<td></td>
<td>CBC every 2-3 months</td>
</tr>
</tbody>
</table>

Sc = subcutaneous; po = orally; im = intramuscularly; ISR = injection site reaction; CBC = complete blood count; LFTs = liver function tests; UA = urinalysis with microscopic examination; Cr = serum creatinine; TBr = tuberculosis reactivation.
disease activity, extra-articular manifestations, medication side effects, and functional capacity. Annual hand and feet radiographs (for joint surface erosions and demineralization) also are recommended.³

**KEY POINTS: MANAGEMENT**

In managing chronic rheumatoid arthritis, the primary care physician should assess course (improvement or progression), net disability, and medication side effects (including osteoporosis with chronic steroid use). Ongoing surveillance for infection, tuberculosis, and malignancy (age-appropriate screening), osteoporosis and immunizations (influenza vaccine and pneumovax) are essential components of care. Cardiovascular risk factor reduction is warranted due to a higher risk for development of coronary artery disease related to the underlying disease or medications.

**SUMMARY**

Prompt and accurate diagnosis, early aggressive treatment, including disease-modifying antirheumatic drugs or biologics, symptom control, and close monitoring of disease state and medication toxicity are the keys to effective management of the patient with rheumatoid arthritis. Subspecialty referral should be considered in all patients with moderate-severe disease or demonstrating incomplete response.

**References**

PHYSICAL FINDINGS

Clubbing of the Digits

Thomas J. Marrie, MD, Neil Brown, MD
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The original description of clubbing of the digits, one of the most important clinical signs in all of medicine, is attributed to Hippocrates (460 BC). Clubbing continues to fascinate students, clinicians, and researchers, as evidenced by 165 articles on clubbing published from 1975 to August of 2006. Clubbing is easy to recognize in its advanced stages compared with the early stages, as evidenced by only moderate agreement among experienced clinicians on the presence of clubbing.2

FEATURES OF CLUBBING

Clubbing is painless unless associated with pulmonary hypertrophic osteoarthropathy, and then there is periarticular pain and swelling, most often in the wrists, ankles, knees, and elbows.2 Most patients are unaware of the presence of clubbing.

The physical features of clubbing occur in stages, the first of which is periungual erythema (Figure 1) and a softening of the nail bed, giving a spongy sensation on palpation, followed by an increase in the normal 160-degree angle between the nail bed and the proximal nail fold.3 Eventually the depth of the distal phalange increases (Figure 2), and the distal interphalangeal joint may become hyperextensible. In 1961, Rice and Rowland described the ratio of the distal phalangeal to interphalangeal depth of more than 1:1 as a sign of clubbing.2,3 The whole process usually takes years, but occasionally it may develop suddenly.3 In 1938, Lovibond described the sign that bears his name: Lovibond’s angle. When viewed from the lateral aspect, an angle of greater than 180 degrees (Figure 2) made by the nail as it exits the proximal nail fold can differentiate true clubbing from other conditions, such as nail curving and pronychia.3 In 1976, Leo Schamroth, an internationally recognized electrocardiologist from Johannesburg, South Africa, described the sign that bears his name. He had 3 episodes of infective endocarditis in 1975 and developed clubbing. He noted that the normal diamond-shaped window created by placing the dorsal surfaces of opposite terminal phalanges together was obliterated in clubbing (Figure 3).4

PATHOPHYSIOLOGY

After more than 3 decades of research, Martinez-Lavin1 concluded that vascular endothelial growth factor may play a central role in the development of clubbing. It is a platelet-derived factor induced by hypoxia and is produced by diverse malignancies. It produces vascular hyperplasia, edema, and fibroblast/osteoblast proliferation. High circulating levels of vascular endothelial growth factor and increased local expression of vascular endothelial growth factor are found in different groups of patients with digital clubbing. In hypoxic conditions with extrapulmonary shunting of blood, large megakaryocyte fragments fail to enter the pulmonary circulation (where they would be trapped) and thus gain access to the systemic circulation where they impact at the most distal sites, releasing growth factors and inducing clubbing.1

CONDITIONS IN WHICH CLUBBING MAY BE FOUND

Clubbing is found in a large number of conditions. These are best grouped into categories as shown in Table 1.

Figure 1 Periungual erythema and clubbing in a patient with endocarditis.
All patients with cyanotic congenital heart disease have clubbing, and one third have hypertrophic pulmonary osteoarthropathy. The major causes of clubbing may vary from country to country. In North America, 80% of acquired clubbing is associated with pulmonary disease.

ANCILLARY STUDIES TO CONFIRM THE PHYSICAL SIGN
Ancillary studies to confirm clubbing are generally not necessary. Arteriography of the hands of patients with clubbing shows hypervascularization, manifested as an increase in the number and size of distal digital arteries or arteriovenous communications. Magnetic resonance imaging shows hypervascularization, and positron emission scanning shows increased glucose metabolism in all of the digits of the fingertips of patients with clubbing.

Figure 2  Lateral view of a finger showing a marked increase in the depth of the distal phalanx. Even without measuring, it is evident that the ratio of the depth of the distal phalanx to the depth of the interphalangea is more than 1. Also note that Lovibond’s angle is more than 180 degrees.

Figure 3  Schamroth’s sign. The normal diamond-shaped window created by placing the dorsal surfaces of opposite terminal phalanges together is obliterated in clubbing.

APPRAISAL TO THE PATIENT WITH CLUBBING
If the cause of the clubbing is not immediately obvious (Table 1), an algorithmic approach, such as that advocated by Spicknall and colleagues, is useful.

Table 1  Conditions in Which Clubbing Might Be Found

<table>
<thead>
<tr>
<th>Pulmonary Conditions</th>
<th>Cardiovascular Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppurative pulmonary disease</td>
<td>Cyanotic congenital heart disease</td>
</tr>
<tr>
<td>Lung abscess</td>
<td>Subacute bacterial endocarditis</td>
</tr>
<tr>
<td>Empyema</td>
<td>Infected arterial grafts*</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Brachial arteriovenous fistulas†</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Hemiplegic stroke†</td>
</tr>
<tr>
<td>Diffuse pulmonary disease</td>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>Idiopathic pulmonary disease</td>
<td>Cardiac tumors</td>
</tr>
<tr>
<td>Asbestosis</td>
<td>Gastrointestinal Conditions</td>
</tr>
<tr>
<td>Pulmonary arteriovenous malformations</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Neoplastic pulmonary disease</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Primary biliary cirrhosis</td>
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<td>Metastatic osteogenic sarcoma</td>
<td>Lymphoma of the gastrointestinal tract</td>
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<tr>
<td>Malignant mesothelioma</td>
<td>Metabolic Conditions</td>
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<td></td>
<td>Graves disease</td>
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<td>Thyroid acropachy</td>
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<td></td>
<td>Severe secondary hyperparathyroidism</td>
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<tr>
<td>Other Pulmonary Conditions</td>
<td>Miscellaneous Conditions</td>
</tr>
<tr>
<td>Tuberculosis (reported in 30% of patients from Africa but not commonly reported in North America)</td>
<td>Human immunodeficiency virus infection</td>
</tr>
<tr>
<td></td>
<td>POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), a rare paraneoplastic syndrome secondary to a plasma cell dyscrasia.</td>
</tr>
</tbody>
</table>

*Clubbing involves the digits distal to the infected graft. †Usually unilateral clubbing.
Colonoscopic Clues Cinch the Diagnosis

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PRESENTATION
In the absence of clear localizing symptoms, abdominal pain can prove challenging to accurately diagnose. In this case, a 26-year-old male arrived at our hospital emergency department after 4 days of generalized, persistent abdominal pain. Although he had a fever, he denied any other concomitant constitutional symptoms or any change in bowel habits. Eating did not worsen his pain, and he reported no associated joint aches, blurry vision, or rash. He reported that the pain was relieved, but only temporarily, by ibuprofen.

ASSESSMENT
The patient was otherwise healthy with no history of medical conditions or surgical procedures. A lifelong non-smoker and nondrinker, he was taking no medications and had a noncontributory family history. A review of systems was positive for sub-acute onset of abdominal pain and was notably negative for evidence of gastrointestinal hemorrhage, dysuria, back pain, or recent trauma.

Physical examination revealed a young male in no acute distress. He had a blood pressure of 121/63 mm Hg; heart rate of 63 bpm; respiratory rate of 14 breaths/min; temperature of 98.9°F; and O2 saturation of 97% on room air. His abdomen was soft and non-distended, with normal bowel sounds. He exhibited mild tenderness to palpation in both lower quadrants but no rebound or guarding. No hepatosplenomegaly or mass was present, and he had no rash on his extremities and no joint effusions. Rectal examination revealed normal anal tone with no masses or frank blood.

Laboratory testing revealed that his white blood cell count was 13.0 K/µL (normal 3.8–10.5 K/µL) with 80% neutrophils, his hemoglobin was 13.8 g/dL (13.6–17.2 g/dL), and his platelets were 310 K/µL (160–370 K/µL). No evidence of metabolic acidosis was present, and his liver function tests were within normal limits. A computed tomography (CT) scan of the abdomen and pelvis showed a normal-looking appendix that was notably without surrounding inflammation; however, a soft tissue density appeared to be present in the cecum. The patient was discharged from the emergency department with follow-up instructions to further investigate with colonoscopy.

The patient continued to have tolerable abdominal pain over the next 24 h while preparing for his colonoscopy. The colonoscopy results were normal through the rectum and the sigmoid, descending, transverse, and ascending colon. However, at the entry to the cecum, there was frank pus draining from the appendiceal orifice with surrounding erythema (Figure 1A, B). The terminal ileum showed evidence of diffuse colitis extending approximately 10 cm.

DIAGNOSIS
The patient was diagnosed with sub-acute appendicitis and reactive ileitis. Appendicitis is most frequently caused by luminal obstruction of the appendix, commonly by a fecalith, fibrosis, or neoplasia. The obstruction causes the appendix to swell as the lumen is filled with mucinous secretions, eventually leading to occlusion of small blood vessels, ischemia, and necrosis. Bacterial overgrowth ensued, with both anaerobes and enteric pathogens involved.1

In the majority of cases, acute appendicitis is a clinical diagnosis relying heavily on the medical history, physical exam, and laboratory tests. Many clinicians include temperature, white blood cell count, and inflammatory markers such as CRP in their evaluation of suspected appendicitis. Studies have shown a statistical association between elevated white blood cell count, fever, and increased inflammatory markers and the diagnosis of appendicitis, but sensitivities and specificities were moderate at best.2,3 One can conclude from these studies that the presence of an elevated temperature and/or abnormal laboratory studies might aid in the diagnosis of appendicitis, but the history and physical exam are ultimately most important.
false-negative diagnosis of appendicitis is a relative lack of intra-abdominal fat, which normally serves as a natural contrast agent that allows inflammatory changes to be easily noted. A second condition that plays a role in a missed diagnosis on CT is the presence of small bowel dilatation caused by the inflamed appendix. This small bowel dilatation may mimic an obstruction, thus presenting a reasonable alternative diagnosis, or it may affect entry of oral contrast agent into the cecum, thus preventing optimal visualization of the cecum. A third significant contributor to a CT diagnosis is the clinical history provided on the radiology request form. Of the patients correctly diagnosed with appendicitis on CT, 90% had clinical indications that specifically raised the suspicion of appendicitis prior to CT. On the other hand, of those cases in which CT missed the appendicitis diagnosis, only 33% had specific clinical indications of appendicitis ($P < .0001$).  

Diagnosis of appendicitis via colonoscopy is uncommon, but when the clinical picture is ambiguous and radiographic imaging is not diagnostic, colonoscopy can be useful in evaluating patients for common conditions such as acute colitis (inflammatory, infectious, or ischemic), malignancy,
or diverticulitis. In 2002, Chang et al described 21 cases of appendicitis diagnosed by colonoscopy. This group of patients was elderly, had symptoms lasting more than 10 days, and had CT diagnoses other than appendicitis. The most common findings on colonoscopy were mucosal edema, bulging in the area of the appendiceal orifice, and hyperemia. Purulent drainage from the appendiceal orifice was visible in seven of the 21 cases and was considered diagnostic for appendicitis. Histopathologic evaluation confirmed appendicitis, and Chang et al concluded that, in their study cohort, diagnosis with colonoscopy was 100% sensitive and 99% specific. Two additional cases of appendicitis diagnosed with colonoscopy have been reported in the literature; in both cases, the diagnosis was confirmed at surgery.

**MANAGEMENT**

Based on the colonoscopy results, our patient was admitted to the hospital and on the following day underwent laparoscopic appendectomy. Histopathology of his appendix confirmed appendicitis (Figure 2A, B). Biopsies of the inflamed terminal ileum obtained at the time of colonoscopy revealed nonspecific inflammation without evidence of crypt abscesses, glandular architectural distortion, or mucosal destruction. The patient’s abdominal pain resolved after the surgery, and he was discharged on hospital day 3.

In conclusion, most cases of acute appendicitis can be diagnosed on the basis of history, physical examination, or radiographic imaging. When these tools do not provide a conclusive diagnosis, however, colonoscopy can safely be used for an accurate diagnosis of appendicitis. Given the high incidence of appendicitis and the high morbidity and mortality resulting from missed diagnoses, all physicians performing colonoscopy should be familiar with the colonscopic appearance of appendicitis.

**References**

Sun-banned

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PRESENTATION

A 62-year-old man presented to our outpatient dermatology clinic for evaluation of a diffuse cutaneous eruption. This was present for several months and had gradually worsened. He was in overall good health and reported no other medical or surgical problems. The patient did complain of joint aches but denied seizures or other neurologic problems. He also noted that his eruption worsened with sun exposure.

ASSESSMENT

Physical examination revealed diffuse erythematous and scaly plaques on the patient’s face, arms, chest, back, and thighs (Figure 1). He also had prominent oral ulcers (Figure 2). A routine potassium hydroxide preparation confirmed the absence of dermatophyte infection. Recent laboratory analyses disclosed a normocytic anemia and elevated blood urea nitrogen and creatinine. Urinalysis indicated proteinuria. Immunologic testing was positive for antinuclear antibody (1:580) and anti-double-stranded DNA (dsDNA) antibody. Histologic examination revealed interface changes, follicular plugging, and the presence of mucin.

DIAGNOSIS

The laboratory and histologic findings were consistent with a diagnosis of cutaneous lupus erythematosus. Systemic symptoms secondary to common autoimmune diseases such as rheumatoid arthritis, scleroderma, mixed connective tissue diseases, and the array of lupus pathologies are variable and wide-ranged. Patients might present with constitutional concerns or with any of an assortment of specific complaints, such as cutaneous, musculoskeletal, cardiovascular, respiratory, or gastrointestinal symptoms. The differential diagnosis is wide, encompassing sunburn, rosacea, drug eruptions, eczema, polymorphous light eruption, Jessner’s lymphocytic infiltrate, lymphoma cutis, dermatophyte infection, dermatomyositis, scleroderma, and other connective tissue diseases.

Cutaneous lupus predominantly presents as a papulosquamous eruption, often with scale. Because it presents at different stages, it is difficult to characterize within a static definition. However, fungal infection is rapidly eliminated from the differential diagnosis with a negative potassium hydroxide preparation.

While perhaps as many as 85% of patients with cutaneous lupus do not subsequently develop systemic lupus erythematosus, many patients with systemic disease also have the cutaneous form. Systemic lupus erythematosus classically occurs among young to middle-aged women; women outnumber men 6 to 1. Compared with white women, African American women have a 4-fold higher incidence of the disease. Its severity also is worse among African Americans when compared to those of other ethnicities.

Arthralgias are likely the most common initial complaints of patients who have yet to be diagnosed with systemic lupus erythematosus. These frequently progress to a full arthritis. Most organ systems can be acutely or chronically affected, a probable consequence of lupus-associated vasculitis and the concomitant hypercoagulable state that predisposes to thrombosis. Renal involvement, ranging from an active nephritis to end-stage renal failure, is perhaps the most recognized systemic manifestation.

The American College of Rheumatology has devised clinical and laboratory standards for diagnosing patients with systemic lupus erythematosus. Progression of the pathology can be slow, maintaining a mild chronic picture, or subclinical signs and symptoms can rapidly evolve into life-threatening organ failure. The current criteria for diagnosis of systemic lupus erythematosus require patients to have 4 of 11 laboratory and clinical features (Table). These criteria are believed to have an overall sensitivity and specificity of 96%, preventing most patients with the disease from going undiagnosed.

Systemic lupus erythematosus is associated with the formation of autoantibodies. Molecular mimicry has been pos-
tulated to occur, wherein a designated antigen cross-reacts with lupus autoantigens, leading to epitope formation and subsequent propagation of the immune response. The most recognized laboratory value correlated with systemic lupus erythematosus is the antinuclear antibody titer. Although this laboratory value is sensitive (greater than 99% of patients will have a positive titer), a positive value is prevalent in other connective tissue diseases as well. Depending on the circumstances, a patient may warrant further autoantibody tests.

The antinuclear antibody pattern—peripheral, homogeneous, nucleolar, centromere, or speckled—often proves useful in differentiating connective tissue diseases. Among the more common antibodies that might signal systemic lupus erythematosus are anti-dsDNA, anti-Smith (anti-Sm), anti-ribosomal RNP, anti-single-stranded DNA, Anti-SSA (Ro), Anti-SSB (La), cardiolipin antibodies, anti-U1RNP, rheumatoid factor, and autoantibodies to β-2 glycoprotein 1, some of which are cardiolipin antibodies; the C1q complement component protein is another potential harbinger. After a screening antinuclear antibody test, the most useful diagnostics are tests for dsDNA, anti-Sm, and anti-rRNP, which are found in 60%, 30% and 7%, respectively of patients with systemic lupus erythematosus. The dsDNA level may reflect disease activity, especially when decreased complement levels are noted.

Laboratory testing is somewhat less reliable in identifying cutaneous lupus. Therefore, a lesional biopsy remains the diagnostic test of choice. While the results of routine histology generally depend on the patient’s subtype of cutaneous lupus, thickening of the basement membrane, mucin deposition, and follicular plugging are often seen—as they were in our patient. Immunopathology can be used to confirm the diagnosis. Direct immunofluorescence of lesional skin usually reveals antibody deposition at the dermal-epidermal junction; examination of non-lesional skin may be useful in some subtypes of lupus, as it is in patients with chronic cutaneous lupus. For example, studies in patients with systemic lupus erythematosus indicate that direct immunofluorescence unveils characteristic immune deposits in 50-100% of lesional biopsy sites; 73-90% of non-lesional sites exposed to sun; and 26-92% of non-lesional sites that have not been exposed to sun.

Classifications for cutaneous lupus erythematosus include acute, subacute, chronic, tumid, or lupus panniculitis. While acute cutaneous lupus often affects the face, especially the malar region, subacute cutaneous lupus affects the cheeks and other sun-exposed areas, such as the neck and forearms. Chronic cutaneous lupus is common on the scalp, face, and conchal bowl of the ears. Follicular plugging is usually prominent and aids in diagnosis. Tumid lupus lacks epidermal involvement and manifests as an erythematous plaque. Lupus panniculitis is marked by atrophic plaques, often seen on the face, arms, trunk, and thighs. Its clinical picture is nearly diagnostic, especially when combined with a history of connective tissue disease. Other forms include lupus-
lichen planus overlap syndrome, bullous lupus erythematosus, and chilblain lupus.

**MANAGEMENT**

Disease progression of systemic lupus erythematosus must be curbed to prevent end-organ damage. Preventive tactics for systemic lupus erythematosus and cutaneous lupus include avoidance of sun exposure, extreme temperatures, and trauma. Any of these can ignite a disease flare. Treatment modalities rely on topical and intralesional corticosteroids combined with strict sun avoidance. Therapy may warrant the addition of antimalarials, retinoids, and immunosuppressive agents. Some success has been found with azathioprine, methotrexate, rituximab, and cyclophosphamide. It must be stressed that an aggressive medication regimen in the absence of sun avoidance often leads to a lack of improvement for systemic disease. Patients must be educated about types of sunscreens and their proper use. It is often recommended that car windows incorporate UVA and UVB protection as well.

Our patient was prescribed a strict regimen of sun avoidance, a brief course of oral corticosteroids, and maintenance use of topical corticosteroids. This course cleared his cutaneous lesions within several weeks.

**References**

PRESENTATION

Here’s a case with an unexpected happy ending. A 56-year-old woman with a history of cardiomyopathy presented with bradycardia and near syncope. She had been experiencing lightheadedness and generalized weakness, but not loss of consciousness, chest pain, palpitations, or dyspnea. Her cardiac condition began approximately 12 months earlier, after a viral upper respiratory tract infection.

At that time, her ejection fraction was markedly depressed at 28%. Viral serologies were not helpful. Cardiac dysfunction was treated empirically with antifailure therapy. Since then, the patient’s cardiac status had recovered steadily so that her exercise tolerance was excellent, allowing her to walk up to 0.62 miles (1 km) daily. Her medication regimen included carvedilol, digoxin, furosemide, and lisinopril.

ASSESSMENT

At 61 inches (1.55 m) and 141.5 pounds (64.2 kg), the patient was overweight (body mass index, 26.6). Her pulse rate was 56 beats per minute and regular; blood pressure was 130/70 mm Hg with no postural change; jugular venous pressure was not elevated; lung fields were clear; and she had peripheral edema in both ankles. A 12-lead ECG showed sinus bradycardia with a rate of 60 beats per minute, first-degree heart block (PR interval of 0.22 sec), and complete left bundle branch block (Figure 1). An x-ray film of the chest displayed a normal cardiac silhouette with no evidence of congestive cardiac failure. The patient’s electrolytes were normal; the potassium level was 4.2 mEq/L (reference range, 3.5-5.5 mEq). Her troponin I level also was normal at 0.01 μg/L (reference range, <0.04 μg/L). She had a serum digoxin level of 1.9 nmol/L, which was within the therapeutic window (therapeutic range, 1.0-2.6 nmol/L).

The patient was closely monitored in the coronary care unit. A transthoracic echocardiogram disclosed a normally contracting left ventricle, normal valvular function, and a 68% ejection fraction. Coronary angiography confirmed that the vessels were normal; left ventricular end diastolic pressure was normal as well.

Upon further questioning, the patient said that she had gained about 17.6 lbs (8 kg) over 6-8 months, despite 30-45 minutes of daily exercise. In addition, she reported brittle nails, severe constipation, menorrhagia, and increased lethargy and lassitude. She had no personal or familial history of thyroid disease. Additional blood work revealed a thyroid-stimulating hormone level of 100.1 mIU/L (reference range, 0.4-4.0 mIU/L), with an undetectable free thyroxine level of <3.7 pmol/L (reference range, 10.3-24.5). She had high titers of thyroid antimicrosomal antibodies and thyroglobulin antibodies; 1:102,400 and 1:51,200, respectively (reference range, 1:400 for both). Her serum cortisol, measured at 8:00 AM, was satisfactory at 612 nmol/L (reference range, 160-640 nmol/L).

DIAGNOSIS

The patient’s bradycardia and conduction disturbance were due to autoimmune primary hypothyroidism. Keeping her cardiac history in mind, levothyroxine was prescribed at a very small starting dose of 25 μg daily. Digoxin was stopped, despite the reassurance provided by the therapeutic drug level; hypothyroidism can make patients more sensitive to the drug.

In the ensuing 5 days, the patient reported marked symptomatic improvement with no further chest pain. Her levothyroxine dosage was increased to 50 μg daily upon discharge. On day 14, an ECG showed sinus rhythm with a rate of 55 beats per minute, a left anterior hemiblock, and baseline artifacts, likely due to muscle shivering, which is common in hypothyroid patients (Figure 2). Although left bundle branch block can be masked in the presence of bradycardia, we...
thought it likely that our patient’s block was resolving in response to levothyroxine therapy.

This patient’s signs and symptoms very much resembled myxedema, which can be manifested not only by cardiac complications, but by coma, renal irregularities, and respiratory failure. Bradyarrhythmias and conduction disturbances have been well-described, commonly entailing sinus bradycardia and AV block. Torsades de pointes, ventricular tachycardia, and fibrillation have been reported, often with concurrent ischemia. In addition, prolongation of the PR interval, low amplitude P waves, and QRS complexes with flattened or inverted T waves have been noted.\textsuperscript{1-3}

Although left bundle branch block is very common with ischemia, it has not been previously reported with hypothyroidism, to the best of our knowledge. Overall, the prevalence of conduction disturbance in this setting is probably rare, despite the relatively high prevalence of primary hypothyroidism. Rhythm disturbances have been reported in cases with undetectable free thyroxine levels, except for 1 case of subclinical hypothyroidism.\textsuperscript{4-6}

However, the diagnosis should be one of exclusion. The initial acute rhythm disorder should be assumed to be arising de novo. Myocardial ischemia, electrolyte disturbance, and structural abnormalities should be completely ruled out. Ischemia was excluded in our patient, because her troponin I level and coronary angiogram were normal. While hypothyroidism can boost creatine kinase to abnormally high levels, troponin I tends to remain normal, indicating that no myocardial injury has occurred.\textsuperscript{7} Digoxin toxicity also was ruled out.

Hypothyroid-associated cardiomyopathy was an alternative explanation for the patient’s rhythm disturbance, but a normal left ventriculogram, a normal left ventricular end-diastolic pressure, and the subsequent response of the bradycardia to levothyroxine made this unlikely. Her cardiomyopathy also antedated the diagnosis of hypothyroidism and had essentially resolved before this current episode.

The mechanisms by which the absence of thyroid hormones induces rhythm and conduction disturbances are essentially unknown. However, they can be assumed to be the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1}
\caption{This is the patient’s initial ECG.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2}
\caption{With drug therapy, ECG findings began to improve. The arrow indicates a baseline artifact that mimics atrial fibrillation.}
\end{figure}
reverse of those at work in hyperthyroidism. In rat myocytes, triiodothyronine has an important effect on the action-potential duration, which is prolonged in hypothyroidism and corrected upon re-incubation with the hormone. Triiodothyronine also is a key determinant of repolarization because it affects the time- and voltage-gated potassium channels (Kv1.5, Kv4.2, and Kv4.3). Triiodothyronine deficiency also impairs the function of membrane-bound sodium and calcium exchangers, and sodium and potassium ATPases, which are critical in phases 0, 1, and 3 of the action potential curve. Moreover, a lack of thyroid hormones reduces the number and performance of calcium ATPases in red blood cells. Since calcium ATPase channels are present in abundance on cardiac myocytes, a shortage of calcium ATPases might well contribute to the reduced myocardial contractility and cardiomyopathy associated with chronic hypothyroidism.

Another plausible consideration is that, in hypothyroidism, some conduction abnormalities might be triggered by relative hypoperfusion and subsequent vasoconstriction. Sluggish coronary blood flow affects the anterior and posterior fascicles, resulting in complete left bundle branch block. As levothyroxine is administered, coronary circulation improves. The left posterior fascicle, with its dual blood supply, would unblock first, resulting in a left anterior hemiblock pattern. Clearing of the anterior fascicle follows, and the QRS complexes normalize. In our patient’s case, this is not the complete explanation, as her right bundle branch was spared.

**MANAGEMENT**

At 4 weeks, our patient was well, with a thyroid-stimulating hormone measurement of 18.9 mIU/L and an unchanged ECG. Her levothyroxine dosage was increased to 100 μg daily, and at 3 months, her thyroid-stimulating hormone level was 2.8 mIU/L, and her ECG was completely normal (Figure 3). In fact, it was nearly identical to tracings recorded 12 months earlier, when her cardiomyopathy did not affect rhythm. She had no left bundle branch block at a heart rate of about 100 beats per minute, indicating that the defect had truly responded to levothyroxine—as did other hypothyroid symptoms.

This is one of a very few situations where bradycardia and conduction disturbances can be completely cured. Both should resolve upon thyroxine replacement, once hypothyroid-induced abnormalities have been identified. We initiated thyroxine at a low dosage, and the arrhythmia resolved slowly, almost in a dose-related fashion, a phenomenon that has not been fully documented until now.

**References**

An Unexpected Culprit

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PRESENTATION

The importance of lifestyle factors, such as diet, exercise, and body weight, as well as genetic factors and comorbidities, such as diabetes, in the pathophysiology of heart disease is well recognized. However, heart disease can also spring from an unexpected source.

A 47-year-old Hispanic female arrived at our clinic complaining of a 2-month history of exertional chest pain and difficulty breathing. She reported no fevers, palpitations, fainting, or edema. Her past medical history was significant for Hodgkin’s lymphoma at age 14, for which she underwent staging laparotomy including splenectomy and external beam mantle radiation therapy. Her medical history also included hyperlipidemia, acquired hypothyroidism, and premature menopause.

ASSESSMENT

Physical examination revealed a left cervical bruit and a grade 1/6 systolic ejection murmur at the upper sternal border. An exercise echocardiogram revealed a 2-mm ST-segment depression, poor functional capacity, and a blunted blood pressure response to exercise. Resting echocardiographic images showed a preserved ejection fraction of 60% and mild aortic-valve stenosis. At peak exercise, there was severe hypokinesis of the left ventricular apex and anterior wall. The cervical bruit was evaluated by carotid duplex ultrasound imaging, which revealed mild bilateral stenosis of the carotid arteries and severe stenosis of the left subclavian artery.

Left cardiac catheterization was performed based on the abnormal stress test. Coronary angiography revealed an isolated critical ostial stenosis of the left main trunk with no further obstructive disease in the coronary arterial system (Figure 1). It also showed a focal 90-95% stenosis of the left subclavian artery proximal to the left vertebral artery (Figure 2).

DIAGNOSIS

Based on the angiographic and ultrasound imaging results and the patient’s medical history, we determined that our patient was suffering from radiation-induced heart disease (RHD). This disease gained recognition several decades after the wide adoption and use of radiation to treat malignancies, mostly Hodgkin’s lymphoma and breast cancer. In survivors of radiotherapy-treated Hodgkin’s lymphoma and breast cancer, the estimated prevalence of RHD is 6 to 30%. In these patients, it tends to develop an average of 13 to 16 years after radiotherapy. Although the pathophysiology of RHD differs from that implicated in atherosclerotic heart disease, there is some overlap. The distinguishing patho-
logic feature in RHD is arterial medial thinning and adventitial fibrosis, and its arterial lesions occur most frequently in the ostium and proximal portions of epicardial coronary arteries.

**MANAGEMENT**

In the evaluation of patients who have received prior external beam radiation therapy, special awareness and serial surveillance is required due to the diffuse pan-arterial and cardiac injuries that can develop during the latent post-radiation period (median 9-22 years). Surgical revascularization is the recommended treatment for RHD because of the relative youth of the patient population and the frequency of coexisting valvular disease (which can be treated concomitantly), and because percutaneous coronary intervention with bare metal stenting has been associated with a high rate of in-stent restenosis.

We performed stent angioplasty of our patient’s left subclavian artery in preparation for use of her left internal mammary artery as a conduit for surgical revascularization. She subsequently underwent coronary artery bypass grafting with a left internal mammary artery graft to the left anterior descending artery and a reverse saphenous vein graft to the obtuse marginal branch of the circumflex artery. She is now 1 year post-revascularization and remains free of recurrent symptoms.

This case highlights the importance of addressing both the coronary and non-coronary vasculature in RHD patients; assessment should include a targeted investigation of the severity of aortic calcification and of the patency of arch vessels and the internal mammary artery.

**References**

Smoking and the Risk of Psoriasis in Women: Nurses’ Health Study II

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ABSTRACT

BACKGROUND: Psoriasis is a common, chronic, inflammatory skin disorder. Smoking may increase the risk of psoriasis, but no prospective data are available on this relation.

METHODS: We prospectively examined over a 14-year time period (1991-2005) the relation between smoking status, duration, intensity, cessation, and exposure to secondhand smoke, and incident psoriasis in 78,532 women from the Nurses Health Study II. The primary outcome was incident, self-reported, physician-diagnosed psoriasis.

RESULTS: We documented 887 incident cases of psoriasis. Compared with those who had never smoked, the multivariate relative risk (RR) of psoriasis was 1.78 (95% confidence interval [CI], 1.46 to 2.16) for current smokers and 1.37 (95% CI, 1.17 to 1.59) for past smokers. Compared with nonsmokers, the multivariate RR of psoriasis was 1.60 (95% CI, 1.31 to 1.97) for those who had smoked 11-20 pack-years and 2.05 (95% CI, 1.66 to 2.53) for those who had smoked ≥21 pack-years. Compared with never smokers, the multivariate RR of psoriasis was 1.61 (95% CI, 1.30 to 2.00) for those who quit smoking <10 years ago, 1.31 (95% CI, 1.05 to 1.64) for 10-19 years ago, and 1.15 (95% CI, 0.88 to 1.51) for ≥20 years ago. Prenatal and childhood exposure to passive smoke was associated with an increased risk of psoriasis.

CONCLUSIONS: In this prospective analysis, current and past smoking, and cumulative measures of smoking were associated with the incidence of psoriasis. The risk of incident psoriasis among former smokers decreases nearly to that of never smokers 20 years after cessation. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Cessation; Cigarette; Cohort; Pack-years; Passive; Prospective; Psoriasis; Risk factors; Smoking

Psoriasis is a chronic, inflammatory disease of the skin that affects approximately 2% of the population and poses a lifelong burden for those affected. A survey by the National Psoriasis Foundation found that 75% of patients with psoriasis reported a moderate to large negative impact of the disease on the quality of their life with an alteration of everyday activities. The negative impact of psoriasis may not be limited to its cutaneous or psychosocial manifestations. A recent large cohort study based on the General Practice Research Database in the United Kingdom found psoriasis to be an independent risk factor for myocardial infarction.

Previous cross-sectional and case-control studies have suggested a link between cigarette smoking and psoriasis, but no prospective data are available. Cigarette smoke contains many potentially toxic materials and may affect the immunopathogenesis of psoriasis, including T cell activation and overproduction of pro-inflammatory cytokines (e.g., tumor necrosis factor α [TNF-α], interleukin [IL]-2, IL-6,
had lived with a smoker as an adult in the following categories: none or <1 year, 1-4 years, 5-9 years, 10-19 years, 20-29 years, and 30+ years. Participants also were asked about reproductive factors (age at menarche, regularity of menses, length of breastfeeding, parity, menstrual status, and postmenopausal hormonal use) and husband’s level of education.

The endpoint of the current study was a self-reported, physician diagnosis of incident psoriasis. The baseline and biennial follow-up questionnaires inquired about weight, height, and alcohol intake. The reproducibility and validity of the questionnaires have been previously documented in the Nurses Health Study cohort.12–14

**CLINICAL SIGNIFICANCE**

- Both increasing duration and intensity of cigarette smoking increase the risk of psoriasis in women.
- With >10 pack-years of smoking, the risk of psoriasis increases in a dose-dependent manner.
- After smoking cessation, it takes 20 years for the risk of psoriasis to return to that of never smokers.

**Statistical Analysis**

We computed person-time of follow-up for each participant from the return date of the 1991 questionnaire to the date of diagnosis of psoriasis, death from any cause, or the end of the study period, whichever came first. We used Cox proportional hazards modeling to estimate the multivariate relative risk (RR) of incident psoriasis. We categorized smoking status as never, current, and past. Cumulative exposure to smoking was assessed by pack-years in the following categories: never, 1-10, 11-20, and ≥21. Years since quitting smoking was assessed in the following categories: never smoked, <10 years, 10-19 years, and ≥20 years. Intensity of smoking was analyzed in 4 categories of cigarettes per day: never, 1-14, 15-24, and ≥25. Duration of smoking was categorized as never, <20 years, 20-29 years, and ≥30 years for current smokers, and as never, <10 years, 10-19 years, and ≥20 years for past smokers. Exposure to the different types of passive smoke was examined as an indicator variable (yes or no).

Multivariate models were adjusted for age (continuous), alcohol intake (7 categories: none, 1-4 g/d, 5-9 g/d, 10-14 g/d, 15-29 g/d, 30-49 g/d, and 50+ g/d), and body mass index (BMI: <21 kg/m², 21-22.9 kg/m², 23-24.9 kg/m², 25-29.9 kg/m², 30-34.9 kg/m² and ≥35 kg/m²). We evaluated the potential impact of reproductive factors (age at menarche, regularity of menses, length of breastfeeding, parity, menstrual status, and postmenopausal hormonal use) and husband’s level of education by entering each term into the multivariate model. Tests for linear trends were calculated using continuous values for smoking exposure. We calculated the population-attributable risk, an estimate of the percentage of psoriasis cases in this population that would theoretically not have occurred if participants had never smoked, assuming a causal relation between smoking and incident psoriasis. For all RRs, we calculated 95% confidence intervals.
(CIs). All *P* values are 2-sided. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

The Partners Health Care System institutional review board approved this study. Return of a completed questionnaire was accepted by the institutional review board as implied informed consent.

### RESULTS

#### Baseline Characteristics

We documented 887 incident cases of psoriasis during the 14 years of follow-up. The baseline characteristics of the cohort according to smoking status are shown in Table 1. Alcohol consumption tended to increase from the never to the current smoker group, as did duration of smoking and number of cigarettes smoked per day. Current smokers were more likely to have been exposed to passive smoking than were never and past smokers.

#### Smoking Status, Intensity, Duration, and Risk of Incident Psoriasis

Compared with those who never smoked, the multivariate RR for incident psoriasis was 1.37 for past smokers and 1.78 for current smokers (Table 2). In age-adjusted and multivariate models, pack-years were associated with a graded increase in the risk for psoriasis. Compared with never smokers, the overall multivariate RR was 1.20 for 1–10 pack-years, 1.60 for 11–20 pack-years, and 2.05 for ≥21 pack-years. For current smokers, the multivariate RRs for the corresponding pack-year categories were 1.05, 1.57, and 2.25 (*P* for trend <.001). A significant trend also was present with increasing pack-year categories among past smokers (*P* for trend <.001) (Table 2). When we additionally adjusted for the female reproductive factors or husband’s level of education to either the age-adjusted or the multivariate models, these RRs did not change materially.

---

**Table 1** Baseline Characteristics within Categories of Smoking Status (1991) in the Nurses’ Health Study II

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Past</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>51,779</td>
<td>17,730</td>
<td>9023</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>35.3</td>
<td>36.6</td>
<td>36.1</td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>24.4</td>
<td>24.6</td>
<td>24.5</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>2.4</td>
<td>4.4</td>
<td>5.4</td>
</tr>
</tbody>
</table>

**Table 2** Relative Risk of Psoriasis by Smoking Status and Pack-Years among Women

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Cases of Psoriasis</th>
<th>Person-Years</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Multivariate RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>494</td>
<td>711,823</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Past</td>
<td>262</td>
<td>265,298</td>
<td>1.40 (1.20-1.62)</td>
<td>1.37 (1.17-1.59)</td>
</tr>
<tr>
<td>Current</td>
<td>131</td>
<td>104,804</td>
<td>1.82 (1.50-2.21)</td>
<td>1.78 (1.46-2.16)</td>
</tr>
<tr>
<td><em>P</em> for trend</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>494</td>
<td>711,823</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–10</td>
<td>158</td>
<td>190,389</td>
<td>1.20 (1.00-1.43)</td>
<td>1.20 (1.00-1.44)</td>
</tr>
<tr>
<td>11–20</td>
<td>120</td>
<td>104,463</td>
<td>1.67 (1.37-2.04)</td>
<td>1.60 (1.31-1.97)</td>
</tr>
<tr>
<td>≥21</td>
<td>115</td>
<td>73,781</td>
<td>2.19 (1.78-2.70)</td>
<td>2.05 (1.66-2.53)</td>
</tr>
<tr>
<td><em>P</em> for trend</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pack-years for current smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>494</td>
<td>711,823</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–10</td>
<td>17</td>
<td>23,655</td>
<td>1.06 (0.65-1.71)</td>
<td>1.05 (0.64-1.71)</td>
</tr>
<tr>
<td>11–20</td>
<td>37</td>
<td>34,863</td>
<td>1.59 (1.14-2.23)</td>
<td>1.57 (1.12-2.20)</td>
</tr>
<tr>
<td>≥21</td>
<td>75</td>
<td>45,359</td>
<td>2.35 (1.84-3.00)</td>
<td>2.25 (1.76-2.89)</td>
</tr>
<tr>
<td><em>P</em> for trend</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pack-years for past smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>494</td>
<td>711,823</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–10</td>
<td>140</td>
<td>165,719</td>
<td>1.21 (1.00-1.46)</td>
<td>1.22 (1.01-1.47)</td>
</tr>
<tr>
<td>11–20</td>
<td>82</td>
<td>68,857</td>
<td>1.69 (1.33-2.14)</td>
<td>1.61 (1.27-2.04)</td>
</tr>
<tr>
<td>≥21</td>
<td>37</td>
<td>27,756</td>
<td>1.78 (1.27-2.50)</td>
<td>1.61 (1.14-2.26)</td>
</tr>
<tr>
<td><em>P</em> for trend</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*The multivariate model adjusts for age, BMI, and alcohol intake.*
Similarly, there was a graded association between smoking intensity and the risk of psoriasis (Table 3). For current smokers, as compared with nonsmokers, the multivariate RR for psoriasis was 1.40 for smoking 1-14 cigarettes a day, 2.00 for 15-24 cigarettes a day, and 2.54 for 25 cigarettes a day. The corresponding multivariate RRs for past smokers were 1.34, 1.39, and 1.53. The significant trends persisted with smoking duration in both current and past smokers (Table 3).

### Time since Quitting Smoking and Risk of Incident Psoriasis

There was a graded reduction in the risk of psoriasis with increasing years of smoking cessation, and the risk of psoriasis became comparable to that of nonsmokers 20 or more years after smoking cessation (Table 4).

### Passive Smoke and Risk of Incident Psoriasis

The age-adjusted RRs of incident psoriasis by exposure to passive smoke were 1.31 for those whose mother smoked while pregnant with them, 1.26 for those with exposure to passive smoking as a child, and 1.35 for those with passive smoke exposure after age 18 (Table 5). After additionally adjusting for BMI, alcohol consumption, and self-smoking status, the multivariate RRs were attenuated to 1.21 (95% CI, 1.04 to 1.41), 1.18 (95% CI, 1.02 to 1.35) and 1.10 (95% CI, 0.95 to 1.28), respectively.

### Population-Attributable Risk

In our cohort, 14% of the incident psoriasis cases were attributable to having ever smoked. For past smokers, 27%

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**Table 3** Relative Risk of Psoriasis by Intensity and Duration of Smoking among Past and Current Women Smokers (1991-2005)

<table>
<thead>
<tr>
<th>Cases of Psoriasis</th>
<th>Person-Years</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Multivariate RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking intensity (cigarettes/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>494</td>
<td>71,1823</td>
<td>1.00</td>
</tr>
<tr>
<td>1-14</td>
<td>50</td>
<td>51,197</td>
<td>1.40 (1.05-1.87)</td>
</tr>
<tr>
<td>15-24</td>
<td>52</td>
<td>37,124</td>
<td>2.06 (1.54-2.74)</td>
</tr>
<tr>
<td>≥25</td>
<td>28</td>
<td>14,754</td>
<td>2.81 (1.92-4.11)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Smoking duration (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>494</td>
<td>71,1823</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;20</td>
<td>21</td>
<td>28,047</td>
<td>1.09 (0.70-1.70)</td>
</tr>
<tr>
<td>20 to 29</td>
<td>67</td>
<td>51,662</td>
<td>2.07 (1.60-2.68)</td>
</tr>
<tr>
<td>≥30</td>
<td>41</td>
<td>24,636</td>
<td>2.05 (1.48-2.85)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Past smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking intensity (cigarettes/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>494</td>
<td>71,1823</td>
<td>1.00</td>
</tr>
<tr>
<td>1-14</td>
<td>140</td>
<td>149,011</td>
<td>1.33 (1.10-1.61)</td>
</tr>
<tr>
<td>15-24</td>
<td>76</td>
<td>74,947</td>
<td>1.43 (1.13-1.83)</td>
</tr>
<tr>
<td>≥25</td>
<td>44</td>
<td>37,057</td>
<td>1.68 (1.23-2.29)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking duration (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>494</td>
<td>71,1823</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;10</td>
<td>41</td>
<td>50,760</td>
<td>1.15 (0.83-1.58)</td>
</tr>
<tr>
<td>10-19</td>
<td>156</td>
<td>163,423</td>
<td>1.38 (1.15-1.65)</td>
</tr>
<tr>
<td>≥20</td>
<td>62</td>
<td>49,311</td>
<td>1.67 (1.28-2.19)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*The multivariate model adjusts for age, BMI, and alcohol intake.

**Table 4** Relative Risk of Psoriasis by Years since Quitting Smoking (1991-2005)

<table>
<thead>
<tr>
<th>Cases of Psoriasis</th>
<th>Person-Years</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Multivariate RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>494</td>
<td>71,1823</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;10</td>
<td>103</td>
<td>87,766</td>
<td>1.71 (1.38-2.11)</td>
</tr>
<tr>
<td>10-19</td>
<td>96</td>
<td>109,760</td>
<td>1.33 (1.07-1.66)</td>
</tr>
<tr>
<td>≥20</td>
<td>63</td>
<td>67,006</td>
<td>1.14 (0.87-1.49)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>.004</td>
</tr>
</tbody>
</table>

*The multivariate model adjusts for age, BMI, and alcohol intake.
of the risk was attributable to smoking; for current smokers, 44% of the risk was attributable to smoking.

**DISCUSSION**

Our objective was to prospectively evaluate the relation between smoking and the incidence of psoriasis in a large cohort of women. We found that both past and current smokers were at increased risk for developing psoriasis, and the risk was greater for current smokers. The risk was graded and increased with the duration, intensity, and pack-years of smoking. Furthermore, the risk of incident psoriasis decreased with increasing years of smoking cessation reaching nearly that of never smokers 20 years after cessation. These associations were independent of other purported risk factors. The current study provides the first prospective evidence that smoking is a strong risk factor for incident psoriasis.

The impact of smoking on psoriasis has been evaluated in a cross-sectional study that compared 557 psoriatic patients attending the University of Utah Dermatology Clinics, with external population databases. The prevalence of smoking in the psoriatic patients was higher than in the general Utah population (37% vs 25%; P < .001). A previous study that evaluated the role of smoking preceded the occurrence of new cases of psoriasis. Furthermore, no graded response was observed across smoking intensity and duration, unlike our findings. Our prospectively obtained smoking history data, coupled with a larger sample size, may explain the differences. Whereas previous cross-sectional studies left uncertainty about the temporal relationship between smoking and psoriasis, our prospective longitudinal data indicate that increased smoking precedes the occurrence of new cases of psoriasis.

Psoriasis is a T-cell immune-mediated disease that involves over-expression of proinflammatory cytokines and chemokines such as TNF-α, IL-2, IL-6, IL-8, and γ-interferon. There are several speculated mechanisms by which cigarette smoke could augment the risk of psoriasis. Cigarette smoke contains many potentially toxic materials such as nicotine, reactive oxygen species, nitric oxide, peroxynitrite, and free radicals of organic compounds, and may affect the immunopathogenesis of psoriasis. Abnormalities in T-cell function, reduction in natural killer cells, impairment of humoral immunity, and elevated levels of inflammatory markers such as interleukin-6 and C-reactive protein have been observed in smokers. Specifically, nicotine may stimulate the functional capacity of antigen-presenting cells leading to T-cell proliferation and release of proinflammatory cytokines, which are thought to be involved in the pathogenesis of psoriasis. Some studies also have shown that cigarette smoking induces an overproduction of interleukin IL-1β, and increases the production of TNF-α and transforming growth factor-β, which have been associated with psoriasis severity.

The constituents of cigarette smoke, including mutagenic, neurotoxic, and fetotoxic agents, can pass through the placenta and are detectable in the urine of newborns. Maternal smoking is known to increase a woman’s risk of spontaneous abortion, preterm delivery, and lower birth weight. A previous study that evaluated the role of
passive smoking in psoriasis did not find it to be a risk factor. However, the study did not evaluate separately for prenatal, childhood, and adult exposure. Our study found passive exposure to serve as a risk factor in the first 2 groups. It is conceivable that for psoriasis, passive exposure to smoke has greater negative consequences earlier rather than later in life.

Conversely, smoking cessation may be an important target for prevention and management of psoriasis. Smoking cessation may decrease the degree of smoke-induced inflammation by lowering the level of circulating inflammatory cytokines or restoration of T-cell impairments. Indeed, our study found that the risk for psoriasis in past smokers was consistently lower than it was for current smokers. The risk progressively decreased with increasing years of smoking cessation and became insignificant, 20 years after cessation. Furthermore, among patients with existing psoriasis, higher intensity and duration of smoking was associated with increased clinical severity of psoriasis. These findings, along with well-established hazardous health effects of smoking, provide clear incentives for smoking cessation in those at risk for and suffering from psoriasis. Beyond the potential effect on psoriasis, smoking cessation would lead to a better overall clinical outcome in psoriasis patients, who often suffer co-morbidities related to smoking.

There are several strengths and limitations of our study. It is the largest prospective assessment of multiple markers of smoking status, duration, and intensity in relation to the risk of psoriasis. Similar to other population-based epidemiologic studies of psoriasis, we did not confirm the nurses’ self-reported physician-diagnosis of psoriasis clinically with an examination by a dermatologist. A recent French study of a non-health-professional population reported that the agreement between self-reported and dermatologists’ diagnoses of psoriasis was moderate, although it was the second best among 5 common skin disorders. Although we expect the overall accuracy of self-reported physician diagnosis of psoriasis to be higher among registered nurses, as was the case with other health data in our cohort, the corresponding accuracy against a dermatologist’s examination is not available. Nevertheless, when we additionally adjusted for self-reported physician-diagnosed co-morbidities associated with increased smoking such as asthma, chronic obstructive lung disease, cardiovascular disease, and hypertension, our results did not change materially. These data suggest that these co-morbidities associated with smoking did not contribute to an increased ascertainment of psoriasis among women smokers in our cohort. Furthermore, any nondifferential misclassification of psoriasis would have biased the study results toward the null and would not explain the strong associations observed in this study. Nonetheless, confirmation of these results using more specific case definitions of psoriasis as well as evaluation of psoriasis subtypes would be valuable.

The restriction to registered nurses in our cohort is both a strength and a limitation. The cohort of well-educated women minimizes the potential for confounding associated with socioeconomic status, and we were able to obtain high quality data with minimal loss to follow-up. Although the absolute rates of psoriasis and frequency of smoking may not be representative of a random sample of US women, the biological effects of smoking should be similar. Our findings would be most directly generalizable to white women with no history of psoriasis. Furthermore, between the reported bimodal peaks of psoriasis onset time (23 and 55 years), the age range of our cohort during the follow-up tended to overlap more with the second peak of incidence. Thus, our results may be more applicable to the later-onset cases of psoriasis.

In conclusion, this prospective study suggests that the risk of incident psoriasis in women is increased in past and current smokers, and with increasing duration and intensity of smoking. The risk of incident psoriasis among former smokers decreases nearly to that of never smokers 20 years after cessation. Smoking cessation may be a potentially important target for the prevention and management of psoriasis.

ACKNOWLEDGMENTS

We thank the participants in the Nurses Health Study II for their dedication and continued participation; the entire staff of the Nurses Health Study II; and Rong Chen, for her assistance with programming.

References


Hypertension affects more than 50 million people in the United States and is an independent risk factor for cardiovascular disease. It is well established that there exists a graded and continuous relationship between blood pressure and cardiovascular disease risk. Therefore, determination of predictors of increasing blood pressure over time in nonhypertensive individuals may identify a subgroup that is at high risk for progression to hypertension and the development of cardiovascular disease. The present study investigates the factors that are associated with clinically significant increases in systolic and diastolic blood pressure over a 1-year period in a community sample of nonhypertensive individuals who are enrolled in the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) study.

METHODS AND MATERIALS
Source Population
The source population consists of 2000 participants enrolled in the Heart SCORE study. Heart SCORE is an ongoing single-center, prospective, community-based participatory
research cohort study. Baseline enrollment began on June 16, 2003 and was completed on October 11, 2006. Eligibility criteria include age 45 to 75 years, residence in the greater Pittsburgh metropolitan area, ability to undergo baseline and annual follow-up visits, and absence of known comorbidities expected to limit life expectancy to less than 5 years (eg, metastatic cancer, end-stage heart failure). Within this full cohort, the mean age at study entry was 59.1 years, 65% were female, 54% were white, 43% were black, 61% were married, and 81% had at least some college education beyond a high school diploma. The institutional review board at the University of Pittsburgh approved the study protocol, and all study subjects provided written informed consent. Data collection included demographics, medical history, lipids/lipoproteins, physical activity, and psychologic status as previously described. Body mass index (BMI) was calculated as kilograms/meters squared.

**Study Population**
Of the 2000 Heart SCORE participants, 1349 (67%) were enrolled in the study for at least 1 year and had 1-year follow-up data, including blood pressure measurement and current medication use. Of these 1349 participants, 509 (38%) were categorized as being nonhypertensive (ie, normal blood pressure or prehypertension) in accordance with criteria established by the Seventh Report of the Joint National Commission on High Blood Pressure. Specifically, these participants had a baseline systolic blood pressure of less than 140 mm Hg, diastolic blood pressure of less than 90 mm Hg, and no current use of antihypertensive medications, thereby constituting the study population. Prehypertension was defined as a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg. The mean age of the 509 study participants at entry was 57.8 years, 68% were female, 73% were white, 24% were black, 66% were married, and 86% had at least some college education.

**Blood Pressure Measurement**
Under the supervision of study investigators, experienced cardiovascular research coordinators measured blood pressure by using a manual sphygmomanometer and an appropriately sized cuff. Subjects rested for 5 minutes in a seated position before the initial blood pressure measurement, and 2 separate readings were obtained during the study visit. Routine calibration and, if necessary, replacement of blood pressure equipment were performed. This protocol is similar to those of larger epidemiologic studies.

**Primary Outcome**
The primary outcome was a clinically “significant” increase in blood pressure from baseline to 1-year follow-up, defined as any of the following changes: increase in systolic blood pressure of greater than 20 mm Hg, increase in diastolic blood pressure of greater than 10 mm Hg, or use of antihypertensive medication at the 1-year visit. For sensitivity analyses, 2 alternate definitions were constructed: the conservative definition—same as the primary outcome except diastolic blood pressure of greater than 15 mm Hg rather than greater than 10 mm Hg; the liberal definition—same as the primary outcome except systolic blood pressure of greater than 15 mm Hg rather than greater than 20 mm Hg.

**Statistical Analysis**
Factors at baseline and changes in participant factors from baseline to 1 year were compared among participants with and without a “significant” increase in blood pressure (as previously defined) by chi-square tests for categoric variables and Student t tests and Wilcoxon tests (based on distributional properties) for continuous variables. To assess factors independently associated with a significant increase in blood pressure, relative risks (RRs) and 95% confidence intervals (CIs) were estimated by log binomial regression. Separate models were fit for the primary and alternative outcome definitions, with the baseline variables systolic blood pressure, diastolic blood pressure, age, and gender forced into all models, and stepwise selection used to identify additional predictors. All analyses were performed using the Statistical Analysis System software, version 9.1.3 (SAS Inc, Cary, NC).

**RESULTS**
At baseline, 202 of the 509 study participants (39.7%) had normal blood pressure and the remaining 307 participants (60.3%) were prehypertensive. By using the primary outcome definition, 114 of the 509 participants (22.4%) experienced a clinically “significant” increase in blood pressure from the baseline to 1-year assessment. This included 18 participants (3.5%) with an increase in systolic blood pressure of greater than 20 mm Hg, 56 participants (11.0%) with an increase in diastolic blood pressure of greater than 10 mm Hg, 15 participants (2.9%) initiating antihypertensive medication, and 25 participants (4.9%) meeting multiple criteria. By using the conservative and liberal definitions (as defined in “Methods and Materials”), 75 (14.7%) and 125...
(24.6%) of all participants, respectively, experienced a significant increase in blood pressure.

Changes in blood pressure also were evaluated in subgroups of participants with normal blood pressure and prehypertension. Some 61 of 202 baseline normotensive participants (30%) experienced a significant increase in blood pressure at 1 year. Of these 61 participants, 8 (13%) remained within the normal blood pressure category, 40 (66%) progressed to the prehypertension category, and the remaining 13 (21%) progressed to the hypertension category. Some 53 of 307 baseline prehypertensive participants (17%) experienced a significant increase in blood pressure at 1 year. Of these 53 participants, 24 (45%) remained within the prehypertension category and the remaining 29 (55%) progressed to the hypertension category. Thus, the study definition of a significant increase in blood pressure usually led to participants being classified in a higher blood pressure category.

Distribution of Change in Blood Pressure

At 1-year follow-up, 10.8% of all participants had a systolic blood pressure of 140 mm Hg or higher, exceeding the baseline inclusion criterion of less than 140 mm Hg. However, the mean change in systolic blood pressure from baseline to 1 year in the entire study cohort increased only nominally from 120.8 ± 10.4 to 121.9 ± 13.8. Similarly, average diastolic blood pressure was essentially unchanged from baseline to 1 year (74.4 ± 7.5 to 74.5 ± 8.5). Only 3.9% of all participants at 1 year had a diastolic blood pressure of 90 mm Hg or higher, exceeding the baseline inclusion criterion of less than 90 mm Hg. However, these observed differences in the distribution of blood pressure between baseline and 1-year measurements do not account for the 2.9% of participants who began taking antihypertensive medications between baseline and 1-year visits.

Baseline Characteristics Associated with Significant Increase in Blood Pressure

Age, gender, and race were not associated with a significant increase in blood pressure (Table 1). In contrast, compared with participants without an increase, those with a significant increase in blood pressure had higher baseline mean BMI, cynicism scores, and level of education.

Baseline to 1-Year Change Measures Associated with Significant Increase in Blood Pressure

Compared with participants without an increase in blood pressure, those with a significant increase in blood pressure

| Table 1 | Baseline Characteristics by Significant Increase in Blood Pressure |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Baseline Characteristic | No Increase (N = 395) | Increase (N = 114) | P Value |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age (y), mean, SD | 57.7, 7.3 | 57.9, 7.7 | .79 |
| Race, % | | | | | | | | | | | |
| White | 74.4 | 66.7 | .39 |
| Black | 21.8 | 32.5 | |
| Other | 3.8 | 0.9 | |
| Female, % | 67.8 | 70.2 | .73 |
| Education; Bachelors degree or higher, % | 60.0 | 48.3 | .03 |
| Current smoker, % | 10.4 | 5.3 | .10 |
| BMI, mean, SD | 27.3, 4.8 | 28.6, 5.2 | .01 |
| Systolic blood pressure, mean, SD | 121.6, 10.4 | 118.1, 9.9 | .002 |
| Diastolic blood pressure, mean, SD | 75.2, 7.2 | 71.4, 7.7 | <.001 |
| Resting pulse (per minute), mean, SD | 62.0, 9.1 | 63.3, 10.5 | .24 |
| Total cholesterol (mg/dL), mean, SD | 219.2, 40.9 | 221.9, 48.7 | .51 |
| LDL cholesterol (mg/dL), mean, SD | 146.2, 35.1 | 148.0, 37.9 | .54 |
| HDL cholesterol (mg/dL), mean, SD | 59.9, 15.9 | 60.7, 16.4 | .74 |
| Triglycerides (mg/dL), mean, SD | 116.9, 70.9 | 114.0, 67.2 | .48 |
| Glucose (mg/dL), mean, SD | 92.7, 19.6 | 96.1, 41.5 | .98 |
| Metabolic status (ATP-3), % | | | | | | | | | | | |
| Normal | 83.0 | 86.0 | .39 |
| Metabolic syndrome | 11.9 | 7.5 | |
| Diabetes | 5.1 | 6.5 | |
| Psychosocial measures | | | | | | | | | | | |
| Depression (CESD score ≥ 16), % | 12.5 | 9.9 | .74 |
| CMHI Cynicism scale score, mean, SD | 3.1, 2.7 | 3.8, 2.8 | .01 |
| CMHI Hostility scale score, mean, SD | 1.3, 1.2 | 1.3, 1.3 | .97 |
| CMHI Aggressive scale score, mean, SD | 2.9, 1.5 | 2.8, 1.6 | .53 |
| STAI Anxiety scale score, mean, SD | 6.6, 4.7 | 6.2, 4.4 | .44 |
| STAI Anger scale score, mean, SD | 5.6, 3.6 | 4.9, 3.5 | .05 |
| Cohen Stress score, mean, SD | 4.4, 3.0 | 4.3, 3.0 | .86 |

SD = standard deviation; BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ATP-3 = Adult Treatment Panel 3; CESD = Center for Epidemiologic Studies Depression Scale; CMHI = Cook-Medley Hostility Inventory; STAI = State-Trait Anxiety Inventory.
over 1 year were more likely to have exhibited an increase in body weight of more than 5% (22% vs 10%) and an increase in waist circumference of greater than 5% (33% vs 17%) over 1 year as shown in Table 2. There also was a nonsignificant trend for an increase in total cholesterol of more than 10% (26% vs 17%) to be associated with a significant increase in blood pressure, whereas changes in physical activity and depressive symptoms were not associated with significant increases in blood pressure.

**Independent Predictors of Significant Increase in Blood Pressure**

In multivariable analysis, several baseline factors and changes in factors over 1 year were independently associated with a significant increase in blood pressure (Table 3). At baseline, a higher BMI was associated with a significant increase in blood pressure (adjusted RR = 1.34 per increase of 5 kg/m²; 95% CI, 1.14-1.57). At 1 year, it was observed that an increase in body weight of more than 5% (adjusted RR = 1.61; 95% CI, 1.18-2.19) and an increase in waist circumference (adjusted RR = 1.19 per 5 cm; 95% CI, 1.08-1.30) were each independent predictors of a significant increase in blood pressure.

For the alternate conservative definition, older age (adjusted RR = 1.24 per 5 years; 95% CI, 1.05-1.47), higher baseline BMI (adjusted RR = 1.32 per increase of 5 kg/m²; 95% CI, 1.09-1.62), increase in body weight of more than 5% (adjusted RR = 1.95; 95% CI, 1.19-3.19), and increase

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline to 1-Year Change Measure by Significant Increase in Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline to 1-Year Change</strong></td>
<td><strong>No Increase (N = 395)</strong></td>
</tr>
<tr>
<td>Change in weight (kg), mean, SD</td>
<td>0.2, 6.3</td>
</tr>
<tr>
<td>Change in weight ≥ 5%* (%)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>9.8</td>
</tr>
<tr>
<td>Same</td>
<td>79.8</td>
</tr>
<tr>
<td>Increase</td>
<td>10.4</td>
</tr>
<tr>
<td>Change in waist circumference (cm), mean, SD</td>
<td>−0.4, 5.9</td>
</tr>
<tr>
<td>Change in waist circumference ≥ 5%* (%)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>21.4</td>
</tr>
<tr>
<td>Same</td>
<td>61.2</td>
</tr>
<tr>
<td>Increase</td>
<td>17.3</td>
</tr>
<tr>
<td>Change in total cholesterol ≥ 10%* (%)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>26.8</td>
</tr>
<tr>
<td>Same</td>
<td>56.2</td>
</tr>
<tr>
<td>Increase</td>
<td>17.0</td>
</tr>
<tr>
<td>Change in LDL cholesterol ≥ 10%* (%)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>31.5</td>
</tr>
<tr>
<td>Same</td>
<td>46.0</td>
</tr>
<tr>
<td>Increase</td>
<td>22.5</td>
</tr>
<tr>
<td>Change in HDL cholesterol ≥ 10%* (%)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>19.6</td>
</tr>
<tr>
<td>Same</td>
<td>62.0</td>
</tr>
<tr>
<td>Increase</td>
<td>18.5</td>
</tr>
<tr>
<td>Change in triglycerides ≥ 20%* (%)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>30.1</td>
</tr>
<tr>
<td>Same</td>
<td>44.2</td>
</tr>
<tr>
<td>Increase</td>
<td>25.7</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td></td>
</tr>
<tr>
<td>Baseline = no; Year 1 = no</td>
<td>89.9</td>
</tr>
<tr>
<td>Baseline = yes; Year 1 = no</td>
<td>2.1</td>
</tr>
<tr>
<td>Baseline = no; Year 1 = yes</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline = yes; Year 1 = yes</td>
<td>7.8</td>
</tr>
<tr>
<td>Regularly engage in strenuous activity, %</td>
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<tr>
<td>Baseline = no; Year 1 = no</td>
<td>53.6</td>
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<tr>
<td>Baseline = yes; Year 1 = no</td>
<td>8.5</td>
</tr>
<tr>
<td>Baseline = no; Year 1 = yes</td>
<td>15.0</td>
</tr>
<tr>
<td>Baseline = yes; Year 1 = yes</td>
<td>22.8</td>
</tr>
<tr>
<td>Depression (CESD score ≥ 16), %</td>
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</tr>
<tr>
<td>Baseline = no; Year 1 = no</td>
<td>82.4</td>
</tr>
<tr>
<td>Baseline = yes; Year 1 = no</td>
<td>7.0</td>
</tr>
<tr>
<td>Baseline = no; Year 1 = yes</td>
<td>5.2</td>
</tr>
<tr>
<td>Baseline = yes; Year 1 = yes</td>
<td>5.4</td>
</tr>
</tbody>
</table>

SD = standard deviation; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CESD = Center for Epidemiologic Studies Depression Scale. Missing cases exist for some variables.

*Mantel-Haenszel chi-square test of trend.
in waist circumference (adjusted RR = 1.18 per 5 cm; 95% CI, 1.04-1.34) were independently associated with a significant increase in blood pressure. For the liberal definition, a higher baseline BMI (adjusted RR = 1.26 per increase of 5 kg/m²; 95% CI, 1.08-1.47) and an increase in waist circumference (adjusted RR = 1.18 per 5 cm; 95% CI, 1.06-1.30) were independently associated with a significant increase in blood pressure. Thus, in aggregate, the most consistent independent predictors of a significant increase in blood pressure included higher baseline BMI, an increase in body weight of more than 5%, and an increase in waist circumference of 5 cm.

**Examination of 1-Year Change in Weight and Waist Circumference**

On the basis of the results of multivariable analysis, the relationship between a significant increase in blood pressure and 1-year change in weight and/or waist circumference was further examined. As seen in Figure 1, increases of more than 5% in weight and/or waist circumference over 1 year were associated with a significant increase in blood pressure ($P < .001$), with no appreciable difference in the effects of these 2 anthropometric measures on increases in blood pressure. This observation is demonstrated by analyses indicating that 36% of participants who experienced a greater than 5% increase in weight and/or waist circumference had a significant increase in blood pressure compared with 17% among participants without a greater than 5% increase in weight and/or waist circumference (Figure 1, right).

After statistical adjustment, a more than 5% increase in weight and/or waist circumference was associated with a 2-fold risk of a significant increase in blood pressure (adjusted RR = 2.09; 95% CI, 1.35-3.21) (Table 4). This approximate 2-fold risk was consistently evident in subgroup analyses by age, race, BMI at study entry, and regular exercise. There was an indication that a more than 5% increase in weight and/or waist circumference exerted a greater effect on the risk of a significant increase in blood pressure in females (adjusted RR = 2.44) compared with males (adjusted RR = 1.47); however, a formal test of interaction (differential effect) did not achieve statistical significance ($P = .08$).

**DISCUSSION**

Our results indicate that in a diverse community cohort of nonhypertensive individuals, baseline BMI and changes in

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**Table 3** Independent Predictors of Significant Increase in Blood Pressure

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Primary Definition (n = 458)</th>
<th>Conservative Definition (n = 435)</th>
<th>Liberal Definition (n = 435)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted RR</td>
<td>95% CI</td>
<td>Adjusted RR</td>
</tr>
<tr>
<td><strong>Baseline variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (per 5 mm Hg)</td>
<td>0.97</td>
<td>0.88-1.07</td>
<td>0.90</td>
</tr>
<tr>
<td>Diastolic blood pressure (per 5 mm Hg)</td>
<td>0.76†</td>
<td>0.66-0.88</td>
<td>0.89</td>
</tr>
<tr>
<td>Age (per 5 y)</td>
<td>1.08</td>
<td>0.95-1.22</td>
<td>1.24*</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.81</td>
<td>0.57-1.16</td>
<td>0.89</td>
</tr>
<tr>
<td>BMI (per 5 kg/m²)</td>
<td>1.34†</td>
<td>1.14-1.57</td>
<td>1.32†</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>0.61</td>
<td>0.35-1.05</td>
<td>—</td>
</tr>
<tr>
<td>STAI Anger scale score (per 1 unit)</td>
<td>0.95*</td>
<td>0.90-1.00</td>
<td>—</td>
</tr>
<tr>
<td><strong>Baseline to 1-y change variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increase ≥ 5%</td>
<td>1.61†</td>
<td>1.18-2.19</td>
<td>1.95†</td>
</tr>
<tr>
<td>Change waist circumference (per 5 cm)</td>
<td>1.19†</td>
<td>1.08-1.30</td>
<td>1.18†</td>
</tr>
</tbody>
</table>

RR = relative risk; CI = confidence interval; BMI = body mass index; STAI = State-Trait Anxiety Inventory.

Adjusted RR also adjusted for alcohol use.

* $P < .05$.
† $P < .01$.
‡ $P < .001$.
weight and/or waist circumference over a 1-year period are independent predictors of a significant increase in blood pressure. These findings extend previous associations between weight and blood pressure\(^5\),\(^6\) because they indicate that regardless of baseline BMI, increases in weight and/or waist circumference are independent predictors of increases in blood pressure over 1 year.

### Hypertension, Prehypertension, and Cardiovascular Disease Risk

Several longitudinal studies have demonstrated that people with high normal blood pressure are susceptible to developing hypertension, a primary risk factor in cardiovascular disease.\(^4\),\(^7\),\(^8\) On the basis of these observations, blood pressure classification was revised in 2003 creating a prehypertension category, defined as a systolic blood pressure between 120 and 139 mm Hg or a diastolic blood pressure between 80 and 89 mm Hg.\(^1\) This category includes people who were previously considered as having normal blood pressure under Joint National Committee VI criteria.\(^9\)

Individuals with prehypertension tend to be older and have higher prevalences of anthropometric indices of obesity, such as higher BMI, increased waist circumference, and increased waist-hip ratio, compared with those with normal blood pressure.\(^10\),\(^11\) Individuals with prehypertension also have a higher prevalence of diabetes, impaired fasting glucose, and less favorable lipid profiles, suggesting that insulin resistance is a common feature in this group.\(^12\),\(^13\)Individuals with prehypertension have elevations in inflammatory markers such as C-reactive protein, serum amyloid-A, tumor necrosis factor-alpha, and fibrinogen compared with normotensive subjects.\(^14\),\(^15\) Individuals with prehypertension have evidence of subclinical atherosclerosis,\(^16\)-\(^18\) increased left ventricular mass,\(^16\),\(^19\) and left ventricular diastolic dysfunction.\(^19\),\(^20\) These observations support the concept that prehypertension is a pathologic state in the blood pressure continuum and suggest that studies should consider blood pressure as a continuous variable rather than a measured categorical value.

### Predictors of Clinically Significant Increases in Blood Pressure

Our study indicates that baseline BMI and 1-year changes in weight and/or waist circumference are independent predictors of clinically significant increases in systolic or diastolic blood pressure among individuals with normal blood pressure or prehypertension. Our definition of an increase in blood pressure over 1 year is clinically relevant because patients who exhibit this degree of blood pressure change will move from normal to prehypertension or from prehypertension to hypertension categories unless their initial blood pressure is less than 100/70 mm Hg. Previous studies have indicated epidemiologic long-term associations between obesity and hypertension.\(^5\),\(^6\) Our results confirm these findings and demonstrate that high BMI is a short-term predictor of a significant increase in blood pressure. Our results indicate that increases in weight and/or waist circumference are risk factors for blood pressure increases in individuals across the continuum of normal weight to obesity.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Weight/Waist Δ &lt;5%</th>
<th>Weight/Waist Δ ≥5%</th>
<th>RR</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>466</td>
<td>16.8%</td>
<td>36.0%</td>
<td>2.14</td>
<td>2.09</td>
<td>1.35-3.21</td>
<td>.001</td>
</tr>
<tr>
<td>Age at study entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-55 y</td>
<td>188</td>
<td>19.3%</td>
<td>34.0%</td>
<td>1.76</td>
<td>1.71</td>
<td>0.76-3.83</td>
<td>.19</td>
</tr>
<tr>
<td>56-65 y</td>
<td>202</td>
<td>14.5%</td>
<td>34.4%</td>
<td>2.37</td>
<td>1.96</td>
<td>1.21-3.16</td>
<td>.006</td>
</tr>
<tr>
<td>66-75 y</td>
<td>76</td>
<td>16.7%</td>
<td>45.5%</td>
<td>2.73</td>
<td>2.62</td>
<td>0.42-16.17</td>
<td>.30</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>142</td>
<td>20.5%</td>
<td>26.7%</td>
<td>1.30</td>
<td>1.47</td>
<td>0.75-2.92</td>
<td>.26</td>
</tr>
<tr>
<td>Female</td>
<td>324</td>
<td>14.9%</td>
<td>38.5%</td>
<td>2.59</td>
<td>2.44</td>
<td>1.39-4.27</td>
<td>.002</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>340</td>
<td>15.4%</td>
<td>31.1%</td>
<td>2.02</td>
<td>1.90</td>
<td>1.02-3.54</td>
<td>.04</td>
</tr>
<tr>
<td>Black</td>
<td>113</td>
<td>21.7%</td>
<td>56.7%</td>
<td>2.61</td>
<td>2.31</td>
<td>1.39-3.82</td>
<td>.001</td>
</tr>
<tr>
<td>BMI at study entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>356</td>
<td>14.3%</td>
<td>32.4%</td>
<td>2.26</td>
<td>2.25</td>
<td>1.27-4.00</td>
<td>.006</td>
</tr>
<tr>
<td>≥30</td>
<td>110</td>
<td>25.0%</td>
<td>47.1%</td>
<td>1.88</td>
<td>1.61</td>
<td>0.96-2.71</td>
<td>.07</td>
</tr>
<tr>
<td>Exercise/labor ≥3 times/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>150</td>
<td>19.6%</td>
<td>35.4%</td>
<td>1.81</td>
<td>2.10</td>
<td>1.22-3.63</td>
<td>.007</td>
</tr>
<tr>
<td>Yes</td>
<td>311</td>
<td>15.3%</td>
<td>37.1%</td>
<td>2.42</td>
<td>2.25</td>
<td>1.19-4.23</td>
<td>.01</td>
</tr>
</tbody>
</table>

BP = blood pressure; RR = relative risk; CI = confidence interval; BMI = body mass index.

*Adjusted for baseline systolic and diastolic blood pressure, age, gender, alcohol, body mass index, and Anger scale.
Our study did find that lower baseline systolic and diastolic blood pressures were associated with a higher incidence of a significant increase in blood pressure. An individual’s true blood pressure may reflect the mean of a series of longitudinal blood pressure measurements. Therefore, an individual with a lower baseline blood pressure measurement on a single occasion may regress to the mean with a higher blood pressure measurement later.

Clinical Implications of Weight Gain and Increases in Blood Pressure

The Joint National Committee VII guidelines identify a group of individuals susceptible to developing hypertension who would benefit from lifestyle modification. The PREMIER trial demonstrated that a behavioral intervention program directed at patients with prehypertension or stage 1 hypertension can improve control of blood pressure and achieve weight loss. The successful interventions in the PREMIER trial included intensive counseling on weight loss, increase in moderate-intense physical activity of at least 180 minutes per week, reduction in dietary sodium, limitations in alcohol consumption, and adherence to the Dietary Approaches to Stop Hypertension diet. Our study serves to provide a mechanism to risk stratify individuals who may benefit from these types of interventions by simple measurement of baseline BMI and recent changes in weight or waist circumference. Moreover, our results also indicate that similar studies should be conducted to assess the effectiveness of behavioral modification strategies in nonhypertensive and nonobese individuals with recent changes in weight or waist circumference to prevent increases in blood pressure.

Limitations

Our study’s sample size is smaller than that of previous studies on prehypertension and hypertension. Therefore, we may not have had sufficient power to detect other risk factors for smaller and less clinically relevant changes in blood pressure. Second, referral and volunteer biases may have enrolled a study cohort inherently interested in cardiovascular health, a possibility indicated by the low prevalence of smokers in our population. However, it should be noted that a high proportion of our “healthy volunteers” developed a clinically significant increase in blood pressure after only 1 year. Third, we did not use ambulatory blood pressure monitoring, which may be a more useful measure of blood pressure. However, most clinicians do not use this tool. Thus, our method of measuring blood pressure more closely resembles common clinical practice. Fourth, biological variability (e.g., circadian variation) and potential error measurement in baseline to 1-year assessments of blood pressure may have occurred, with the most likely net consequence of underestimation of the true magnitude of associations. Finally, we can only comment on those variables that predict blood pressure increase over 1 year. Longer follow-up of the Heart SCORE cohort may reveal other variables associated with significant long-term blood pressure increases.

CONCLUSION

Our results demonstrate that baseline BMI and 1-year changes in weight and waist circumference are independent predictors of a clinically significant increase in blood pressure over 1 year among individuals without hypertension. Moreover, these variables remain predictive across race, gender, and all classes of BMI. These findings serve to stratify individuals who may benefit from close clinical observation and preventive intervention as published in previously conducted trials.

References


In July 2003, the Accreditation Council for Graduate Medical Education (ACGME) instituted residency duty-hours requirements in response to growing concerns regarding clinician fatigue and the incidence of medical errors.1 Similar changes, enacted in part due to the Libby Zion case in 1984, had already been in place in New York State for many years.2 The ACGME requirements limited maximum continuous hours worked to 24, with 6 additional hours for transfer of care and educational activities. The total number of hours per week was limited to 80. The changes also required one 24-hour free period per week and a minimum of 10 hours between periods of work. For many residency programs, these new rules represented 20% or greater reductions in hours worked per week and resulted in a need to significantly restructure the traditional on-call shift structure. These schedule
changes often resulted in a decrease in continuity of care and increased patient hand-offs. Despite implementation of the ACGME-mandated duty-hours regulations nationwide for over 3 years, the impact on quality of care and patient safety is not known.

Some health care experts believe that reducing fatigue and sleepiness by limiting physician work hours would result in an improvement in patient safety. The literature also suggests that well-rested residents may be able to provide a higher quality of care. For instance, studies by Lockley et al and Landrigan et al showed that interns working in the medical intensive care units on the traditional schedule (goal of 80 hours per week with extended work shifts of 24 hours or more every other shift) had more than twice the rate of attention failures and made more serious medical errors compared with interns working on the intervention schedule (goal of 60 hours per week and elimination of extended work shifts). There is also some evidence to suggest that reduction in work hours may improve residents’ quality of life.

Despite these findings, there is concern in the medical community that the new residency work hours have led to increased patient hand-offs and have jeopardized the quality of patient care. There is fear that the increased discontinuity can lead to potential mistakes and delay in patient care. For instance, Laine et al found, in a retrospective cohort study, that after implementation of New York State duty-hours restrictions on quality of care and outcomes of acute coronary syndrome patients on an inpatient cardiology service at a major academic medical center.

**CLINICAL SIGNIFICANCE**

- Implementation of the residency duty-hours restrictions was associated with improved adherence to quality indicators and shorter length of stay.
- Improved quality and efficiency did not adversely impact patient outcomes, including mortality.
- Through systemic implementation of the duty-hours regulations, it is possible to preserve quality without jeopardizing patient safety.
- Risk-adjusted and unadjusted 6-month mortality decreased significantly after implementation of duty-hours changes.

Despite these findings, there is concern in the medical community that the new residency work hours have led to increased patient hand-offs and have jeopardized the quality of patient care. There is fear that the increased discontinuity can lead to potential mistakes and delay in patient care. For instance, Laine et al found, in a retrospective cohort study, that after implementation of New York State duty-hours restrictions on quality of care and outcomes of acute coronary syndrome patients on an inpatient cardiology service at a major academic medical center.

**METHODS**

**Setting and Patients**

We performed a retrospective analysis of 1003 consecutive patients admitted to the University of Michigan Health System between July 2002 and June 2004 with acute coronary syndrome. The University Hospital is an 805-bed tertiary care academic teaching center that supports a large internal medicine residency program. Patients were admitted to our inpatient cardiology service, a 46-bed service including 10 beds in the coronary intensive care unit. Patients were either admitted from the Emergency Department or physicians’ offices, or were transferred from other hospitals. All were diagnosed with acute coronary syndrome based on symptoms consistent with acute cardiac ischemia within 24 hours of hospital presentation and at least 1 of 4 additional criteria: history of coronary artery disease; new documentation of coronary artery disease; electrocardiogram changes; and increase in cardiac biomarkers consistent with myocardial injury (Troponin I, CK-MB, or both).

During the study, there were 4 inpatient cardiology teams admitting patients. Each team consisted of 1 attending cardiologist, 1 senior resident, and 2 interns. A cardiology fellow supervised care in the coronary intensive care units on the traditional schedule on-call shifts for both interns and residents. In July 2003, residency duty hours were implemented. Interns’ on-call shifts were changed to 7 AM to no later than 1 PM the next day (Figure 1). A day float system, consisting of a senior medical resident who worked days-only during the week, was implemented to facilitate compliance with the duty hours. A pre-existing night float system was continued, but senior residents’ on-call shifts were limited to 7 AM-9 PM the same day, whereas in the prior year, senior residents would have taken call with 1 of their 2 interns overnight (Figure 1). All residents were required to take 1 day off in 7 and work no more than 80 hours per week. As a consequence of the changes in shift length, there was also increased discontinuity of patient care on the on-call shifts for both interns and residents.

Patients were stratified by hospital admission during academic year 2002-2003 (before the duty-hours changes) and academic year 2003-2004 (after the duty-hours changes). In July 2002, the institution had initiated a quality improvement initiative designed to improve the quality of acute coronary syndrome care (Guidelines Applied in Practice [GAP] Program). The GAP program utilized standardized order entry and discharge patient instructions for patients with acute coronary syndrome, as well as other efforts to improve quality of care for all acute coronary syndrome patients.

**Data Collection**

Trained abstractors (Physicians and Cardiac RNs) collected data from patient records upon admission and soon after discharge or death. Telephone follow-up was used to ascertain 6-month endpoints. Demographic variables included age and sex. Risk factor data included hyperlipidemia, diabetes, hypertension, and smoking history. Variables of interest in the past medical history included prior myocardial infarction, heart failure, coronary artery bypass graft sur-
surgery, angina, coronary angiogram diagnostic of coronary artery disease, atrial fibrillation, chronic renal failure, stroke or transient ischemic attack, and peripheral vascular occlusive disease.

Patient management data included the use of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and HMG-CoA reductase inhibitors (statins) at time of discharge. Procedural and test data of interest included cardiac stress test, cardiac catheterization, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery. Length of stay was adjusted for in-hospital mortality by removing patients that died during hospitalization. In-hospital adverse events of interest included congestive heart failure, pulmonary edema, cardiogenic shock, cardiac arrest, and death. Later endpoints included 6-month mortality and major adverse cardiovascular events (MACE; e.g., mortality, myocardial infarction, cerebrovascular accident).

**Statistical Analysis**
Continuous data are presented as mean ± SD or median (interquartile [25th to 75th] range). The 2 groups were compared using the chi-squared test, a 2-tailed Student’s t test, or the Wilcoxon-Mann-Whitney rank sum test, as appropriate. Risk adjustment analysis of in-hospital mortality, 6-month mortality, and 6-month MACE was performed using logistic regression models. The variables used in building the model for in-hospital mortality included:

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Characteristics by Time of Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Pre-Duty Hours n = 572* No. (%)</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>64.5 (14.2)</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>351 (61.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>377 (65.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>427 (75.0)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>355 (62.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>190 (33.3)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>78 (13.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>320 (56.1)</td>
</tr>
<tr>
<td>Angina</td>
<td>156 (27.5)</td>
</tr>
<tr>
<td>Positive stress test</td>
<td>32 (5.6)</td>
</tr>
<tr>
<td>Coronary angiogram diagnostic for coronary artery disease</td>
<td>264 (46.4)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>235 (41.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>91 (16.0)</td>
</tr>
<tr>
<td>Percutaneous intervention</td>
<td>156 (27.4)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>122 (21.4)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>56 (9.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>83 (14.2)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>61 (10.8)</td>
</tr>
</tbody>
</table>

*Actual number of patients varied as a result of missing data.
grouping variable, age, sex, cardiac arrest at presentation, Killip class, systolic blood pressure, pulse, initial serum creatinine, and increase in cardiac markers. The variables used in building the model for 6-month mortality and 6-month MACE included: the grouping variable, age, sex, systolic blood pressure, pulse, initial creatinine, history of congestive heart failure, diabetes, and prescription for statin at discharge. A forward selection technique was used to improve the model. C-statistics were used to test the model discrimination, and the Hosmer-Lemeshow Goodness-of-Fit statistic was used to test goodness of fit. Odds ratios were calculated for in-hospital mortality, 6-month mortality, and 6-month MACE comparing the post-duty-hours group to the pre-duty-hours group.

RESULTS

There were 572 patients in the pre-duty-hours group and 431 patients in the post-duty-hours group. The 2 groups were similar with respect to baseline characteristics, except for a greater number of patients with hypertension in the pre-duty-hours group (Table 1).

Quality Indicators

During the academic year after the duty-hours changes, there was improved adherence to evidence-based guidelines for acute coronary syndrome care at time of discharge (Figure 2). There was a statistically significant increase in the usage of beta-blockers (85.8% vs 93.8%, \( P < .001 \)), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (65.7% vs 71.8%, \( P = .046 \)), and statins (76.2% vs 84.0%, \( P = .002 \)) at the time of discharge. The rate of adherence to evidence-based medicines at 6 months following discharge was also higher in the post-duty-hours group (Figure 2). There was increased adherence to the usage of aspirin (90.9% vs 95.3%, \( P = .02 \)), beta-blockers (80.8% vs 89.0%, \( P = .002 \)), and statins (73.8% vs 80.8%, \( P = .02 \)).

Length-of-Stay

As shown in Table 2, there was a 20% reduction in the mean length of stay (5.5 days vs 4.4 days) and a 10% reduction in the median length of stay (3.1 days vs 2.8 days, \( P = .002 \)) of patients admitted post-duty-hours changes compared with patients admitted pre-duty-hours changes.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Length of Stay: Pre-Duty Hours vs Post-Duty Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Stay (Days)*</td>
<td>Pre-Duty Hours</td>
</tr>
<tr>
<td></td>
<td>n = 545</td>
</tr>
<tr>
<td>Mean, SD (range)</td>
<td>5.5 ± 7.5 (1.0-126.0)</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>3.1 (1.9-6.7)</td>
</tr>
</tbody>
</table>

*Adjusted for in-hospital mortality.
†Using the Wilcoxon rank sum test.
Clinical Outcomes

There were no statistically significant differences in in-hospital adverse events and unadjusted 6-month major adverse cardiovascular events (MACE) between the 2 groups: congestive heart failure/pulmonary edema (3.5% vs 4.0%, \( P = .69 \)), cardiogenic shock (4.2% vs 4.4%, \( P = .85 \)), cardiac arrest (5.1% vs 4.0%, \( P = .41 \)), mortality (4.2% vs 2.8%, \( P = .23 \)), 6-month MACE (10.9% vs 8.6%, \( P = .22 \)) (Figure 3). Risk adjustment analysis showed no statistically significant differences in in-hospital mortality (odds ratio [OR] 0.47, 95% confidence interval [CI], 0.18-1.20, \( P = .11 \)) and 6-month MACE (OR 1.29, 95% CI, 0.76-2.20, \( P = .35 \)) between the 2 groups (Figure 4). Post-duty-hours changes, there was a decrease in unadjusted 6-month mortality (8.0% vs 3.8%, \( P = .007 \)) (Figure 3) and risk-adjusted 6-month mortality (OR 0.53, 95% CI, 0.28-0.99, \( P = .05 \)) (Figure 4).

DISCUSSION

We have shown that implementation of the ACGME-mandated residency duty-hours restrictions on an academic in-
patient cardiology service was associated with improved quality of care and efficiency in patients admitted with acute coronary syndrome. During academic year 2003-2004, the year after the duty-hours changes, there was an improved adherence to evidence-based guidelines for acute coronary syndrome care. The quality improvement program we have implemented previously may be the reason for this, but another potential explanation of this finding may be a decrease in residents’ work hours.

A careful review of patients’ medical records is essential to ascertain that acute coronary syndrome patients are discharged on the appropriate medications. Also, patient education is an integral part of the hospital discharge process that ultimately determines adherence to evidence-based therapy. At our hospital, patient discharge instructions, including discharge medications, are completed by either the intern or senior resident on the team. Patient education is provided by multiple members of the medical team, including the intern or senior resident and the nursing staff. The day float resident would rarely be involved in the discharge process. There was no substantial change in who was responsible for these elements of the discharge process after duty-hours reform. These tasks require attention to detail and time to facilitate patient education. Prior studies have suggested that task performance tends to worsen with sleep loss and fatigue. For example, Friedman et al showed that post-call interns performed worse on electrocardiogram reading tasks compared with rested interns. In addition, Taffinder et al showed that post-call residents performed worse on laparoscopic surgery simulators compared with the residents who had a normal night of sleep. It is plausible that one explanation of our findings is that because residents were better rested after the duty-hours changes, they were more thorough in ensuring that patients were discharged on appropriate medications.

We also found that length of stay was decreased during the year after the implementation of duty hours. Such a change can be attributed to several factors. Caregiver sleep deprivation and fatigue can worsen efficiency. With restriction of the residency work hours, residents are able to sleep more and are less fatigued. This, in turn, can hasten the speed at which residents are able to complete day-to-day tasks.

Furthermore, our institution had implemented a day float system to facilitate compliance with the work hours. The role of a day float resident was to assist the team with writing orders, scheduling laboratory tests/studies, obtaining outside hospital records, and performing required procedures. In contrast, before the day float system, residents who had been on duty for >24 hours were required to perform the duties of the day float during the post-call day. The day float resident represented an incremental resident on the team from 7 AM to 1 PM on post-call days (Figure 1). After 1 PM, the team consisted of 2 residents, which is 1 fewer than before duty-hours changes. Thus, the net complement of residents over the typical post-call day was unchanged after duty-hours reform. These changes facilitated residents’ compliance with duty-hours and thus, likely resulted in less sleep deprivation and fatigue.

In our study, improved efficiency did not appear to adversely impact patient outcomes, including mortality. In fact, there was a trend toward improvement in risk-adjusted in-hospital mortality and a statistically significant decrease in risk-adjusted 6-month mortality. Patient safety has been a great concern in the medical community since the implementation of the duty-hours restrictions. Some believe that reduced work hours have led to increased discontinuity of care and may have jeopardized patient care. In a case-control analysis, Petersen et al showed that patients on medical services covered by a cross-cover intern had a higher rate of potentially preventable adverse events when compared with controls covered by a physician from the primary team.

Our results demonstrate that implementation of the duty-hours restrictions did not adversely impact patient outcomes. One explanation for our findings is that at the University of Michigan, the on-call patient coverage system after duty hours was set up such that there is overlap of continuity at all times. On call days, interns stay overnight and the senior resident leaves by 9 PM (Figure 1). This ensures that at least 1 member of the team is caring for the patients at all times. As suggested by Fletcher et al, the continuity between admission and the remainder of care may be more important than continuity from hour to hour. In a study similar to ours, Gottlieb and colleagues studied the effects of schedule changes, including the implementation of a night float system, in an internal medicine program at a Veterans Affairs Hospital. Their findings showed that decreasing residents’ work hours and preserving continuity of care led to improved efficiency and decreased rates of errors. In the new system, our interns and residents worked shorter shifts on call. Our interns’ average shift was reduced by 15%, whereas senior residents did not take overnight call, so their maximum shifts went from >36 hours to only 14 hours (Figure 1). In addition, the presence of a night float resident, while introducing some discontinuity, also provided a new perspective on diagnoses that might have been missed otherwise. The addition of a day float resident could also potentially influence our results. While this was a new role that increased the number of residents on the team in the morning, the impact was likely counterbalanced by fewer residents available in the afternoon. In addition, the day float was not significantly involved in the discharge process or in clinical decision-making on the team.

There are several limitations of our study. First, in July of 2002, our institution had initiated a quality improvement program designed to improve the quality of acute coronary syndrome care (GAP Program). Even though this program was implemented at the beginning of our study period, it could have had an impact on some of our results. Second, some of the improvement in efficiency may have been related to an increase in the number of cardiac catheterizations and percutaneous interventions at our institution. Such
an increase meant that more patients received definitive early treatment for acute coronary syndrome and less need for predischarge stress testing. This could have led to early disposition. Third, with ongoing advancement in medical research and technology, clinical medicine is continuously going through dynamic changes. It is difficult to control for temporal trends in cardiac care over a 2-year study period.

In summary, our findings suggest that with the implementation of the residency duty-hours regulations in our internal medicine residency program, it was possible to maintain, if not improve, quality and efficiency without impacting patient outcomes. It is not clear from our study which changes in work schedules provided the most benefit, nor were we able to separate the impact of duty-hours changes from other quality improvement initiatives in progress during this time. We did show, however, that the implementation of the duty-hours changes was not associated with a negative impact on the quality or efficiency of acute coronary syndrome care in our institution. Future research is needed to further define exactly what structural and care process factors contributed to these improved results. Furthermore, we recommend collaborative investigations across institutions to validate the findings of our study in larger settings.

References

Orthostatic Hypotension-Related Hospitalizations in the United States

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aDepartment of Medicine, Division of Clinical Pharmacology, Vanderbilt University, Nashville, Tenn; bDepartment of Preventive Medicine and cDepartment of Medicine, Vanderbilt University, Nashville, Tenn; dClinical Research Center of Excellence and Geriatric Research and Education Center, Tennessee Valley VA, Nashville, Tenn.

ABSTRACT

BACKGROUND: Orthostatic hypotension has been commonly described in elderly persons and is associated with an increased risk of falls, syncope, and cerebrovascular events. Nevertheless, the precise burden of this condition in the US is currently unknown.

METHODS: We analyzed discharge data from the Nationwide Inpatient Sample to identify orthostatic hypotension-related hospitalizations and associated comorbidities after excluding acute causes of this condition. National hospitalization rates were estimated using US census population estimates, and the medical conditions most frequently associated with orthostatic hypotension were assessed.

RESULTS: In 2004, there were an estimated 80,095 orthostatic hypotension-related hospitalizations, yielding an overall rate of 36 (95% confidence interval, 34 to 38) hospitalizations per 100,000 US adults. Orthostatic hypotension was the primary diagnosis in 35% of these hospitalizations. The number of orthostatic hypotension-related hospitalizations increased steadily with age, and patients aged 75 years or older had the highest annual hospitalization rate, 233 per 100,000 (95% confidence interval, 217 to 249). The median length of hospital stay was 3 days (IQR 2-6) and the overall in-hospital mortality was 0.9%. Caucasian males were most likely to be hospitalized with orthostatic hypotension. Syncope was the most common comorbid condition reported among orthostatic hypotension patients.

CONCLUSIONS: Orthostatic hypotension is a relatively common condition among hospitalized US elderly patients. In light of the progressive aging of the US population, the contribution of orthostatic hypotension to morbidity and mortality is likely to increase, and deserves further scrutiny. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Epidemiology; Orthostatic hypotension; Syncope

Orthostatic hypotension is defined as a fall in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes upon standing.1 Affected patients commonly experience lightheadedness or syncope that predisposes them to falls and impaired quality of life.2,3

In normal individuals, postural changes do not result in major fluctuations in blood pressure because of physiological mechanisms that compensate for the gravitational blood pooling in lower limbs while standing.4 However, in subjects with autonomic nervous system impairment or in those taking medications that alter their response to stimuli these compensatory mechanisms fail and orthostatic hypotension results.

Although orthostatic hypotension is the cardinal manifestation of primary autonomic dysfunctions such as multiple system atrophy or pure autonomic failure,5,6 these conditions are rare. More common diseases associated with orthostatic hypotension include diabetes mellitus and neu-

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Orthostatic hypotension also has been associated with myocardial infarction and stroke.\textsuperscript{10,11} Furthermore, it has been identified as an independent predictor of mortality in elderly\textsuperscript{12,13} and end-stage renal disease patients.\textsuperscript{14,15} In addition, medications such as antihypertensives and antidepressants\textsuperscript{16} can induce de novo orthostatic hypotension or further complicate underlying autonomic dysfunction.

Existing estimates of orthostatic hypotension prevalence range from 6\% among otherwise healthy elderly persons\textsuperscript{17} to 68\% among patients hospitalized in a geriatric ward.\textsuperscript{18} Nevertheless, national estimates of the orthostatic hypotension disease burden are lacking. The objectives of our cross-sectional study using data from the Nationwide Inpatient Sample were to examine the magnitude of orthostatic hypotension-related hospitalizations in the US and to identify patient demographic and clinical characteristics associated with the occurrence of symptomatic orthostatic hypotension.

**METHODS**

The Nationwide Inpatient Sample

The Nationwide Inpatient Sample (NIS), sponsored by the Agency for Healthcare Research and Quality, annually collects discharge-level information about clinical characteristics and resource utilization from a sample that approximates 20\% of admissions to community hospitals in the US. Discharge diagnoses are recorded in up to 15 diagnosis fields using the *International Classification of Diseases 9th revision, Clinical Modification* (ICD9-CM). The first listed diagnosis (primary) is considered the main reason for admission and its original position is preserved in NIS records. The NIS is the largest source of inpatient data publicly available in the US, and its sampling design allows the calculation of national estimates and the examination of relatively uncommon conditions. The present study analyzed NIS data for 2004, the most recent data available. NIS data are devoid of identification elements, and this study was considered exempt from review by the Institutional Review Board of Vanderbilt University.

**Definition of Orthostatic Hypotension and Medical Conditions**

We first identified all hospitalization discharge records that contained a compatible ICD9-CM code 458.0 (“Orthostatic hypotension”) in any listed diagnosis field. We aimed to assess orthostatic hypotension-related hospitalizations associated with conditions that resulted in an impaired autonomic response, rather than acute or transitory events. These nonacute causes of orthostatic hypotension are more likely to have a neurogenic origin. Acute or transitory events encompassed: blood volume depletion, including dehydration and hemorrhage; intravascular volume contraction associated with pheochromocytoma, Addison’s disease, islet of Langerhans neoplasm, renovascular hypertension, and eating disorders; insufficiency of intravascular volume resulting from pregnancy, hyperthyroidism, or beriberi; and circulating vasodilators associated with carcinoid syndrome, mastocytosis, or status postgastric-bypass.\textsuperscript{5} These conditions were identified using ICD9-CM codes (Appendix) and excluded from further analyses. Because orthostatic hypotension is uncommon in children we also excluded subjects younger than 18 years of age.

**CLINICAL SIGNIFICANCE**

- The rate of nonacute orthostatic hypotension-related hospitalization of US adults increases substantially with age, up to 233 per 100,000 adults aged 75 years or older.
- The changing demographics and health characteristics of the US population are expected to increase the rate of orthostatic hypotension-related hospitalization, increasing the burden on health services.
- Whether standard therapies for orthostatic hypotension can reduce this burden has not been determined.

We assessed the primary diagnoses among those records with orthostatic hypotension listed in any diagnosis field. Similarly, we assessed the secondary diagnoses among those records whose primary diagnosis was orthostatic hypotension. In addition, we identified common chronic comorbidities known to result in orthostatic hypotension, including Parkinson’s disease, abnormal degenerative diseases of the basal ganglia (multiple system atrophy, progressive supranuclear palsy, and oligopontocerebellar atrophy), and autonomic neuropathy, regardless of its cause, ie, diabetes mellitus, amyloidosis.

**Statistical Analyses**

All analyses were stratified by age (18-34, 35-44, 45-54, 55-64, 65-74, and 75 years or older). Orthostatic hypotension-related hospitalization rates were estimated by dividing the weighted number of hospitalizations obtained from the NIS by the estimated population figures obtained from the US Census Bureau.\textsuperscript{19} All rates and their respective 95\% confidence intervals were expressed as hospitalizations per 100,000 people, and all estimates used the weight, strata, and cluster variables to account for the NIS complex sampling design. Census data were assumed to be derived from complete enumeration of the US population and thus were considered free of sampling error. All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC) and Sudaan 9.0.1 (Research Triangle Institute, Research Triangle Park, NC).
RESULTS

During 2004, there were an estimated 38,661,786 total hospitalizations in the US. Among these, a total of 164,401 (0.43%) orthostatic hypotension-related hospitalizations were identified. Within this group, 84,306 (51%) orthostatic hypotension-related hospitalizations met our criteria for acute or transitory conditions and were excluded. Excluded patients encompassed 777 children aged 0-17 years. The 2 major reasons for exclusion were: hypovolemia/dehydration (68,540 hospitalizations) and hemorrhage (11,195 hospitalizations), representing about 98% of all excluded observations (Figure 1). The remaining 80,095 orthostatic hypotension-related hospitalizations are the subjects of this study.

Orthostatic hypotension was listed as the primary diagnosis in 28,073 (35%) hospitalizations. Other conditions commonly listed as a primary diagnosis in this group were syncope and collapse (8.5%), cardiac arrhythmias, primarily atrial fibrillation (5.0%), physical therapy and rehabilitation (3.3%), acute pulmonary syndromes (3.0%), coronary atherosclerosis disease (2.9%), cerebrovascular disease (2.8%), congestive heart failure (2.6%), unspecified chest pain (1.7%), and acute infectious diseases (urinary tract infection and gastroenteritis) (1.1%).

Similarly, among those whose primary diagnosis was orthostatic hypotension, the most frequent secondary diagnoses were cardiac arrhythmias, particularly atrial fibrillation (10.7%), hypertension (8.9%), syncope (8.2%), chronic obstructive pulmonary disease (7.7%), congestive heart failure (6.7%), urinary tract infection (4.6%), cardiac valve disease, particularly aortic valve disease (4.1%), diabetes mellitus (3.2%), and chest pain (1.8%).

The overall annual rate for orthostatic hypotension-related hospitalizations listed in any field was 36 per 100,000 (95% confidence interval, 34 to 38) US adults. Rates increased steadily with age when the diagnosis of orthostatic hypotension was listed as primary discharge diagnosis (Figure 2A) or in any diagnostic field (Figure 2B). Orthostatic hypotension-related hospitalization rates were consistently higher in males than in females (Figure 2A and 2B).

Although race information was missing in 27% of records, the analyses of those with race data available indicated that patients hospitalized with orthostatic hypotension were predominantly Caucasians (60%) and African-Americans (7.4%). The remaining race/ethnic groups (Hispanic, Asians, Native Americans) represented 5.6% of the total number of admissions. This race distribution was consistent across all age groups (Table).

Most orthostatic hypotension patients were admitted through emergency departments; the median length of hospitalization was 3 days (interquartile range: 2-6 days) and similar among all age groups. The overall in-hospital mortality was 0.2% when the orthostatic hypotension was listed as primary diagnosis and 0.9% when listed in any field. Overall, 4% of orthostatic hypotension-related hospitaliza-

---

**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute conditions excluded</td>
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</tr>
<tr>
<td>Hypovolemia</td>
<td>68,540</td>
</tr>
<tr>
<td>Any hemorrhage</td>
<td>11,195</td>
</tr>
<tr>
<td>Intravascular volume contraction&gt;3,127</td>
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</tr>
<tr>
<td>Insufficiency of intravascular volume=638</td>
<td></td>
</tr>
<tr>
<td>Circulating vasodilators=29</td>
<td></td>
</tr>
<tr>
<td>Children (0-17 years old)= 777</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1** Stepwise definition of the population studied.

**Figure 2** Hospitalization rates for orthostatic hypotension listed as primary discharge diagnosis (A) or in any diagnosis field (B) according to age and sex, NIS 2004.
## Table
Characteristics of Orthostatic Hypotension-Related Hospitalizations, United States, 2004*

<table>
<thead>
<tr>
<th>Age Groups, Years</th>
<th>18-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
<th>≥75</th>
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<tbody>
<tr>
<td>Discharge Diagnosis Field</td>
<td>Primary</td>
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<td>Primary</td>
<td>Any</td>
<td>Primary</td>
<td>Any</td>
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<tr>
<td>No. of hospitalizations</td>
<td>472</td>
<td>2599</td>
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<td>3211</td>
<td>1829</td>
<td>6354</td>
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<tr>
<td>Female (%)</td>
<td>69.3</td>
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<td>59.6</td>
<td>62.5</td>
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<tr>
<td>Race (%)</td>
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<tr>
<td>White</td>
<td>56</td>
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<td>1.9</td>
<td>1.3</td>
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<td>27.8</td>
<td>26.7</td>
<td>29.4</td>
<td>28.2</td>
<td>27.9</td>
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<td>Admission (%)</td>
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<td></td>
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<tr>
<td>Emergency</td>
<td>61.6</td>
<td>53.6</td>
<td>65.4</td>
<td>57.7</td>
<td>69.3</td>
<td>59.3</td>
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<tr>
<td>Urgent</td>
<td>12.7</td>
<td>19</td>
<td>19.2</td>
<td>19.5</td>
<td>16.4</td>
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<tr>
<td>Elective</td>
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<td>10.1</td>
<td>15.3</td>
<td>10.2</td>
<td>15.3</td>
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<td>0.3</td>
<td>0.4</td>
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<tr>
<td>Other</td>
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<td>7</td>
<td>5.2</td>
<td>7.2</td>
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<td>In-hospital fatality (%)</td>
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<td>0.6</td>
<td>0.6</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>LOS (mean)</td>
<td>3</td>
<td>6</td>
<td>3.3</td>
<td>5</td>
<td>2.9</td>
<td>5</td>
</tr>
<tr>
<td>IQR</td>
<td>(1-3)</td>
<td>(2-6)</td>
<td>(1-4)</td>
<td>(2-6)</td>
<td>(1-4)</td>
<td>(2-6)</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal degeneration of basal ganglia</td>
<td>2.1</td>
<td>0.4</td>
<td>0</td>
<td>0.2</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>0</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>2</td>
<td>3.4</td>
<td>7.1</td>
<td>6.1</td>
<td>2.3</td>
<td>5.5</td>
</tr>
</tbody>
</table>

LOS = length of stay; IQR = interquartile range.

*Data are from the Nationwide Inpatient Sample.
tions were associated with Parkinson’s disease, 4% with autonomic neuropathy, and 0.9% with abnormal degeneration of basal ganglia. There were no material differences in the prevalence of these conditions between those who had orthostatic hypotension as primary diagnosis compared with those who had it in any diagnosis field (Table).

**DISCUSSION**

To the best of our knowledge, this is the first study that examined the epidemiology of orthostatic hypotension among hospitalized patients in the US. We found that orthostatic hypotension-related hospitalization rates increased exponentially with age, and they were consistently higher in elderly males compared with females.

Previous assessments of the burden of orthostatic hypotension focused on geriatric wards, nursing homes, and elderly community dwellers, with estimated prevalence of 68%, 18 54%,2 and 6%,17 respectively. The high prevalence of orthostatic hypotension among institutionalized patients likely reflects the presence of multiple risk factors such as neurodegenerative diseases known to cause orthostatic hypotension and the utilization of vasoactive medications that may impair a proper response to postural changes.18,20 Our findings are consistent with these reports and suggest that symptomatic orthostatic hypotension is a relatively common condition among the hospitalized elderly, and its incidence increases substantially with age. Aging is associated with physiological changes that may predispose to orthostatic problems. For instance, there is a loss of baroreflex responsiveness,21,22 reduced cardiac compliance,23 and attenuation of the vestibular sympathetic reflex.24 Therefore, the association between age and orthostatic hypotension has plausible physiological mechanisms.

We found that orthostatic hypotension-related hospitalizations occurred more frequently among Caucasians than in other racial groups. This is in agreement with previous studies that reported racial differences in the development of orthostatic hypotension particularly between Caucasians and African Americans.25 Differences in orthostatic hypotension prevalence may be due to differences in definitions of orthostatic hypotension in these studies. Furthermore, the differences observed in our study could also be due to differential recognition or recording of orthostatic hypotension as a contributory cause to the hospitalization.

Syncope was the most frequent diagnosis associated with orthostatic hypotension, and the majority of the orthostatic hypotension-related hospitalizations were admitted as emergencies. Previous studies have recognized syncope as a frequent cause of emergency department visits,26 and orthostatic hypotension has been previously documented in 24%-31% of patients presenting to emergency departments with syncope.20,27

Several neurodegenerative conditions can cause orthostatic hypotension. Abnormal degeneration of basal ganglia, autonomic neuropathy, and Parkinson’s disease can damage central or peripheral autonomic pathways, causing inability to engage the sympathetic nervous system upon standing, resulting in orthostatic hypotension.28,29 It is noteworthy that we found a high prevalence of these conditions in orthostatic hypotension-related hospitalizations, indicating that orthostatic hypotension is a common cause of hospitalization in these patients. Parkinson’s disease was reported in 4% of orthostatic hypotension-related hospitalizations, that is, 13 times higher than the estimated prevalence of this condition in the general US population (0.3%).30 Considering the growing burden of this neurological condition in the US, it is expected that orthostatic hypotension-related hospitalization will increase, challenging health policy planners to anticipate the need for health services. In this context, future studies should be directed to determine if the standard therapy available for orthostatic hypotension that increases blood volume (fludrocortisone) or blood pressure (midodrine) effectively prevents orthostatic hypotension-related hospitalizations.

In conclusion, orthostatic hypotension is a relatively common condition among US hospitalized elderly. Considering the dynamics of the US population and the increasing incidence of neurological conditions associated with orthostatic hypotension, the burden of orthostatic hypotension-related hospitalizations is likely to increase over time and certainly deserves further scrutiny.

**Strengths and Limitations**

The interpretation of our results requires the consideration of several caveats. First, the identification of orthostatic hypotension-related hospitalizations relied on discharge diagnosis codes and, although we designed an algorithm to improve our disease ascertainment, it was not possible to validate orthostatic hypotension diagnoses. In addition, there are no procedure codes to identify the tests required to establish an orthostatic hypotension diagnosis (eg, tilt table). Second, data on additional factors potentially related to orthostatic hypotension, such as medication use, were not available. Third, missing data on race/ethnicity precluded further analysis of this information. However, our study likely identified the most severe episodes of orthostatic hypotension that required hospital admission and provides an estimation of the orthostatic hypotension disease burden without regard to specific etiologic conditions.

**ACKNOWLEDGMENTS**

Dr. Shibao is recipient of the International Fellowship in Clinical Pharmacology supported by the Merck Foundation. Dr. Raj is supported by grant K23-RR020783 from the National Institutes of Health.

**References**


**APPENDIX**

ICD9-CM codes to define the following excluded sets:

**Reduced blood volume:**

Volume depletion (276.5), persistent vomiting (536.2), diabetes insipidus (253.5, 588.1), burns (948.x), diarrhea (558.9, 787.91), hemorrhage (hemorrhagic abortion: 640, 634.1, 635.1, 636.1, 637.1, 638.1, 639.1, 666; Gastrointestinal hemorrhage: 456.0, 456.20, 530.21, 530.7, 530.82, 531.0, 531.2, 531.4, 531.41, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 569.85, 578, 578.0, 578.9; hemoptysis: 786.3, hemorrhagic complications: 958.2, 998.1, 998.12, 998.13; Other hemorrhage: 285.1, 459.0).

**Intravascular volume contraction:**

Pheochromocytoma (194.0, 227.0, 255.6), Addison’s disease (255.4, 255.5, 017.6), malignant/benign neoplasm of islet of Langerhans (157.4, 159.0, 211.7, 211.9), renovascular hypertension (584.x), eating disorders (307.1, 307.5).

**Insufficiency of intravascular volume:**


**Vasodilators:**

Carcinoid syndrome (259.2), mastocytosis (202.6), postgastric surgery syndrome (564.2).
Chronic Kidney Disease Prevalence and Rate of Diagnosis

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ABSTRACT

BACKGROUND: Chronic kidney disease is a major public health problem. However, no study to date has estimated the prevalence of chronic kidney disease based on the clinical guidelines established by the National Kidney Foundation and few studies have explored the rate of diagnoses by primary care providers.

SUBJECTS AND METHODS: Cross-sectional study of ambulatory patients in Rochester, NY. The purpose of this study was to estimate the prevalence of chronic kidney disease and the rate of primary caregiver diagnosis in ambulatory patients with chronic kidney disease.

RESULTS: Among the 24,492 outpatients that had at least 2 glomerular filtration rate estimates ≥3 months apart, 6895 had an estimated glomerular filtration rate <60 mL/min/1.73 m², indicating a 28.2% period prevalence of chronic kidney disease. The rate of clinical diagnosis among those with chronic kidney disease was 26.5% (95% confidence interval, 17.9 to 35.1), suggesting that 74% of patients with chronic kidney disease are undiagnosed.

CONCLUSIONS: We demonstrate that the prevalence of chronic kidney disease is substantially higher in health-seeking individuals than in the general population. Moreover, we demonstrate that laboratory reporting of estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation alone does not result in an optimal rate of clinical diagnosis. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Chronic kidney disease; Diagnosis; Glomerular filtration rate; MDRD; Prevalence

Epidemic increases in chronic kidney disease have prompted the National Institutes of Health to include chronic kidney disease as a focus area in the Healthy People 2010 initiative. The 2010 guidelines call for reductions in: the rate of new cases of end-stage renal disease, the mortality rate related to chronic kidney disease, and kidney failure due to diabetes.¹

Recent medical evidence suggests that proper management of chronic kidney disease in the early stages can prevent death from cardiovascular disease, delay the need for dialysis, and improve patient health at the onset of dialysis.²⁻⁷

While incidence and prevalence rates of end-stage renal disease are known, analogous rates for earlier stages of chronic kidney disease are limited. Chronic kidney disease is defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m² of body surface area for ≥3 months.² According to the Third National Health and Nutrition Examination Survey (NHANES III) from 1988-1994, an estimated 8.3 million adults in the US have chronic kidney disease, indicating a prevalence of 4.7%.⁸ However, kidney function is based on a single estimate of GFR, as are similar estimates from other studies.⁹⁻¹³

Lack of epidemiological data on the scope of early-stage chronic kidney disease hinders the development and evaluation of early intervention programs that could reduce the burden of disease. Although early stages of chronic kidney disease are typically asymptomatic, detection can be achieved through laboratory testing. All clinical laboratories in Monroe County, New York have adopted the Modification of Diet in Renal Disease (MDRD) 4-variable equation to aid in estimating patients’ serum creatinine (S₉)⁵-based GFR. The equation has proven most accurate in individuals with

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chronic kidney disease and been further validated by direct measurement in patients >70 years of age.\textsuperscript{2,14-19} The MDRD equation potentially enables early detection of chronic kidney disease, thus providing primary care physicians with an opportunity to delay disease progression. Few studies have attempted to estimate the rate of diagnoses of chronic kidney disease by primary care physicians. However, these studies were limited in that diagnostic decisions were based on $S_c$ values alone.\textsuperscript{12,20}

Two major objectives of this study were: estimation of the period prevalence of chronic kidney disease as defined by MDRD-estimated GFR $<60$ mL/min/1.73 m$^2$ $\geq$3 months, and estimation of the rate of primary caregiver recognition/diagnosis of chronic kidney disease.

**METHODS AND MATERIALS**

**Study Population**

The study was conducted in Monroe County, New York, which has a population of 735,177.\textsuperscript{21} Monroe County demographics are similar to those of the US, with 51\% of residents being female and 13\% aged $\geq$65 years. Monroe County has a slightly higher percentage of African Americans (13.7\%) compared with that in the US (12.3\%), and the median age of residents is slightly older (39.1 years) than that of the US population (35.3 years).\textsuperscript{21,22}

The laboratory at Strong Health (University of Rochester) processes both inpatient and ambulatory specimens, comprising roughly one third of all tests done in Monroe County. The ambulatory specimens are collected from primary care offices throughout the County, which increases the likelihood of a representative sample.

The overall study population included all individuals 18 years of age or older as of June 1, 2003 who had at least one laboratory-estimated GFR from Strong Health between June 1, 2003 and May 31, 2004. Given the potential for renal insult and instability, inpatient estimates were excluded from the study. Individuals with missing demographic information or personal identifiers were also excluded. The study was approved by the Institutional Review Board at the University of Rochester Medical Center in accordance with Health Insurance Portability and Accountability Act guidelines.

**Data Source**

The database utilized in this study was maintained by Clinical Laboratory Services at Strong Health. The database contained patient information that was submitted on the laboratory requisition and provided on the laboratory reports to the requesting physicians. The clinical laboratory of Strong Health measured $S_c$ using an enzymatic method on Vitros 950 analyzers (Ortho Clinical Diagnostics, Rochester, New York). In order to address the issue of bias among the various creatinine assay methods regarding GFR estimation,\textsuperscript{23} a correlation study of 40 patients was performed comparing $S_c$ values using the Vitros 950 enzymatic method to an ADVIA 2400 blank-corrected Jaffe method (Bayer HealthCare, Tarrytown, New York). The ADVIA assay is traceable to a high-performance liquid chromatography reference method and, as per manufacturer, the re-expressed MDRD equation

$$GFR = 175 \times (S_c)^{(-1.154)} \times \frac{\text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})}{\text{age}}$$

is used to calculate GFRs.\textsuperscript{14,24} $S_c$ is measured in mg/dL, age is measured in years. A scatter plot of assay results demonstrated excellent correlation between the methods (R-square 0.9978).

**Outcomes of Interest**

For the purpose of this study, 2 outcomes were considered. First, the period prevalence of chronic kidney disease in patients seeking ambulatory health care was estimated. Chronic kidney disease was defined, utilizing the National Kidney Foundation Kidney Disease Outcomes Initiative (KDOQI) guidelines, as MDRD estimated GFR value $<60$ mL/min/1.73 m$^2$ for $\geq$3 months.\textsuperscript{2} Reduced kidney function to a level of GFR $<60$ mL/min/1.73 m$^2$ represents 50\% or more loss in normal adult kidney function.\textsuperscript{2} This level of kidney dysfunction for $\geq$3 months indicates a chronic loss rather than acute reduction. The period prevalence was determined as the ratio of the number of patients with a GFR $<60$ mL/min/1.73 m$^2$ for $\geq$3 months to the number of patients with estimates $\geq$3 months apart. Estimated GFR results are flagged by the laboratory as abnormal based on normal age and sex limits and are reported as abnormal to the primary care physician for further assessment of chronic kidney disease.

Second, we estimated the rate of primary caregiver recognition/diagnosis of chronic kidney disease as documented in the medical record for patients with chronic kidney disease as defined by the KDOQI guidelines. Sample size calculations for construction of a 95\% confidence interval (CI) to estimate diagnostic reporting rates within $\pm$10\% of the true population rate required that medical records from
100 subjects be reviewed. With proportionate sampling by race, we randomly selected 102 patients among the 6895 who met the KDOQI definition of chronic kidney disease. The recognition/diagnosis of chronic kidney disease was defined as any written evidence in each patient’s record that the physician had diagnosed chronic kidney disease. A diagnosis was noted if the physician ordered further clinical testing for renal impairment, referred the patient to a kidney specialist, or wrote in the patient record that chronic kidney disease was present. The chart review was conducted in 2005 and included all records from 2003 through May 2005.

The initial estimation of GFR in 2003-2004 was determined using enzymatic $S_{cr}$ values and the original MDRD formula:

$$GFR = 186 \times (S_{cr})^{(-1.154) \times (\text{age})^{(-0.203) \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})}}.$$  

These estimated GFR values were reported to the primary physician and used for the selection of chronic kidney disease patients to estimate the rate of diagnosis. The estimated GFRs derived from the original formula were compared with those derived using the re-expressed MDRD formula with no change in chronic kidney disease prevalence.

**Statistical Analysis**

Descriptive statistics are presented as percentages, or means with standard deviations. A mean GFR for each individual was based on the calculation of the group mean. Differences between groups for categorical and continuous variables were examined using chi-squared tests or Student’s $t$ tests, respectively. Statistical significance was ascribed to 2-sided $P$ values $<.05$. Data were normally distributed; analysis was performed using SAS Windows, version 9.1 (SAS Institute Inc., Cary, NC).

**RESULTS**

The initial dataset contained 100,176 unique patients. A total of 9321 patients were excluded due to missing personal identifiers, or demographic information. Additionally, 7879 patients were excluded from the sample due to inpatient status. The final study sample consisted of 82,976 unique patients with 170,581 observations. The cohort demographics were as follows: 56% was female, 82% was Caucasian, mean age was 56.2 ± 17.1 years, and the mean estimated GFR was 77.1 mL/min/1.73 m$^2$ ± 21.54.

**Prevalence of Chronic Kidney Disease**

Among the 82,976 outpatients who had $S_{cr}$ measured, 17,827 had at least one GFR < 60 mL/min/1.73 m$^2$. If we define chronic kidney disease (CKD) as a single GFR < 60 mL/min/1.73 m$^2$, this would indicate a period prevalence of 21.5%. However, using the KDOQI guidelines definition of CKD as a GFR < 60 mL/min/1.73 m$^2$ for ≥ 3 months, we found that the prevalence was higher. Among the 82,976 outpatients, 24,492 had at least 2 estimates ≥ 3 months apart. Among these, 6895 had at least 2 GFR < 60 mL/min/1.73 m$^2$ ≥ 3 months apart, indicating a 28.2% period prevalence of chronic kidney disease. The age-specific prevalence ranged from a low of 3.7% among those 18-39 years of age to a high of 51% among those > 70 years of age. Based on the 24,492 outpatients, the positive predictive value of a single GFR < 60 mL/min/1.73 m$^2$ as indicative of chronic kidney disease appears to be 73%.

The demographic characteristics of the outpatient population with and without CKD are outlined in Table 1. The Figure illustrates estimated GFR distribution. The mean estimated GFR was significantly different in those with CKD (45.15 mL/min/1.73 m$^2$) compared with those without chronic kidney disease (80.04 mL/min/1.73 m$^2$) ($P < .001$) (Table 1). Age was also significantly different, with a mean age of 71.4 ± 14.0 years among those with CKD compared with 54.8 ± 16.6 years among patients without CKD ($P < .001$). Among those with chronic kidney disease, 79% were > 60 years of age. The racial and sex distributions were significantly different ($P < .001$). Caucasians and Native Americans in this sample of health-seeking individuals were disproportionately more likely to have CKD, as were females (9.0%) compared with males (7.4%) ($P < .001$).

**Diagnosis of CKD**

To assess the rate of chronic kidney disease diagnoses by primary care providers, we conducted thorough chart re-
views on a random sample of 102 subjects selected from the 6895 subjects identified as having CKD (Table 2). The rate of clinical diagnosis of CKD documented in the patient’s medical record was 26.5% (95% CI, 17.9 to 35.1), suggesting that 74% of patients are undiagnosed. As shown in Table 2, patients with a clinical diagnosis of CKD (n = 27) had significantly lower GFR (33.16 vs 55.15), and a higher prevalence of anemia (56% vs 23%), hypertension (93% vs 63%), and diabetes (59% vs 29%), compared with those without a clinical diagnosis of CKD (n = 75). However, the prevalence of cardiovascular disease was not significantly different between the 2 groups (52% vs 40%) (P = .286).

Table 3 describes the distribution of GFR by diagnosis.

### DISCUSSION

We demonstrate that the prevalence of chronic kidney disease, defined by a GFR < 60 mL/min/1.73 m² for ≥3 months, was 28.5% in 24,492 health-seeking subjects having multiple GFR measures available. Consistent with previous reports, our study reveals that the prevalence of CKD was higher among women, Caucasians, and the elderly. Furthermore, we estimate that 74% of patients with CKD do

Table 2  Demographics of Outpatient Sample with CKD

<table>
<thead>
<tr>
<th></th>
<th>Confirmed Diagnosis of CKD (n = 27)</th>
<th>Unconfirmed Diagnosis of CKD (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.70 ± 15.92</td>
<td>70.21 ± 10.83</td>
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</tr>
<tr>
<td>Race</td>
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<td></td>
<td>&lt;.008</td>
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<tr>
<td>Caucasian</td>
<td>15 (55.56)</td>
<td>61 (81.33)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>12 (44.44)</td>
<td>14 (18.67)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>&lt;.22</td>
</tr>
<tr>
<td>Female</td>
<td>16 (59.26)</td>
<td>54 (72.00)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (40.74)</td>
<td>21 (28.00)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (diagnosed)</td>
<td>16 (59.26)</td>
<td>22 (29.33)</td>
<td>&lt;.006</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (92.60)</td>
<td>47 (62.67)</td>
<td>&lt;.003</td>
</tr>
<tr>
<td>CVD (diagnosed)</td>
<td>14 (51.85)</td>
<td>30 (40.00)</td>
<td>&lt;.286</td>
</tr>
<tr>
<td>Anemia (diagnosed)</td>
<td>15 (55.56)</td>
<td>17 (22.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MDRD GFR</td>
<td>33.16 ± 16.02</td>
<td>55.15 ± 7.22</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; CVD = cardiovascular disease; MDRD = Modification of Diet in Renal Disease; GFR = glomerular filtration rate.

Note: Values expressed as mean ± standard deviation for age and MDRD estimated GFR. Otherwise values expressed as number and (percent). Differences between groups for categorical and continuous variables were examined using chi-squared tests or Student’s t tests, respectively. Statistical significance was ascribed to 2-sided P-values <.05. MDRD estimated GFR is measured in mL/min/1.73 m². CKD is defined as an estimated GFR < 60 mL/min/1.73 m² for ≥3 months. Anemia is defined as a hemoglobin value < 12.0 g/dL. (Diagnosed) indicates a written diagnosis in the patients’ records.

Table 3  Distribution of GFR by Clinical Diagnosis

<table>
<thead>
<tr>
<th>Distribution of GFR</th>
<th>Confirmed Diagnosis of CKD (n = 27)</th>
<th>Unconfirmed Diagnosis of CKD (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-14</td>
<td>5 (100.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>15-30</td>
<td>10 (83.33)</td>
<td>2 (16.67)</td>
</tr>
<tr>
<td>31-45</td>
<td>9 (39.13)</td>
<td>14 (60.87)</td>
</tr>
<tr>
<td>46-59</td>
<td>3 (4.84)</td>
<td>59 (95.16)</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; CKD = chronic kidney disease.

Note: Values expressed as number and (percent). MDRD estimated GFR are measured in mL/min/1.73 m².
not have a documented diagnosis of CKD in their medical record.

Our findings show that prior estimates of CKD prevalence, defined as a single GFR <60, were inflated by approximately 27%. We also demonstrate that CKD prevalence among health-seeking individuals is substantially higher than in the general population.26 This difference has important implications for identification and management of those with CKD. Given that a majority of the estimated 8.3 million individuals with CKD may already be seeking health care for other reasons, an increased awareness among physicians is likely to maximize detection and management of CKD.

The rate at which primary care physicians recognize chronic kidney disease and diagnose patients as such should shape the development of effective primary care physician education programs. The poor sensitivity of prior screening tools, particularly the use of \( S_C \) values as a marker of renal insufficiency, has been implicated in the lack of CKD diagnosis.27,28 For this reason, Strong Health implemented the MDRD equation in an effort to provide physicians with a more accurate measurement of kidney function to improve the identification of individuals with CKD.

Prior studies have estimated the rate of diagnosis; however, diagnostic decisions in these studies were based on \( S_C \) values.12,20 The primary care physicians in our study were making diagnostic decisions based upon estimated GFR. Despite the increased sensitivity of this method, physicians in our study were not likely to document a diagnosis of CKD, as only 26.5% of patients with chronic kidney disease had documentation of CKD in their medical record. The data also indicate a possible sex bias in recognition of CKD; evidence of clinical diagnosis was found in only 22.8% of medical records of women, compared with 34.4% of these for men (Table 2). Our findings suggest that physicians are more likely to make the diagnosis as severity of disease increases, with early stages going undiagnosed.

Akbari et al found in a limited setting that the use of estimated GFR combined with an educational intervention of physicians significantly improved the rate of CKD diagnosis in Canada.29 The rate of diagnosis increased 3-fold (22.4% to 85.1%) following the implementation of the educational program. It was hypothesized that the implementation of widespread reporting of laboratory GFR without the educational component would increase nephrology referrals and overwhelm specialists. Our findings indicate that, given the low rate of physician-documented diagnosis of CKD, the widespread reporting of laboratory GFR alone is unlikely to result in an increase in nephrology referrals. We are not aware of any such change in these referral trends.

The underdiagnosis of CKD is particularly worrisome given that early identification provides an opportunity to slow the progression and alter the course of disease. Several studies indicate that patients are referred to specialized nephrology care just before the need for dialysis, which is often too late.28,30,31 Our findings suggest that referrals during late stages of CKD may be a result of delay in the early clinical diagnosis of CKD by primary care physicians. We speculate that education of primary care physicians on CKD and increased awareness of risk factors may improve the diagnosis rate.

The lack of data on microalbuminuria is a limitation of our study. The number of individuals with a GFR >60 and microalbuminuria is unknown. As a consequence, we have underestimated the prevalence of CKD among those patients with a GFR >60. Additionally, given that our study includes only individuals seeking health care during the study period, we do not have renal function estimates for the entire catchment population. However, the size and demographic characteristics of our study cohort, and the fact that specimens were collected from primary care offices throughout the County, increase the likelihood of a representative sample. By limiting our study to outpatient \( S_C \) values and the use of one laboratory for estimation of GFR, we increased our confidence in the validity of the estimated GFR values.

It is very important to note that the prevalence of CKD was determined using individuals with 2 observations ≥90 days apart. It is possible that patients with 2 estimates had more medical problems, particularly hypertension and diabetes, resulting in a slightly inflated prevalence. Additionally, the patients without \( S_C \) measurements were likely healthier than those with measured values, and had a lower prevalence than the 28.2% of patients who had 2 or more \( S_C \) values. Finally, although the number of chart reviews was limited, our findings indicate that, at best, the rate of CKD diagnosis was 35.1%, which indicates a need for improvement.

In conclusion, we demonstrate that the prevalence of chronic kidney disease is substantially higher in the health-seeking population based on the National Kidney Foundation clinical definition. The notable difference in the prevalence between health-seeking individuals and the general population has important implications for identification and management of individuals with chronic kidney disease. Moreover, we demonstrate that laboratory reporting of estimated GFR using the MDRD equation alone does not result in an optimal rate of clinical diagnosis, with 74% of patients remaining undiagnosed.

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References


Clinical Symptoms and Course

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ABSTRACT

PURPOSE: A new type of hereditary angioedema was described recently. It was characterized by recurrent bouts of angioedema in various organs and normal C1 inhibitor and was observed mainly in women. Our aim was to conduct a detailed study of the clinical features of this condition.

METHODS: A total of 138 patients with hereditary angioedema and normal C1 inhibitor who belonged to 43 unrelated families were examined through the use of standardized questionnaires.

RESULTS: A majority of patients with hereditary angioedema and normal C1 inhibitor had skin swellings (92.8%), tongue swellings (53.6%), and abdominal pain attacks (50%). Laryngeal edema (25.4%) and uvular edema (21.7%) also were frequent, whereas edema episodes of other organs were rare (3.6%). Facial swellings and tongue involvement occurred considerably more frequently compared with hereditary angioedema caused by C1 inhibitor deficiency. The number of patients with recurrent edema of only 1 organ was higher than in classic hereditary angioedema. The number of patients with disease onset in adulthood was significantly higher in hereditary angioedema with normal C1 inhibitor compared with classic hereditary angioedema. Erythema marginatum was not observed. A subgroup of patients from families with coagulation factor XII mutations showed the same symptoms as the other patients.

CONCLUSIONS: Hereditary angioedema with normal C1 inhibitor levels shows a characteristic pattern of clinical symptoms. The main clinical features include skin swellings, tongue swellings, and abdominal pain attacks. There are many differences in the clinical symptoms and course of disease between this type of hereditary angioedema and classic hereditary angioedema caused by a genetic C1 inhibitor deficiency. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Angioedema; Hereditary Angioedema; Hereditary Angioedema Type III; Coagulation Factor XII; F12 Gene Mutations; C1 Inhibitor Deficiency

Until recently, it was assumed that all patients with hereditary angioedema have a genetically determined deficiency of complement C1 inhibitor (C1-INH). In July of 2000, however, we described a new type of dominantly inherited angioedema that occurred in women and was not associated with a C1-INH deficiency. The reported 36 women belonged to 10 unrelated families, each with 2 to 7 affected women, and all had normal C1-INH concentration and function in plasma. We termed the disease “hereditary angioedema with normal C1-INH” or “hereditary angioedema type III.” Later on, 2 more families were reported in whom all affected individuals were women. In an additional family, men also were affected. In subsequent years, we observed a considerable number of additional families, all with 2 or more affected members. Recently, we identified 2 missense mutations in the same codon of the coagulation factor XII gene as the cause of hereditary angioedema with normal C1-INH in 6 of 20 unrelated families. At a later date, the presence of 1 of these mutations was observed in a seventh family.10

The large number of patients with hereditary angioedema with normal C1-INH whom we observed subsequently now permit a more precise description of the clinical symptoms...
of this condition. The aim of the present study was to delineate the clinical features of hereditary angioedema with normal C1-INH regarding the temporal pattern (ie, age at onset and course of disease) and the spatial pattern of the swelling episodes (ie, the affected organs and body sites). Thus, we intended to investigate whether there is a pattern of symptoms that is specific for this type of hereditary angioedema. The establishment of such a specific pattern of symptoms might enable one to differentiate this novel disease from classic hereditary angioedema caused by C1-INH deficiency by clinical symptoms and course of disease.

METHODS

Study Design

Our analysis was based on retrospective clinical case reports. Data were generated by asking patients about symptoms they experienced during episodes of hereditary angioedema. Criteria evaluated were the frequency of episodes and their body sites at various ages of the patients. Documentation was accomplished through the use of standardized questionnaires. In addition, extensive pedigree information was obtained for all families.

Study Patients

The present study was conducted from 1985 to September of 2006. From a special angioedema outpatient service at the Department of Dermatology, University of Mainz, Germany, we selected patients with hereditary angioedema with normal C1-INH. Hereditary angioedema with normal C1-INH was diagnosed when the following criteria were fulfilled: recurrent angioedema of the skin and/or the gastrointestinal tract and/or other organs; no chronic relapsing urticaria; 2 or more affected family members; and normal C1-INH protein and activity.

A total of 152 patients with hereditary angioedema and normal C1-INH from 43 families initially were included in the study. Forty-six of these patients were mentioned in previous reports5,8,11,12; however, the clinical features of these 46 patients were not analyzed as in the present study. The 152 patients presented now include 23 patients from the 6 families with hereditary angioedema and normal C1-INH in whom missense mutations (Thr309Lys, Thr309Arg) of coagulation factor XII were recently identified.9

Laboratory Methods

Protein levels of C1-INH antigen, C4, and C1q were assayed by radial immunodiffusion. C1-INH activity was determined by use of the chromogenic substrate C2H5CO-Lys(ε-Cbo)-Gly-Arg-pNA (Immunochrom C1-INH, Technoclone, Vienna, Austria).

RESULTS

The pedigrees of 43 unrelated families revealed 152 individuals who were affected by angioedema symptoms and 11 unaffected individuals (6 women and 5 men) who apparently transmitted the disease but had no clinical signs of it. Two to 10 individuals were affected per family (Table 1). In 36 families, only women were affected; Figure 1 shows the pedigree of 1 of these families. In 7 families, 1 man (4 families), 2 men (2 families), or 5 men (1 family) were clinically affected.

The examination of the pedigrees of the 43 families revealed that 2 successive generations were affected in 30 families, 3 successive generations were affected in 9 families, and 4 successive generations were affected in 4 families. These results support the assumption of a dominant inheritance pattern.

Of the 152 patients with hereditary angioedema with normal C1-INH, 14 were excluded from the present analysis because of limited information: 4 patients suffocated as the result of hereditary angioedema, 9 patients died of other diseases, and 1 patient was not able to attend our clinic. Thus, the following data describe 138 patients from 43

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Basic Data Regarding 138 Patients from 43 Families with Hereditary Angioedema and Normal Complement C1 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>138</td>
</tr>
<tr>
<td>No. of families</td>
<td>43</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>48.9 ± 18.5</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/127</td>
</tr>
<tr>
<td>C1-INH protein (g/L)*</td>
<td>0.29 ± 0.07</td>
</tr>
<tr>
<td>C1-INH activity (%)*</td>
<td>98.1 ± 16.6</td>
</tr>
<tr>
<td>C4 (g/L)*</td>
<td>0.26 ± 0.06</td>
</tr>
<tr>
<td>No. of clinically affected members per family†</td>
<td>Families:</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
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<td>5</td>
<td>3</td>
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<td>2</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

C1-INH = complement C1 inhibitor.

*Normal range for C1-INH protein, 0.15 to 0.35 g/L. Normal range for C1-INH activity, 70% to 130%. Normal range for C4, 0.20 to 0.50 g/L.

†All 152 affected members from 43 families.
Temporal Pattern: Symptom-free Periods and Years with Clinical Symptoms

Symptom-free periods lasting longer than 12 months include the years from birth to the first clinical manifestation of the disease, as well as symptom-free years during the phase of clinical symptoms due to either the natural course of the disease or prophylactic treatment.

Age at Disease Onset. In most patients, clinical symptoms started during adolescence or adulthood; the mean age at onset of the disease was 26.8 years (standard deviation ± 14.9 years, range 1-68 years). The onset of clinical symptoms occurred in the first decade of life in 11 patients (8%), in the second decade in 60 patients (43.5%), in the third decade in 22 patients (15.9%), and later in 45 patients (32.6%). In the 11 patients with an onset in the first decade of life, clinical symptoms started within the first year of life in 2 children and at ages 2, 5, and 6 years in 3 children, and at ages 8, 9, and 10 years in 2 children.

Symptom-free Periods After the Onset of Clinical Symptoms. From the onset of the first clinical symptoms to the time of data collection, only 53 of 138 patients had recurrent swelling episodes without symptom-free intervals lasting longer than 12 months. The remaining 85 of 138 patients had an average of 11.8 symptom-free years ranging from 1 to 54 years. Three patients received long-term treatment with danazol or tranexamic acid and were asymptomatic during that time. The other 82 of those 85 patients did not receive any long-term treatment, that is, their symptom-free years were part of the natural course of their disease. The yearly frequency of attacks in the 138 patients is listed in Table 2.

Spatial Pattern: Organ and Body Site Distribution of Edema Attacks

According to Table 3, skin swelling, tongue swelling, abdominal pain attacks, episodes of laryngeal edema, and episodes of pharyngeal edema including edema of the uvula are the cardinal symptoms of the disease. Most patients had only skin swellings (n = 33) or skin swellings and tongue swellings (n = 23). Among the various other combinations of organs that were affected, the combinations “skin swellings, tongue swellings, and abdominal attacks” (n = 21) and “skin swellings and abdominal attacks” (n = 18) were most frequent.

Skin Swellings. The distribution of facial swellings, swellings of the extremities, genital swellings, and skin swellings at other body sites is shown in Table 3. The majority of all

Table 2  Mean Frequency of Attacks per Year in 138 Patients with Hereditary Angioedema Type III

<table>
<thead>
<tr>
<th>Attacks per Year</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>20 (14.5%)</td>
</tr>
<tr>
<td>1-5</td>
<td>48 (34.8%)</td>
</tr>
<tr>
<td>6-11</td>
<td>23 (16.7%)</td>
</tr>
<tr>
<td>12-24</td>
<td>27 (19.6%)</td>
</tr>
<tr>
<td>&gt;24</td>
<td>20 (14.5%)</td>
</tr>
</tbody>
</table>

Table 3  Affected Body Sites in Hereditary Angioedema Type III

<table>
<thead>
<tr>
<th>Affected Sites</th>
<th>All 138 Patients with Hereditary Angioedema Type III</th>
<th>Subgroup of 23 Patients with FXII Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients (%)</td>
<td>No. of Episodes</td>
<td>No. of Patients (%)</td>
</tr>
<tr>
<td>Skin</td>
<td>128 (92.8)</td>
<td>14,089</td>
</tr>
<tr>
<td>Face</td>
<td>127 (92.0)</td>
<td>8406</td>
</tr>
<tr>
<td>Extremities</td>
<td>55 (39.9)</td>
<td>5076</td>
</tr>
<tr>
<td>Genitals</td>
<td>13 (9.4)</td>
<td>241</td>
</tr>
<tr>
<td>Trunk, neck</td>
<td>4 (2.9)</td>
<td>366</td>
</tr>
<tr>
<td>Tongue</td>
<td>74 (53.6)</td>
<td>3599</td>
</tr>
<tr>
<td>Abdominal</td>
<td>69 (50.0)</td>
<td>9898</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>35 (25.4)</td>
<td>453</td>
</tr>
<tr>
<td>Uvula</td>
<td>30 (21.7)</td>
<td>1490</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.6)</td>
<td>123</td>
</tr>
</tbody>
</table>
facial swellings, namely, 6898 episodes in 86 of 127 patients affected only the lips. In 13 patients, 64 facial swellings (range 1-30) were associated with a laryngeal edema. Two patients, members of separate families, reported recurrent hemorrhage into skin swellings in the face or at the extremities 1 or 2 days after the onset of the swellings (Figure 2, A and B). In 1 woman, these hemorrhages occurred in approximately 90 of her 98 skin swellings; in the other woman, these hemorrhages occurred in approximately 30 of her 215 skin swellings. The hemorrhages were limited to the site of the skin swelling. Neither patient received anticoagulants or had a history of any bleeding disorders. Laboratory examinations during the time the hemorrhages were present revealed normal values for coagulation and fibrinolysis. A hereditary or acquired defect of the coagulation system could not be found. No other affected family members had similar hemorrhages. One of the women (Figure 2A) belonged to the group of 23 patients in whom a coagulation factor XII missense mutation was identified. Another 21 women reported that they easily developed skin hemorrhages (“blue spots”) secondary to minor trauma. In 15 of these women, this phenomenon started at the age at which angioedema symptoms began; the remaining 6 women did not remember the time of onset.

No patient reported a gyrated erythematous rash on the chest or other parts of the trunk (the so-called erythema marginatum) preceding or accompanying the edema attacks on the chest or other parts of the trunk—a highly characteristic symptom frequently observed in patients with hereditary angioedema caused by C1-INH deficiency.

**Tongue Swellings.** Swelling of the tongue reached its maximum after 4 to 6 hours and persisted for 1 or 2 days. Among the patients with tongue swellings, 8 had experienced 200 to 520 tongue swellings. In 23 patients and 388 episodes, the tongue swelling, having reached its maximum, was associated with dyspnea and fear of asphyxiation. One woman suffocated at the age of 36 years after a bite on the tongue followed by tongue swelling and, later on, severe dyspnea. In 2 additional women, suffocation also was reported to have been preceded by a tongue swelling.

**Abdominal Pain Attacks.** Half of all patients experienced attacks of abdominal pain. Sonography was performed for 21 abdominal attacks in 6 patients and consistently revealed transient ascites. Five patients erroneously underwent abdominal surgery because hereditary angioedema was not diagnosed and appendicitis was assumed.

**Laryngeal Edema.** In 13 of 35 patients with laryngeal edema, a total of 64 episodes were preceded by and associated with tongue swellings. Two patients were intubated, and a cricothyrotomy was performed in 1 patient.

**Death by Suffocation.** Four patients, all women, asphyxiated as the result of attacks of upper airway obstruction at the ages of 16, 36, 38, and 48 years, respectively. For 3 of these patients, a tongue swelling was reported. For another patient, there was no precise information about a simultaneous tongue swelling. Three of the patients died before the diagnosis of hereditary angioedema with normal C1-INH was established. The fourth patient, who was 48 years old and had known hereditary angioedema with normal C1-INH and numerous tongue swellings in her history, died of asphyxiation after a tongue swelling during hospitalization for pancreatitis of unknown origin.

**Uvular Edema.** Among the 1490 uvular episodes, 884 episodes (range 1-190) in 19 patients occurred in isolation; in 554 episodes (range 1-200) in 11 patients there was a simultaneous tongue swelling; and in 52 episodes (range 1-25) in 6 patients a simultaneous laryngeal edema occurred.

**Edema of Other Organs.** Two women reported 52 and 49 episodes, respectively, that they ascribed to an involvement of the esophagus. The episodes presented with severe pain in the region of the esophagus. During swallowing, the pain moved through the whole esophagus along with the swallowed food. The episodes lasted 1 or 2 days. One woman had a relapsing urethral edema with dysuria; micturition was not possible for 48 hours. A visible swelling of the external orifice of the urethra necessitated a slit incision 4 times. The symptoms were not associated with abdominal

Figure 2  Two women with hereditary angioedema type III and skin hemorrhages at the sites of previous skin swellings.
pain attacks. One patient had suspected cerebral edema with extreme headache associated with a choked papilla. Another patient had 1 episode of massive splenic edema that lasted 3 days and was verified by sonography.

Clinical Symptoms in Patients with Hereditary Angioedema Caused by Coagulation Factor XII Mutations

According to Table 3, the 23 patients from 6 families who had a factor XII missense mutation demonstrated the same clinical symptoms as seen in the whole series of patients with hereditary angioedema and normal C1-INH.

DISCUSSION

The analysis of the present patient series confirms that the clinical symptoms of hereditary angioedema with normal C1-INH occur mainly in women. In many patients, this outcome may be due to the influencing role of estrogens, because oral contraceptives, pregnancy, and estrogen replacement therapy may induce or worsen the disease.\(^5,11,13,14\) The wide range of onset of the clinical symptoms in patients with hereditary angioedema type III is clearly different from hereditary angioedema types I and II, in which the first symptoms usually occur in the first (51.2% of patients) or second decade of life (37.8% of patients).\(^15,16\) Thus, on average, hereditary angioedema with normal C1-INH starts later in life than hereditary angioedema types I and II.

The affected organs in patients with hereditary angioedema type III were the same as in hereditary angioedema caused by C1-INH deficiency: skin, gastrointestinal tract, and larynx. However, the swelling pattern, that is, the frequency of attacks in these organs, differed considerably. Skin swellings are the most frequent symptom in hereditary angioedema type III. Most often they occur on the face, much less frequently at the extremities, and only in rare cases at the genitals. In hereditary angioedema types I and II, swellings of the extremities are more common than swellings at other skin sites; facial and genital swellings occurred in only 3% and 4%, respectively, of all skin swellings in hereditary angioedema caused by C1-INH deficiency.\(^15\) The considerably higher frequency of facial swellings compared with extremity swellings is true in nearly all patients with hereditary angioedema type III and is obviously an important and clear diagnostic clue to this condition.

Two patients recognized hemorrhages in a large number of their skin swellings. This observation suggests the possibility that abnormalities of the coagulation system might take place locally at the swelling site. To the best of our knowledge, similar skin hemorrhages have not been observed in hereditary angioedema caused by C1-INH deficiency. None of the patients reported an erythema marginatum, which is highly characteristic and well known as a preceding or concomitant sign of a portion of abdominal attacks and skin swellings of hereditary angioedema caused by C1-INH deficiency.\(^17,19\)

Tongue swellings occurred in 53% of the patients with hereditary angioedema type III described here; a considerable percentage of all these attacks were isolated tongue swellings. In hereditary angioedema caused by C1-INH deficiency, isolated tongue swellings are rare, having been observed in only 5.7% of patients and 0.08% of attacks.\(^15\) Thus, the frequent occurrence of tongue swellings is a further simple diagnostic clue in diagnosing hereditary angioedema type III by clinical symptoms. The finding that many patients experienced a large number of tongue swellings, however, does not permit the assumption that tongue swellings in hereditary angioedema type III are harmless: In at least 3 patients (there is not enough information about the fourth patient), a tongue swelling preceded their suffocation. In hereditary angioedema type III, abdominal symptoms obviously play a less important role, whereas abdominal attacks are some of the most distressing symptoms of hereditary angioedema caused by C1-INH deficiency.

In conclusion, features of hereditary angioedema with normal C1-INH that serve to differentiate it from hereditary angioedema caused by C1-INH deficiency are:

- Patients have normal C1-INH protein and activity.
- Mainly women are clinically affected.
- The number of children already affected before the age of 10 years is low. Clinical symptoms start in adulthood in more patients than in hereditary angioedema caused by C1-INH deficiency.
- There are more disease-free intervals during the course of the disease.
- Symptoms are less frequent compared with hereditary angioedema caused by C1-INH deficiency.
- Facial swellings, mainly lip swellings, are relatively more frequent.
- The tongue is considerably more often affected: Recurrent tongue swelling is observed in many patients and is a cardinal symptom of the condition.
- Many patients have only skin swellings.
- Many patients have only recurrent skin swellings and tongue swellings.
- Abdominal attacks are less frequent.
- Suffocation may be preceded and caused by a tongue swelling.
- There is no erythema marginatum (gyrated erythematous rash), as is highly characteristic of hereditary angioedema caused by C1-INH deficiency.
- Hemorrhages into skin swellings were observed in hereditary angioedema with normal C1-INH.

It is not clear why in hereditary angioedema with normal C1-INH the swelling pattern differs from that of hereditary angioedema caused by C1-INH deficiency. Most probably the clinical differences have their basis in different underlying gene defects associated with different pathogenetic events. Whereas in hereditary angioedema types I and II the genetic basis is well understood,\(^4,20\) only limited data on the molecular basis of hereditary angioedema type III are cur-
rently available. Recently, we obtained highly significant evidence for a role of missense mutations (Thr309Lys, Thr309Arg) of coagulation factor XII in approximately one third of families with clinically defined hereditary angioedema type III. Our present study includes 23 patients from the 6 families with factor XII mutations reported previously. Our present results demonstrate that this subgroup of patients with coagulation factor XII mutations shows the same spatial swelling pattern as observed for the whole group of patients with hereditary angioedema and normal C1-INH, a pattern that differs considerably from that of hereditary angioedema caused by C1-INH deficiency. Future molecular and clinical studies will further aim to differentiate subgroups of patients with hereditary angioedema and normal C1-INH, that is, the subgroup of patients carrying a factor XII mutation and 1 or more subgroups carrying another, presently unknown, genetic defect.

References
CLINICAL RESEARCH STUDY

TIMI Risk Index and the Benefit of Enoxaparin in Patients with ST-Elevation Myocardial Infarction

Christian T. Ruff, MD, Stephen D. Wiviott, MD, David A. Morrow, MD, MPH, Satishkumar Mohanavelu, MS, Sabina A. Murphy, MPH, Elliott M. Antman, MD, Eugene Braunwald, MD, for the ExTRACT-TIMI 25 Investigators
TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass.

ABSTRACT

PURPOSE: The purpose of the study was to evaluate the cause of death, risk of nonfatal complications, and relative outcomes with an enoxaparin versus unfractionated heparin strategy in ST-elevation myocardial infarction stratified using the Thrombolysis in Myocardial Infarction (TIMI) Risk Index (TRI).

METHODS: We evaluated 30-day outcomes in 19,941 patients with ST-elevation myocardial infarction treated with fibrinolysis and unfractionated heparin or enoxaparin. Patients were categorized on the basis of prespecified ranges of the TRI [heart rate \(/\) (age/10)\(^2\)/systolic blood pressure].

RESULTS: There was a strongly graded increase in 30-day mortality with increasing TRI (1.2%-20.7%, \(P < .0001\)). The proportion of deaths due to mechanical causes (congestive heart failure, shock, and myocardial rupture) increased progressively with the TRI. There also was a significant positively graded association between the TRI and nonfatal heart failure or shock (0.4%-4.4%, \(P < .0001\)). In contrast, death resulting from recurrent ischemic events predominated in the lowest TRI group. The relative reduction in death/myocardial infarction with the enoxaparin strategy appeared inversely graded with the TRI. There was a 38% reduction in the lowest risk group (relative risk 0.62, 95% confidence interval 0.45-0.86) and a decrease in the relative benefit of enoxaparin with increasing risk index.

CONCLUSIONS: The TRI was a strong predictor of all-cause mortality in a broad population, with a positive association with the risk of death due to mechanical complications and an inverse association with deaths due to recurrent ischemia. The enoxaparin strategy was superior to unfractionated heparin in a majority of patients with ST-elevation myocardial infarction, except for the group at the highest risk for severe mechanical complications, in whom the 2 anticoagulant strategies showed similar results. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Enoxaparin; Fibrinolysis; Myocardial infarction; Prognosis; TIMI Risk Index

In the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25) trial, a strategy of enoxaparin administered until hospital discharge was shown to be superior to treatment with a strategy of unfractionated heparin for 48 hours in patients receiving fibrinolysis for ST-elevation myocardial infarction, with a highly significant 17% relative reduction in the rate of death or nonfatal myocardial infarction at 30 days.\(^1\) Although the risk of major bleeding with enoxaparin was increased, the net clinical benefit (death, recurrent myocardial infarction, and major bleeding) favored the enoxaparin strategy. Given the central role of rapid and effective risk stratification in triaging patients and predicting response to therapy across the spectrum of acute coronary syndromes (acute coronary syndrome), an analysis of the efficacy and net clinical benefit of enoxaparin stratified by baseline risk was planned as part of the design of ExTRACT-TIMI 25.\(^2\)

The Thrombolysis in Myocardial Infarction (TIMI) Risk
Index (TRI) is a simple, generalizable, and well-validated instrument based on age and initial vital signs for risk assessment of patients presenting with myocardial infarction. The risk index was developed for predicting 30-day mortality from any cause among 13,253 patients enrolled in a phase III trial of fibrinolysis for ST-elevation myocardial infarction and has been validated in other clinical trials and a registry of patients with ST-elevation myocardial infarction. However, the TRI has not been evaluated relative to the cause of death or nonfatal clinical outcomes. In addition, we prospectively planned to use the TRI to evaluate the relationship between baseline mortality risk and the outcome of the enoxaparin strategy versus unfractionated heparin as adjunctive antithrombin therapy in ST-elevation myocardial infarction.

**CLINICAL SIGNIFICANCE**

- Rapid targeting of appropriate therapy in patients presenting with ST-elevation myocardial infarction is important in outcomes.
- The TIMI Risk Index is a practical bedside tool for predicting mortality at initial presentation in patients with ST-elevation myocardial infarction.
- On the basis of our findings, the TIMI Risk Index is useful in predicting the relative benefit of the enoxaparin strategy along with fibrinolysis.

**METHODS**

**Patient Population**

To be eligible for enrollment in ExTRACT-TIMI 25, patients were required to be at least 18 years of age, have at least 20 minutes of ischemic symptoms while at rest within 6 hours before randomization, have ST-segment elevation or left bundle-branch block on electrocardiogram, and be scheduled to undergo fibrinolysis with streptokinase, t-PA, alteplase, or reteplase. Patients were ex-scheduled to undergo fibrinolysis with streptokinase, t-PA, or left bundle-branch block on electrocardiogram, and be excluded if they presented with cardiogenic shock, contraindication to fibrinolysis, pericarditis, symptoms of aortic dissection, known renal insufficiency, receipt of a low-molecular-weight heparin within the previous 8 hours, or a life expectancy less than 12 months. All patients received aspirin unless contraindicated and were randomized to receive a strategy of enoxaparin during the hospitalization (up to 8 days) or unfractionated heparin for 48 hours in a double-blind fashion. The primary efficacy end point was the composite of death from any cause or nonfatal recurrent myocardial infarction in the first 30 days after randomization. Events were adjudicated by an independent clinical events committee blinded to treatment allocation.

**Stratification by TIMI Risk Index**

For this analysis, patients were categorized using the TIMI risk index, calculated using the equation [heart rate × (age/10)²/systolic blood pressure], and grouped in prespecified ranges based on the original derivation (group 1: ≤12.5; group 2: >12.5-17.5; group 3: >17.5-22.5; group 4: >22.5-30; group 5: >30). Consistent with the development and validation of this tool, only patients with heart rates between 50 and 150 beats/min were included. Thus 19,941 (97.4%) of the 20,479 patients in the intention to treat cohort were included in this analysis. Only 1 patient had missing data for calculation of the TRI. Cause of death was determined and recorded on the case report form by the local investigator, blinded to treatment allocation and using all other available data. Source documentation was reviewed by trained study monitors.

**Statistical Methods**

Baseline characteristics were compared across risk groups using the chi-square test for categoric variables and the Kruskal-Wallis rank test for continuous variables. Differences in event rates across risk index ranges were assessed using the chi-square test for trend. The prognostic discriminatory capacity of the risk index was expressed as the c-statistic, representing the area under the receiver operator curve for prediction of the stated outcome. The effect of a strategy using enoxaparin versus unfractionated heparin within each risk group was assessed using the chi-square test and is presented with relative and absolute risk reductions. Two-tailed P values less than .05 were considered significant. Statistical analyses were performed using Stata/SE, version 9.2 (StataCorp, College Station, Tex).

**RESULTS**

The distribution of the TRI in the 19,941 patients in ExTRACT-TIMI 25 was similar to that of the original derivation set from InTIME II and the general US population of patients with ST-elevation myocardial infarction receiving reperfusion therapy (Figure 1). The baseline characteristics stratified by the TIMI Risk Index strata are shown in Table 1. By definition, patients with higher TRI were older and had higher heart rates and lower systolic blood pressure on presentation (P < .0001 for each). In addition, those with higher TRI were more often diabetic, hypertensive, and more likely to have a history of myocardial infarction or renal dysfunction (P ≤ .0001 for each).

**Fatal Outcomes Stratified by TIMI Risk Index**

The TRI was a robust predictor of all cause mortality, demonstrating a strongly graded increase in death at 30 days (Table 2, 1.2%-20.7%, P < .0001, c-statistic 0.78). Of the 1968 deaths in the 19,941 patients who formed the basis of this analysis, 43% were considered to be mechanical (congestive heart failure, shock, or myocardial rupture), 22% were due to an arrhythmia, 8% were due to recurrent ischemia or infarction, and 6.3% were due to bleeding. There
were 2.9% noncardiac deaths. We found that deaths due to mechanical causes increased progressively with the TRI (Figure 2). In contrast, the proportion of deaths due to recurrent ischemic events was highest in the lowest quintile of the TRI \((P <.0001)\).

Secondary Outcomes Stratified by TIMI Risk Index

There was a significant positively graded association between the TRI and nonfatal end points (Table 2). The

### Table 1  Baseline Characteristics

<table>
<thead>
<tr>
<th>TIMI Risk Index Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) median</td>
<td>44</td>
<td>53</td>
<td>60</td>
<td>67</td>
<td>74</td>
<td>.0001</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>40-49</td>
<td>49-57</td>
<td>55-65</td>
<td>63-72</td>
<td>70-78</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm) median</td>
<td>69</td>
<td>72</td>
<td>74</td>
<td>76</td>
<td>86</td>
<td>.0001</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>60-79</td>
<td>63-82</td>
<td>64-84</td>
<td>68-86</td>
<td>76-100</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg) median</td>
<td>140</td>
<td>136</td>
<td>135</td>
<td>130</td>
<td>125</td>
<td>.0001</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>127-151</td>
<td>120-150</td>
<td>120-150</td>
<td>120-150</td>
<td>110-140</td>
<td></td>
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<tr>
<td>HTN (%)</td>
<td>30.1</td>
<td>38.5</td>
<td>45.5</td>
<td>52.2</td>
<td>54.1</td>
<td>.0001</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>15.5</td>
<td>19.0</td>
<td>19.5</td>
<td>18.8</td>
<td>17.8</td>
<td>.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>7.5</td>
<td>12.7</td>
<td>16.0</td>
<td>19.2</td>
<td>20.3</td>
<td>.0001</td>
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<tr>
<td>Prior MI (%)</td>
<td>7.9</td>
<td>10.2</td>
<td>12.7</td>
<td>14.5</td>
<td>20.3</td>
<td>.0001</td>
</tr>
<tr>
<td>Anterior infarct (%)</td>
<td>40.8</td>
<td>41.3</td>
<td>44.1</td>
<td>45.3</td>
<td>52.4</td>
<td>.0001</td>
</tr>
<tr>
<td>CrCl (mL/min) median</td>
<td>108.5</td>
<td>95.0</td>
<td>82.6</td>
<td>70.3</td>
<td>58.7</td>
<td>.0001</td>
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<tr>
<td>Interquartile range</td>
<td>90.9-131.5</td>
<td>78.9-114.8</td>
<td>66.8-101.5</td>
<td>57.1-86.4</td>
<td>46.2-72.9</td>
<td></td>
</tr>
<tr>
<td>Killip class (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>3.0</td>
<td>.0001</td>
</tr>
<tr>
<td>II</td>
<td>5.2</td>
<td>7.0</td>
<td>8.8</td>
<td>11.7</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>Time from symptoms to lysis (h) median</td>
<td>2.8</td>
<td>2.9</td>
<td>3.1</td>
<td>3.3</td>
<td>3.5</td>
<td>.0001</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2.0-4.0</td>
<td>2.0-4.1</td>
<td>2.2-4.3</td>
<td>2.3-4.5</td>
<td>2.4-4.6</td>
<td></td>
</tr>
</tbody>
</table>

*TIMI = Thrombolysis in Myocardial Infarction; CrCl = creatinine clearance; HTN = hypertension; MI = myocardial infarction; SBP = systolic blood pressure. Data are presented as the percentage of subjects or median value with interquartile range.*
incidence of nonfatal heart failure or shock was 0.4% to 4.4% ($P < .0001$, c-statistic 0.69). In contrast, the TRI was not associated with the risk of nonfatal myocardial infarction (3.2% to 3.5%, $P = .12$, c-statistic 0.52) and showed statistically significant but weakened discrimination with respect to the safety end point: TIMI major bleeding (0.9%-2.4%, $P < .0001$, c-statistic 0.60).

### Treatment Effect

When stratified by the TRI at presentation, the relative reduction of death or myocardial infarction with the enoxaparin strategy showed an inversely graded pattern with the TRI (Figure 3). In the 2 lowest TRI groups, the enoxaparin strategy reduced the risk of death and myocardial infarction by 38% and 44%, respectively, compared with unfractionated heparin, whereas there was a reduction in the relative benefit with increasing risk index ($P$ interaction < .01), with a 0% risk reduction in the highest risk group. Although the relative risk reduction showed an inverse relationship with TRI, the absolute risk difference between treatment arms was more consistent across TRI groups (range 1.6%-3.3%), with the exception of group 5 in which no difference was observed. We also evaluated the possibility that the relative decrease in the benefit of enoxaparin with higher TRI was related to a predominance in the higher risk groups of patients aged more than 75 years, in whom the protocol required a reduction in the dose of enoxaparin. However, the pattern of greater efficacy in low-risk groups persisted after excluding patients for whom a dose-reduction in enoxaparin was directed by the protocol. The net clinical benefit (death/myocardial infarction/TIMI major bleed) showed a similar inversely graded pattern when stratified by the TRI ($P$ interaction < .01). There was a 35% risk reduction with the enoxaparin strategy compared with the unfractionated heparin strategy in group 1 (relative risk [RR] 0.65, 95% CI 0.53-0.81).

### Table 2 Relationship Between TIMI Risk Index and Outcomes at 30 Days (%)

<table>
<thead>
<tr>
<th>TIMI Risk Index Group</th>
<th>1 N = 3445</th>
<th>2 N = 4654</th>
<th>3 N = 4067</th>
<th>4 N = 4126</th>
<th>5 N = 3649</th>
<th>Group 5 vs 1</th>
<th>$P$ Trend</th>
<th>c-Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.2</td>
<td>2.3</td>
<td>3.8</td>
<td>8.9</td>
<td>20.8</td>
<td>17.3</td>
<td>&lt;.0001</td>
<td>0.78</td>
</tr>
<tr>
<td>Nonfatal and fatal MI</td>
<td>3.3</td>
<td>3.7</td>
<td>3.9</td>
<td>5.1</td>
<td>4.9</td>
<td>1.5</td>
<td>&lt;.0001</td>
<td>0.54</td>
</tr>
<tr>
<td>CHF or shock</td>
<td>0.9</td>
<td>2.0</td>
<td>3.0</td>
<td>6.4</td>
<td>14.4</td>
<td>16</td>
<td>&lt;.0001</td>
<td>0.76</td>
</tr>
<tr>
<td>CHF or shock (nonfatal)</td>
<td>0.4</td>
<td>1.2</td>
<td>1.5</td>
<td>2.7</td>
<td>4.4</td>
<td>11</td>
<td>&lt;.0001</td>
<td>0.69</td>
</tr>
<tr>
<td>Death/MI</td>
<td>4.4</td>
<td>5.9</td>
<td>7.5</td>
<td>13.5</td>
<td>24.2</td>
<td>5.5</td>
<td>&lt;.0001</td>
<td>0.70</td>
</tr>
<tr>
<td>Death/MI/CHF or shock</td>
<td>4.7</td>
<td>7.0</td>
<td>8.8</td>
<td>15.8</td>
<td>28.3</td>
<td>6.0</td>
<td>&lt;.0001</td>
<td>0.70</td>
</tr>
<tr>
<td>TIMI major bleeding*</td>
<td>0.9</td>
<td>1.2</td>
<td>1.7</td>
<td>2.3</td>
<td>2.4</td>
<td>2.7</td>
<td>&lt;.0001</td>
<td>0.60</td>
</tr>
<tr>
<td>Death/MI/TIMI major bleeding</td>
<td>5.0</td>
<td>6.6</td>
<td>8.6</td>
<td>14.5</td>
<td>25.3</td>
<td>5.1</td>
<td>&lt;.0001</td>
<td>0.69</td>
</tr>
</tbody>
</table>

**Notes:**
- TIMI = Thrombolysis in Myocardial Infarction; CHF = congestive heart failure; MI = myocardial infarction.
- Data are presented as percentage of subjects.
- *Limited to the prespecified safety cohort for the trial (as-treated analysis).

**Figure 2** TIMI risk index versus cause of death. Data are presented as a proportion of the total number of deaths in each risk index group. “Other” causes of death include cancer, nonhemorrhagic stroke, other cardiovascular, pulmonary embolism, respiratory failure, revascularization (percutaneous coronary intervention or coronary artery bypass graft), other, and unknown. TIMI = Thrombolysis in Myocardial Infarction; MI = myocardial infarction; RI = recurrent ischemia; CHF = congestive heart failure.

**Figure 3** Treatment effect on death or myocardial infarction at 30 days (%). Data are presented as a percentage of patients. RRR = relative risk reduction; ARD = absolute risk reduction; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.
confidence interval [CI], 0.48-0.88), a 39% risk reduction in group 2 (RR 0.61, 95% CI, 0.0.48-0.76), and a 0% risk reduction in group 5 (RR 1.00, 95% CI, 0.90-1.2). There was no group in which the rate of death or myocardial infarction was numerically higher with the enoxaparin strategy.

DISCUSSION
Risk stratification is a critical early step in evaluating patients with acute coronary syndrome and may be valuable in forecasting the potential for response to specific interventions. In a population of more than 19,000 patients with ST-elevation myocardial infarction in the ExTRACT-TIMI 25 trial, we confirmed that a previously described simple index based on age and vital signs performed well for the assessment of short-term risk of death. For the first time we analyzed the association of the TRI with specific causes of mortality and found that death from mechanical causes (heart failure, shock, ruptured myocardium) was significantly associated with increasing TRI. The TRI also was found to be strongly related to severe heart failure but not to recurrent myocardial infarction. The benefit of a strategy using enoxaparin was present in the 4 lowest TRI categories with no difference compared with unfractionated heparin in the highest risk group. This pattern may be explained, at least in part, by the new insight into the relationship between the TRI and the causes of death revealed in this study. Patients who present with a higher TRI are much more likely to die of heart failure, shock, or myocardial rupture and, therefore, may derive less benefit from a therapy targeted at reducing recurrent ischemia and infarction.

TIMI Risk Index and Cause of Death
The TRI has been shown to provide a convenient, practical tool with strong performance for the assessment of short-term mortality in patients with ST-elevation myocardial infarction both in clinical trials and a community registry that included patients with ST-elevation myocardial infarction and non-ST elevation acute coronary syndromes. The TRI is a simple and effective tool because it combines the 3 clinical predictors (age, heart rate, and systolic blood pressure) that have shown the strongest association with adverse outcomes in ST-elevation myocardial infarction in analyses of both clinical trials and community registries. Any paramedical or clinical personnel can assess these characteristics easily. We validated the performance of the TRI to rapidly assess mortality risk at initial presentation in the large, contemporary, internationally representative population of patients with ST-elevation myocardial infarction treated with fibrinolysis who were enrolled in ExTRACT-TIMI 25. Our observation that patients in higher risk index groups were more likely to die of heart failure, shock, and ventricular rupture support our previous mechanistic hypothesis that the relationship between the TRI and mortality is based on its reflection of underlying pump dysfunction. We recently showed a strong association between the TRI and the left ventricular ejection fraction after acute myocardial infarction, and in the present analysis we found that a higher TRI was associated with a longer time from symptom onset to fibrinolysis, as well as more frequent presentation with heart failure (higher Killip class) and anterior infarct location. We cannot exclude that knowledge of the components of the TRI (age, heart rate, and systolic blood pressure) could influence the categorization of cause of death. Previous data were obtained before treatment allocation, and all deaths were investigator adjudicated with a review of source documents by a monitor. Validation in a community setting of the new observations regarding the relationship between the TRI and nonfatal outcomes, as well as cause of death, would be valuable in assessing the ability to generalize our findings from a clinical trial. Moreover, although a randomized clinical trial provides the optimal comparison of 2 interventions, such as the enoxaparin and unfractionated heparin strategies, it is important to recognize that the overall lower risk (eg, younger age) of a population enrolled in a clinical trial may affect the ability to generalize the findings to the general community.

Implications for Treatment
The inverse relationship between the TRI and the relative efficacy of the enoxaparin strategy seems unexpected in that it is counter to the more common observation of increasing benefit of more potent or aggressive therapy among patients with acute coronary syndrome at higher risk for recurrent events. However, this pattern may be explained in part by our findings regarding the causes of death within each risk group. Patients with a higher TRI have clinical evidence of and risk factors for larger, completed, more frequently anterior infarctions, manifested with a higher incidence of heart failure at presentation. Such patients are at highest risk for mechanical complications and are more likely to die of heart failure and shock than of reinfarction. This concept is illustrated by an analogous pattern in patients presenting with non–ST-elevation myocardial infarction, among whom higher concentrations of troponin T are associated with increasing mortality; however, the highest rates of recurrent myocardial infarction occur in patients with low-level increases in the concentration of troponin T. Similarly, in our present study of patients with ST-segment elevation myocardial infarction, among patients in the lowest TRI group (Table 3), recurrent myocardial infarction was the most frequent complication; in contrast, deaths due to events other than myocardial infarction predominated the complications in the highest TRI group. Because the enoxaparin strategy principally reduces recurrent ischemia and infarction in patients with ST-elevation myocardial infarction, it is not surprising that we observed no difference in efficacy compared with unfractionated heparin in this subgroup at highest risk for mechanical complications and lower risk for recurrent myocardial infarction. In contrast, patients in TRI groups 1 to 4, who constitute a large majority of patients with ST-elevation myocardial infarction, have a substantially lower risk of death due to mechanical
complications, but nonfatal reinfarction and death due to recurrent ischemic complications are more important in them. These patients plausibly have the most to gain from a treatment that reduces reinfarction, such as with a strategy using enoxaparin.

CONCLUSION
The TRI is a powerful tool for risk assessment in patients presenting with ST-elevation myocardial infarction. We found the TRI to be a strong predictor of all-cause mortality in a broad multinational population, with a particular positive association to the risk of death due to mechanical complications and an inverse association to deaths due to recurrent ischemic events. A strategy using enoxaparin was associated with greater benefit than unfractionated heparin in a majority of patients with ST-elevation myocardial infarction, except for the group at the highest risk for severe mechanical complications, in whom the 2 anticoagulant strategies showed similar results.

References
ABSTRACT

BACKGROUND: Transferrin saturation is widely considered the preferred screening test for hemochromatosis. Unsaturated iron-binding capacity has similar performance at lower cost. However, the within-person biological variability of both these tests may limit their ability at commonly used cut points to detect HFE C282Y homozygous patients.

METHODS: The Hemochromatosis and Iron Overload Screening Study screened 101,168 primary care participants for iron overload using transferrin saturation, unsaturated iron-binding capacity, ferritin, and HFE C282Y and H63D genotyping. Transferrin saturation and unsaturated iron-binding capacity were performed at initial screening and again when selected participants and controls returned for a clinical examination several months later. A missed case was defined as a C282Y homozygote who had transferrin saturation below the cut point (45% for women, 50% for men) or unsaturated iron-binding capacity above the cut point (150 μmol/L for women, 125 μmol/L for men) at the initial screening or the clinical examination, or both, regardless of serum ferritin.

RESULTS: There were 209 C282Y previously undiagnosed homozygotes with transferrin saturation and unsaturated iron-binding capacity testing performed at the initial screening and clinical examination. Sixty-eight C282Y homozygotes (33%) would have been missed at these transferrin saturation cut points (19 men, 49 women; median serum ferritin level of 170 μg/L; first and third quartiles, 50 and 474 μg/L), and 58 homozygotes (28%) would have been missed at the unsaturated iron-binding capacity cut points (20 men, 38 women; median serum ferritin level of 168 μg/L; first and third quartiles, 38 and 454 μg/L). There was no advantage to using fasting samples.

CONCLUSIONS: The within-person biological variability of transferrin saturation and unsaturated iron-binding capacity limits their usefulness as an initial screening test for expressing C282Y homozygotes. © 2007 Elsevier Inc. All rights reserved.
The diagnosis of hemochromatosis was previously based on a combined clinical and laboratory assessment that included history and physical examination, elevated transferrin saturation and serum ferritin, liver biopsy, iron removed by phlebotomy, and pedigree studies identifying other family members with iron overload. Since the discovery of the hemochromatosis gene (HFE) in 1996, most studies from referral centers have shown that more than 90% of typical patients with hemochromatosis are homozygous for the C282Y mutation of the HFE gene. Before DNA-based testing, it was assumed that most patients with hemochromatosis have elevated transferrin saturation. However, population screening studies have shown that many C282Y homozygotes have a normal transferrin saturation and may never develop clinical signs and symptoms related to iron overload. Transferrin saturation has been recommended in many studies to be the ideal screening test for hemochromatosis because it is widely available and may be increased even in young adults with a genetic predisposition to hemochromatosis. It has been suggested that transferrin saturation is preferable to DNA-based testing as an initial screening test because it might detect other types of iron overload in addition to those associated with HFE mutations and iron deficiency. Screening for iron overload with transferrin saturation might reduce the risks of potential genetic discrimination that some authors suggest is associated with identification of a C282Y homozygote with normal serum iron test results. Important characteristics of a screening test are its reproducibility over time and diagnostic sensitivity.

In this study, we sought to determine the variability of transferrin saturation and unsaturated iron-binding capacity, as well as the impact on their use as a practical and sensitive screening test for hemochromatosis.

CLINICAL SIGNIFICANCE

- Most typical patients with hemochromatosis are homozygous for the HFE C282Y allele, but not all C282Y homozygotes exhibit clinical symptoms.
- Within-person biological variability in transferrin saturation and unsaturated iron-binding capacity limits the utility of these tests for hemochromatosis screening.
- Fasting does not affect the sensitivity, specificity, or variability of either test.
- With clinically relevant cutoff points, these 2 tests fail to identify one third of C282Y homozygotes.

METHODS AND MATERIALS

The study design and overall results of the Hemochromatosis and Iron Overload Screening (HEIRS) study have been reported. Participants were recruited from 5 field centers that serve ethnically and socioeconomically diverse populations. The study was approved by all local institutional review boards and recruited all participants aged 25 years or more who gave informed consent. All participants underwent random testing for serum unsaturated iron-binding capacity, serum iron, and serum ferritin (without intentional fasting), and were genotyped for the C282Y and H63D mutations of the HFE gene. In this analysis, participants who reported a previous diagnosis of hemochromatosis or iron overload (treated or untreated) were excluded because of the potential effects of phlebotomy or other interventions on the serum transferrin saturation and unsaturated iron-binding capacity.

Transferrin saturation was calculated using the serum iron/(serum iron + unsaturated iron-binding capacity) and expressed as a percentage. Serum iron and unsaturated iron-binding capacity were measured using a ferrozine-based colorimetric assay (Hitachi 917 analyzer, Roche Diagnostics/Boehringer Mannheim Corp., Indianapolis, Ind). Initial transferrin saturation samples from field centers located in the United States were tested at the University of Minnesota Medical Center, Fairview, Minneapolis, Minnesota, and those from London, Ontario, were tested at MDS Laboratory Services, Toronto, Canada. Initial samples from Toronto, Ontario (n = 2000) and all follow-up Canadian samples were tested in Minneapolis. Method biases were assessed 3 times yearly using external proficiency testing samples provided by the College of American Pathologists Surveys (Northfield, Ill) and using blind replicate samples that were collected from 2% of all participants and analyzed in both laboratories. In addition, comparisons between the MDS Laboratory Services and the Central Laboratory were conducted before starting the testing, and 2% of the MDS samples were repeated at the Central Laboratory throughout the study. Internal quality control pools at normal and high iron levels were included with each analytic batch, and methods were calibrated using Roche calibrator materials and instructions (Roche Diagnostics/Boehringer Mannheim Corp.).

HFE C282Y and H63D were detected in DNA obtained from whole-blood EDTA samples using a modification of the Invader assay (Third Wave Technologies, Madison, Wis) that increases the allele-specific fluorescent signal by including 12 cycles of locus-specific polymerase chain reaction before the cleavage reaction. Transferrin saturation and unsaturated iron-binding capacity were performed at the initial screening and again when selected participants and controls returned for a clinical examination several months later. Clinical examinations were performed on participants with elevated transferrin saturation and ferritin, all C282Y homozygotes, and control participants (matched for age, gender, and race) without HFE mutations and normal transferrin saturation and ferritin (n = 2285). Initial screening specimens were
obtained randomly throughout the day (i.e., without intentional fasting); samples for transferrin saturation and unsaturated iron-binding capacity measurements at clinical examination were obtained after fasting (mean time since last meal, 13 hours). This study represents modeling based on the HEIRS Study data; the actual cut points and detection of C282Y homozygotes have been reported.14

At cut points for transferrin saturation and unsaturated iron-binding capacity (transferrin saturation $\geq 45\%$ for women, $\geq 50\%$ for men, unsaturated iron-binding capacity is $<150$ $\mu$mol/L in women, $<125$ $\mu$mol/L% in men), the potential number of missed C282Y homozygotes was modeled at the initial screening and the clinical examination. A missed case was defined as a C282Y homozygote who had transferrin saturation below the cut point or unsaturated iron-binding capacity above the cut point at either the initial screening or the clinical examination, or both, regardless of serum ferritin. This assumes that for an ideal screening test,
a case will have a positive test result at the time of each test, and a non-case will have a negative test result at the time of each test. Missed cases were expressed as patients missed divided by the total number of patients, rather than total number of tests.

Control participants for the clinical examination had neither C282Y or H63D HFE mutations detected and a transferrin saturation between the 25th and 75th percentile. These selection criteria for the controls result in an apparent “gap” in the transferrin saturation distribution of approximately 40% (Figure 1).

Fasting and nonfasting samples were compared using receiver operating characteristic curve analysis and comparisons of area under the curve.

**RESULTS**

The HEIRS Study recruited 101,168 participants from February of 2001 to February of 2003. There were 1261 participants (97 C282Y homozygotes) excluded from this analysis (1216 had a previous diagnosis of hemochromatosis or iron overload, and 45 had a missing unsaturated iron-binding capacity). There were 236 undiagnosed C282Y homozygotes in this analysis (91 men and 145 women). Non-C282Y homozygotes included 37,04 men and 62,667 women. The median age of all participants in this study was 50 years (range 25-100 years). By self-identified race/ethnicity, the sample included whites (44%), African Americans (27%), Asians (13%), Hispanics (13%), Pacific Island-

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**Table 1**  
Effect of Fasting on Detection of C282Y Homozygotes by Transferrin Saturation and Unsaturated Iron-Binding Capacity

<table>
<thead>
<tr>
<th></th>
<th>Non-homozygote</th>
<th>C282Y homozygote</th>
<th>Sensitivity (%), 95% CI</th>
<th>Specificity (%), 95% CI</th>
<th>PPV (%), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting TS normal</td>
<td>29495</td>
<td>16</td>
<td>76.8 (64.8-85.8)</td>
<td>92.8 (92.5-93.0)</td>
<td>2.3 (1.7-3.0)</td>
</tr>
<tr>
<td>Fasting TS elevated*</td>
<td>2301</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting UIBC normal</td>
<td>29994</td>
<td>14</td>
<td>79.7 (68.0-88.1)</td>
<td>94.3 (94.1-94.6)</td>
<td>3.0 (2.3-3.9)</td>
</tr>
<tr>
<td>Fasting UIBC decreased†</td>
<td>1802</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfasting TS normal</td>
<td>60895</td>
<td>40</td>
<td>74.8 (67.2-81.2)</td>
<td>94.8 (94.6-95.0)</td>
<td>3.5 (2.9-4.1)</td>
</tr>
<tr>
<td>Nonfasting TS elevated</td>
<td>3335</td>
<td>119</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfasting UIBC normal</td>
<td>61281</td>
<td>33</td>
<td>79.3 (71.9-85.1)</td>
<td>95.4 (95.2-95.6)</td>
<td>4.1 (3.4-4.9)</td>
</tr>
<tr>
<td>Nonfasting UIBC decreased†</td>
<td>2949</td>
<td>126</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPV = positive predictive value for detecting a C282Y homozygote; TS = transferrin saturation; UIBC = unsaturated iron-binding capacity; CI = confidence interval.

Fasting refers to a blood sample drawn at least 8 hours after eating. Participants with missing values for “hours since last food” were excluded.

*An elevated TS is >45% in women and >50% in men.
†A decreased UIBC is <150 μmol/L in women and <125 μmol/L in men.
ers (0.7%), Native Americans (0.7%), and those of mixed or unknown race (2%). Ninety-four percent of the C282Y homozygotes were white. There were 5 Hispanic and 3 African American C282Y homozygotes. An elevated serum ferritin level was found in 86% of the male C282Y homozygotes (>300 μg/L) and in 58% of the female homozygotes (>200 μg/L).

Analytic variation estimated from a sample of blind replicates at the initial screening visit comprised 1.3% of the total variation in transferrin saturation and 4.4% of the total variation in unsaturated iron-binding capacity, and the correlation between replicates was 0.98 for transferrin saturation and 0.99 for unsaturated iron-binding capacity. Figures 1 and 2 display substantial variability from the initial screening to clinical examination visit among both C282Y homozygotes and non-C282Y homozygotes. Because the analytic variability is a small percentage, the observed visit-to-visit variability is primarily within-person biological variability. The correlation between initial screening and examination visit values among non-C282Y homozygote men was 0.47 for transferrin saturation and 0.58 for unsaturated iron-binding capacity; the corresponding values for C282Y homozygote men were 0.62 and 0.49, respectively. The results for women and estimates from the subset who were fasting at both visits were similar.

There were 209 previously undiagnosed C282Y homozygotes with transferrin saturation and unsaturated iron-binding capacity testing performed at the initial screening and the clinical examination (Figures 1 and 2). The number of missed homozygotes at a clinically relevant cut point for transferrin saturation and unsaturated iron-binding capacity was assessed (transferrin saturation >45% for women, transferrin saturation >50% for men, unsaturated iron-binding capacity <150 μmol/L for women, <125 μmol/L for men). Sixty-eight C282Y homozygotes (33%) would have been missed at these transferrin saturation cut points (19 men, 49 women; median serum ferritin level at initial screening = 170 μg/L; first and third quartiles, 50 and 474 μg/L), and 58 homozygotes (28%) would have been missed at the unsaturated iron-binding capacity cut points (20 men, 38 women; median serum ferritin level at initial screening = 168 μg/L; first and third quartiles, 38 and 454 μg/L). The percentage of missed homozygotes increases as the transferrin saturation cut point increases or the unsaturated iron-binding capacity cut point decreases (Figure 3). Forty-nine percent of transferrin saturation values increased and 55% of unsaturated iron-binding capacity values decreased with the second fasting sample.

A subanalysis was performed that excluded participants initially tested at MDS Laboratories to remove all interlaboratory variability. All of these participants underwent testing at the Minneapolis site (n = 126 homozygotes). In this subanalysis, the percentage of missed homozygotes by transferrin saturation (34%) and unsaturated iron-binding capacity testing (29%) did not differ from that of the larger sample (n = 199 homozygotes).

The random testing included 29,994 participants who provided fasting samples. The sensitivity and specificity of a fasting transferrin saturation and unsaturated iron-binding capacity (>8 h since eating) compared with a nonfasting transferrin saturation and unsaturated iron-binding capacity for the detection of C282Y homozygotes (>45% for women, >50% for men) are shown in Table 1. The receiver operating characteristic areas under the curve were compared for men and women using fasting and nonfasting samples. For men, the area under the curve was 0.96 (0.92-1.0, 95% confidence interval) for fasting samples and 0.93 (0.89-0.97) for nonfasting samples. For women, the area under the curve was 0.89 (0.83-0.95) for fasting samples and 0.91 (0.87-0.95) for nonfasting samples. There were no significant differences between fasting and nonfasting samples.

DISCUSSION

Many advisory documents on screening for hemochromatosis recommend that the initial screening test should be the transferrin saturation.6,10,15,16 This is based on the assumption that most iron-loaded patients with hemochromatosis will have elevated transferrin saturation. Screening with a phenotypic test will detect primarily iron-loaded cases requiring treatment regardless of genotype and also will detect iron deficiency. The initial studies on transferrin saturation were performed in tertiary referral centers, and subsequent population-based studies demonstrated a lower sensitivity of transferrin saturation for the detection of C282Y homozygotes.4,17 Furthermore, elevated transferrin saturation has often been embedded in the case definition, which does not allow for an independent evaluation. The unsaturated iron-binding capacity has been shown in population studies to be similar in screening performance to the transferrin saturation and can be performed at a lower cost.17 However, both of these tests are subject to analytic and biological variability, which limit their usefulness as screening tests for C282Y-linked hemochromatosis. In this study we demonstrated that at a clinically relevant cut point for transferrin saturation and unsaturated iron-binding capacity, initial phenotyping with transferrin saturation or unsaturated iron-binding capacity could miss approximately 30% of cases, and that 40% of these missed cases had an elevated ferritin. Therefore, it is not simply a matter of non-expressing cases being missed by phenotypic screening.

Within-person biological variability in iron tests has been described, and diurnal fluctuations have been described primarily for serum iron.18-22 Transferrin saturation is a calculated value determined from the serum iron divided by one of the following: total iron-binding capacity, unsaturated iron-binding capacity plus serum iron, or serum transferrin multiplied by a constant. The higher variability of transferrin saturation compared with unsaturated iron-binding capacity may be related to the fact that it is a 2-step test rather than the 1-step unsaturated iron-binding capacity test. It has been reported that
CONCLUSIONS

Both the transferrin saturation and unsaturated iron-binding capacity have significant within-person biological variation in C282Y homozygotes discovered through a primary care screening program. This limits their utility as ideal screening tests for HFE-associated hemochromatosis. Other screening approaches, such as HFE genotyping followed by measurement of serum ferritin, require further evaluation.

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References
CLINICAL COMMUNICATION TO THE EDITOR

Dose Conversions: Opportunity for Error

To the Editor:

Most medication errors occur at the ordering stage and are largely preventable.¹ We report a “near miss” in our hospital that would have almost certainly resulted in harm to our patient if it remained undetected. Our 86-year-old patient was admitted to the hospital for repair of a fractured hip. Her medical history included established osteoporosis, hypertension, and transient ischemic attack. She was unable to swallow and her treating surgeon switched all of her oral medications to an alternative route. Unfortunately, the surgeon also changed metoprolol 50 mg orally twice a day to 50 mg intravenously (IV) twice a day. The pharmacy department was contacted to deliver the IV metoprolol because the orthopedic ward did not normally stock this. The pharmacist noticed the error after a pharmacy technician realized that there was not a 50 mg metoprolol ampule available and sought advice from the pharmacist on how to deal with the request. The prescriber was then contacted and alerted to the error. The surgeon was not aware that there was a need to convert the oral dose to a different IV dose (metoprolol 5 mg IV twice daily would have been an appropriate dose).

Steps are needed to be taken to ensure any potential errors are minimized as much as possible. For example, electronic prescribing systems may assist in preventing similar errors by alerting the prescriber before the order can be processed. In addition, pharmacists on the hospital wards who prescribers can consult easily may assist in preventing errors at the ordering stage. A large observational study by Bond et al² identified that clinical pharmacy services in hospitals are associated with improvement in mortality, drug costs, cost of care, and length of stay. Bond et al³ also reported lower medication error rates as the number of clinical pharmacists increased per occupied bed.

Kaboli et al⁴ recently reviewed the literature from the last 20 years and concluded that the addition of clinical pharmacist services in the care of inpatients generally resulted in improved care, with no evidence of harm.

Most 10-fold errors seem to occur due to misplaced decimal points, for example, adding an extra zero.⁵ Our case involving a 10-fold error should alert doctors for the need to be vigilant when converting oral administration to alternative routes. In addition, it is prudent for prescribers to have their prescriptions checked, preferably by a pharmacist. Fortunately, in our case any likely harm was averted.

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CLINICAL COMMUNICATION TO THE EDITOR

A ‘Natural’ Threat

To the Editor:

The use of herbal/alternative medicine has been on the rise in the United States. Red yeast rice supplement (Cholestin, Pharmanex, Provo, Utah) has been marketed to lower cholesterol, but its side effects have not been well documented. We are reporting a case of myositis caused by Cholestin.

CASE REPORT

A 46-year-old Mexican man with hyperlipidemia presented with progressive muscle pain and generalized weakness for 3 weeks. He had been taking Cholestin for 6 weeks before presentation. He denied illegal drug use and alcohol abuse. He had symmetric muscle weakness (motor strength, 4/5 in biceps, triceps, and quadriceps); the muscles were not tender to palpation. Laboratory studies showed a creatine phosphokinase of 866 IU/L (normal range 30-160), aldolase of 34 IU/L (normal range 0-6), and aspartate aminotransferase of 66 IU/L (normal range 10-35). Complete blood count, basic metabolic panel, alanine aminotransferase, thyroid functions, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and anti-Jo antibodies were unremarkable. He was advised to discontinue Cholestin, and at the 2-week follow-up, his symptoms of muscle pain and weakness had completely resolved. Repeat creatine phosphokinase and aldolase were 43 IU/L and 4 IU/L, respectively. He was diagnosed with myositis caused by Cholestin (red yeast rice supplement).

DISCUSSION

Red yeast rice as a food flavoring and coloring agent has been an ingredient in Asian cuisine since 800 of the common era. Traditionally, it was prepared by fermenting cooked white rice with red yeast (Monascus purpureus). Lovastatin (mevinolin) was isolated from Aspergillus terreus by Alberts (at Merck, Whitehouse Station, NJ) in November 1978. In February 1979, Endo (in Japan) isolated lovastatin analogue from Monascus yeast and named it “monakolin K.” Later that year, lovastatin and monakolin K were determined to be the same compound, and soon thereafter, the United States Patent Office granted Merck a patent for lovastatin.

On the basis of Endo’s discovery, Cholestin was subsequently marketed by Pharmanex, a supplement company in California. Several studies showed the benefits of Cholestin in decreasing low-density lipoprotein cholesterol complex levels. A multicenter clinical trial showed that subjects who received Cholestin had a statistically significant decrease in total cholesterol and low-density lipoprotein cholesterol complex levels at 4 and 8 weeks of treatment when compared with controls ($P < .001$). No important clinical adverse events were reported in this trial. Specifically, there was no mention of myopathy/myositis, although a mean...
increase in creatine phosphokinase levels of 46% in the Cholestin-treated group was noted.

An exhaustive literature review disclosed 1 case of rhabdomyolysis in a patient receiving chronic hemodialysis and 1 case of myositis in a patient who was taking red yeast rice supplement. In 1998, the Food and Drug Administration concluded that because Cholestin is identical to lovastatin, it is, in fact, an unapproved drug, not a nutritional supplement, under the terms of the Dietary Supplement Health and Education Act. Cholestin was banned from the US market in 2001. Nevertheless, it is still readily available in other countries and the United States through purchase over the Internet.

Our case reminds the reader that Cholestin and other red yeast rice supplements are chemically related, or identical to lovastatin, and whatever complications may be seen with lovastatin may also result from their use. With increasing availability of herbal and supplemental medicines, primary care providers should elicit information about the use of such drugs and be aware of their potential side effects.

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Laughter-Induced Syncope: No Laughing Matter

To the Editor:

Laugh-induced syncope has been described rarely in the literature. We present a case of a 29-year-old previously healthy man who had witnessed a coworker trip and hit his head on the sink at approximately 10 A.M. He subsequently went into a severe fit of uncontrollable laughter that involved leaning forward and crouching down, at which point he began to feel light-headed and dizzy. He collapsed for 3 seconds with definite loss of consciousness and nonspecific arm twitching. He regained consciousness within those 3 seconds and was oriented properly and prepared to resume his work duties. Staff nearby who had witnessed the event immediately found his blood pressure to be 109/60 mm Hg with a heart rate of 96 beats/min. He was sent to the emergency department, and electrolyte, blood glucose, complete blood count, electrocardiogram, and echocardiogram testing results were normal. The tilt-table testing result was positive for neurocardiogenic syncope.

This is the third described case of laughter-induced syncope. The first case, in 1997, was a 62-year-old patient who had multiple episodes of syncope while laughing and watching Seinfeld on television.1 This clinical syndrome was thereby given the eponym of “Seinfeld syncope.” However, this patient had significant cardiovascular disease, including hypertension, prior coronary artery bypass grafting, and carotid disease. A second case was reported in 2005 in a healthy 32-year-old barber who heard a very funny story from a client.2 However, this patient had no demonstrable cardiovascular disease and normal laboratory results, similar to our patient.

Laughter-induced syncope is similar to other causes of vasovagal syncope, such as cough, micturition, defecation, and Valsalva-induced syncope. There is an increase in intrathoracic pressure that causes an exaggerated response of the autonomic nervous system. Increased parasympathetic stimulation coupled with decreased sympathetic tone result in a decrease in heart rate, blood pressure, and cardiac output, which in turn causes global hypoperfusion and a transient decrease in cerebral hypoperfusion. Symptoms usually improve in a matter of seconds.

Vagally mediated syncope is a benign diagnosis. Most patients have decreased symptoms over time.3 This may be associated to pharmacologic treatment or improved recognition of prodromal symptoms and lifestyle modifications.

Conservative treatment of vagally mediated syncope involves recognition of prodromal and maneuvers to abort attacks. Avoidance of precipitating factors, such as prolonged standing, rapid postural changes, and excessive alcohol intake, should be emphasized. Liberalization of salt and fluid intake coupled with compression stockings also decrease events. Discontinuation of vasodilators also may decrease episodes of syncope.

Pharmacologic treatment of vagally mediated syncope primarily involves initiation of beta-blockers. Their primary effect is in the reduction of myocardial contractility, which prevents the stimulation of the C fibers in the heart and the Bezold-Jarisch-type reflex that occurs. Beta-blockers also may decrease circulating catecholamines that are found in patients who develop syncope.4

Laughter-induced syncope or vagally mediated syncope is a benign disorder. Conservative therapy, including patient education, discontinuation of potentially offending medications, and treatment with beta-blockers, is the preferred initial therapeutic intervention.

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Myocardial Infarction After Oral Sumatriptan Use in a Woman with Normal Coronary Arteries

To the Editor:

Sumatriptan is an agonist of 5-hydroxytryptamine type 1 (5-HT1) receptors that is widely used in the treatment of migraine. It improves migrainous symptoms through intracranial vasoconstriction, mediated by inhibition of neuroinflammatory peptide release.1 5-HT1 receptors also are found within coronary vessels, and a modest vasoconstrictor effect of sumatriptan has been demonstrated during coronary angiography.2 The clinical significance of this effect is uncertain. Sumatriptan and other 5-HT1 receptor agonists cause a sensation of chest tightness without electrocardiographic abnormalities in 3% to 5% of patients,3 and more rarely might provoke myocardial ischemia4 or cardiac dysrhythmia.5

Transmural myocardial infarction after triptan use is rare, and in all reported cases to date,6-8 it has occurred after parenteral administration or in patients with atheromatous coronary artery disease. We report a case of transmural myocardial infarction after oral sumatriptan use in a woman with angiographically normal epicardial coronary arteries.

CASE REPORT

A 50-year-old woman presented acutely with onset of severe retrosternal chest pain approximately 1 hour after oral ingestion of 100 mg sumatriptan for presumed migraine. A smoker with a long history of migraine (treated successfully on 2 previous occasions with oral sumatriptan), the patient had presented 4 days earlier to the same hospital with a severe occipital headache. A clinical diagnosis of migraine was made at that time after normal computed tomography brain scan findings and prompt resolution of the headache with simple analgesia. Lumbar puncture had not been performed.

The electrocardiogram on readmission revealed an acute anterior ST-elevation myocardial infarction. The presence of headache delayed the decision to thrombolize. By the time the patient had been referred to a tertiary center for consideration of primary angioplasty, her symptoms had settled. She had reperfused electrocardiographically, with a resultant Q-wave anterior myocardial infarction. Subsequent troponin I estimation was greater than 100 μg/L, and transthoracic echocardiography revealed a dilated, severely impaired left ventricle with an akinetic, aneurysmal, anteropapical segment (Figure 1).

Early outpatient coronary angiography revealed a right-dominant, normal epicardial coronary arterial system (Figure 2). The patient was treated with standard secondary preventive therapies and advised to permanently avoid triptan use.

DISCUSSION

To our knowledge this is the first report of myocardial infarction after oral triptan use in a patient with normal coronary arteries. Earlier reports have described triptan-related myocardial infarction in the context of atheromatous coronary artery disease,6 after parenteral triptan use,7 or vasospastic disease.8

Patients with coronary artery disease may be more susceptible to the vasomotor effect of sumatriptan and related drugs through increased expression of coronary hydroxytryptamine receptors,2 and triptan therapy is not recommended in these individuals. Our case suggests that normal cardiac evaluation does not guarantee safety. A small and unpredictable risk of serious cardiac effects exists even in the absence of vascular disease. Although nonspecific chest discomfort is frequently encountered in the context of triptan use, this case emphasizes the importance of rigorous evaluation of cardiac symptoms in such patients.

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References


Figure 1 Transthoracic echocardiogram showing apical 2-chamber view at (a) end diastole and (b) end systole. Akinesis of the anterior wall is noted; the contractility of the inferior wall is normal.

Figure 2 Diagnostic coronary angiogram (right anterior oblique projection with cranial tilt) illustrating a normal left coronary system.
Anosmia Induced by Amiodarone

To the Editor:

Amiodarone is a potent antiarrhythmic agent for various cardiac arrhythmias. However, the use of amiodarone is limited due to its serious noncardiac adverse effects, including lung toxicity, thyroid dysfunction, corneal deposition, and so on. Peripheral neuropathy is one of the adverse effects, although minor.1 However, amiodarone-induced cranial neuropathy involving smell dysfunction is extremely rare. Here, we report a patient with arrhythmogenic right ventricular cardiomyopathy (ARVC) treated with amiodarone, which induced anosmia.

A 66-year-old man was referred for the treatment of ventricular tachycardia (VT), which was refractory to conventional antiarrhythmic agents and required DC countershock. After obtaining written informed consent, he underwent cardiac catheterization including an electrophysiologic study (EPS). Several days before catheterization, antiarrhythmic agents were discontinued for EPS, and, thereafter, VT was spontaneously documented. The finding of right ventriculography was compatible with ARVC, showing aneurysms in the right ventricular inflow and apical areas. Considering the induced VT to be polymorphic, radiofrequency catheter ablation was discontinued and amiodarone (400 mg/day) was administered. Approximately 3 years after starting the successful medication, he complained of olfactory disturbance. After reducing the maintenance dose of amiodarone from 200 to 100 mg/day, anosmia was partially resolved. Major adverse effects of amiodarone, such as lung toxicity and thyroid dysfunction, were not encountered. Ophthalmologists indicated no corneal deposition. Computed tomography indicated no particular abnormalities in the central nervous system including the olfactory brain.

Drug-induced anosmia is considered to be rare, and its exact prevalence and mechanisms remain to be elucidated. This is due to the lack of satisfactory diagnostic criteria and effective treatments of olfactory disturbance, and, moreover, the indifference of clinicians toward this disorder. The etiology of this olfactory disorder is either: binding abnormalities of odorant receptor, the loss of postreceptor transduction mechanisms, olfactory nerve inactivation via Na or Ca channel inhibition, or some combination of these effects.2 Amiodarone is known to be a lipophylic agent, with unique pharmacokinetics suppressing cardiac ion channels including Na, Ca, and various K channels,1 suggesting that it is accumulated in neuronal phospholipid membranes and influences various nervous activities. Considering that drugs postulated to cause anosmia include various cardioactive agents, such as nifedipine, metoprolol, diltiazem, and enalapril,3 this rare adverse effect, which is often neglected, should be taken into account in the long-term medication of patients with cardiac diseases.

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LETTER

Adult Learning Theory in Medical Education

To the Editor:

The recent article by Torre and colleagues1 on learning theories for medical educators was interesting and laid out a potential framework for educators to follow. However, they failed to mention the Adult Learning Theory, which has an important place in both graduate and undergraduate medical education. Although the humanist model they described covers this theory in part, it deserves a more detailed discussion.

The Adult Learning Theory has been in use for more than 2 decades, but more recently it has been used in academic models for teaching evidenced-based medicine.2-4 The goal of the Adult Learning theory is to develop skills for self-directed lifelong learning. The basic tenants of this theory are that adults learn best when they know why they need to learn something, they can use self-directed learning, the learning involves real-life situations (patients), and the stimulus for learning is internal rather than external.4 An ambulatory curriculum based on this theory was implemented for junior and senior medicine residents at a university-based internal medicine program and demonstrated it could increase evidenced-based medicine skills and behaviors.4

A recent Society of General Internal Medicine task force on improving resident education stressed that residency programs must prepare residents for lifelong learning by teaching them the skills to ask and answer questions that arise while taking care of patients.5 Although the theories outlined by Torre et al1 may help accomplish that goal, the Adult Learning Theory provides another proven approach that medical educators should be cognizant of and implement when possible.

Disclaimer: The views expressed are those of the authors and should not be construed to represent the positions of Walter Reed Army Medical Center, the Department of the Army, or the Department of Defense.

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References

LETTER

The Reply:

In his letter to *The American Journal of Medicine*, Hartzell responded to and critiqued our article, “Overview of Current Learning Theories for Medical Educators.” We welcome his critique and are pleased to have the opportunity to continue the discussion on learning theories applied to medical education.

We would like to respond to Hartzell’s points that our article did not mention adult learning theory and that adult learning theory might be a better approach to accomplishing the goal set by the Society of General Internal Medicine of preparing residents for lifelong learning.

In his letter, Hartzell seems to indicate that there is only 1 adult learning theory. We respectfully disagree with this assertion and point out that all of the learning orientations discussed in the article are part of adult learning theory. The point of our article was to say that there is no one grand theory that applies to all medical education situations. Rather, medical educators can draw on theories and concepts from multiple different learning orientations to enhance their practice. In addition, Hartzell cites Malcolm Knowles as the author of adult learning theory. Although Knowles is a well-known figure in the field of adult education, his work has been critiqued as being more of a description of the characteristics of adult learners rather than a theory of how adults learn. The work by Knowles does provide some insight into self-direction as a concept within the humanistic learning orientation, but it lacks an in-depth analysis of the concept of self-direction as a process or outcome. We chose to provide a broad analysis of multiple learning orientations based on the work of Merriam and coworkers, rather than a one size fits all approach as is sometimes attributed to Knowles.

Second, we agree with Hartzell’s statement, “that residency programs must prepare residents for life-long learning by teaching them the skills to ask and answer questions that arise while taking care of patients.” In our view, the only way to reach this goal is by incorporating a variety of teaching and learning practices into medical education. Learning to ask and answer questions, for example, is a skill that can be developed more fully through cognitive, constructivist, and social learning approaches in concert with the humanistic approach.

Finally, we agree with Hartzell that adults learn best when they know why they need to learn something, they can use self-directed learning, the learning involves real-life situations, and the stimulus for learning is internal. However, we believe that by combining behavioral, cognitive, social, constructivist, and humanistic approaches, medical educators can reach this goal more fully.

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LETTER

Comments Regarding “Pain and a Purple Lesion”

To the Editor:

The recent case report of *Clostridium septicum* necrotizing fasciitis (NF) published by Fragoulis et al.\(^1\) highlighted a number of important aspects of the clinical presentation, diagnosis, and treatment of NF, but several comments made by the authors deserve clarification. They correctly note that there are 2 broad categories of NF divided according to the microorganisms cultured from the involved tissues or bloodstream.\(^2\) Although Fragoulis et al suggest that type I NF involves anaerobic bacteria or non-Lancefield group A streptococci, the common definition is broader.\(^2\) Type I infections are polymicrobial, involving mixed aerobic or anaerobic bacteria. Type II NF describes cases involving group A \(\beta\)-hemolytic *Streptococcus* (GAS; *S. pyogenes*), either in a polymicrobial or monomicrobial setting. Monomicrobial clostridial NF, which often involves neighboring muscle tissue (ie, myositis), is generally considered as a distinct syndrome.\(^3\) Saltwater *Vibrio* spp., which also cause monomicrobial NF in susceptible patients, have also been considered a separate NF type.\(^4\)

In regard to management, Fragoulis et al\(^1\) note the importance of rapid surgical debridement of involved tissues, but their comments regarding medical management are oversimplified. Although the authors state that “Combination therapy with penicillin G (benzylpenicillin) and clindamycin is now the recommended treatment,” it is unclear whether they are referring specifically to clostridial disease or NF in general. According to recent guidelines for the diagnosis and management of skin and soft-tissue infections published by the Infectious Diseases Society of America,\(^3\) the combination of penicillin plus clindamycin is appropriate for established necrotizing clostridial infections or GAS infections. However, empiric therapy for patients presenting with evidence of NF should be broad, covering aerobic and anaerobic Gram-negative and Gram-positive pathogens.\(^3\) Clindamycin should be included in the initial management to treat both anaerobic bacteria and GAS because clindamycin may reduce disease severity in type II NF.\(^5\) An example of such a regimen, recommended in the recent guidelines, is ampicillin-sulbactam plus clindamycin plus ciprofloxacin.\(^3\) With the emergence of community-onset methicillin-resistant *Staphylococcus aureus* in cases of NF,\(^6\) empiric therapy might also include drugs targeted to this pathogen, although such a decision needs to be based on the local epidemiology of staphylococcal infections and drug susceptibility patterns. In regard to hyperbaric oxygen therapy, this treatment modality remains a controversial adjunct to the standard therapy for NF.\(^5\)

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doi:10.1016/j.ajmmed.2006.11.022

References

Conflict of interest statement for comments regarding “Pain and a Purple Lesion.” David M. Aronoff, MD, and Zuber D. Mulla, PhD, DMA, have received honoraria for speaking from AstraZeneca, Pfizer, and Merck. Z. D. M. has no conflicts.
The Reply:

We agree with the comment made by Aronoff et al that type I necrotizing fasciitis episodes are polymicrobial. In fact, we mentioned in our case report that Type I necrotizing fasciitis is a type of mixed infection, usually involving anaerobic bacteria (including *Clostridium* species) and streptococci other than Lancefield serogroup A.\(^1\) In addition, we agree with their comment regarding the empirical antimicrobial treatment of patients with necrotizing fasciitis, specifically that such treatment should be directed against a broad spectrum of microorganisms, covering both aerobic and anaerobic pathogens. Following this principle, our patient received broad-spectrum antimicrobial treatment, including meropenem.

Also, data regarding the evolving epidemic of community-acquired methicillin resistant *Staphylococcus aureus* (MRSA) infections in patients in various parts of the world combined with our own previous experience with such infections\(^2\) made us include linezolid in the initially administered empirical antimicrobial regimen when the diagnosis of necrotizing fasciitis was entertained. Finally, we agree with Aronoff et al that clindamycin is an important addition to penicillin for the treatment of patients with clostridial necrotizing fasciitis. We have been recommending\(^3\) the use of the combination of these antibiotics for patients with clostridial necrotizing fasciitis, because there also are supportive experimental data regarding *Clostridium perfringens* infections.

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References
Molluscum or a Mimic? Add *Penicillium marneffei*!

To the Editor:

Three issues discussed in the recently published case of disseminated cryptococcosis deserve a comment.¹

First, de Souza¹ listed microorganisms associated with cutaneous lesions in human immunodeficiency virus-positive patients but did not mention *Penicillium marneffei*, a dimorphic fungus endemic in Southeast Asia. Penicilliosis typically occurs late in the course of human immunodeficiency virus infection and is associated with skin lesions in up to 85% of patients. Second, the dosage of fluconazole should be 400 mg/d during the consolidation phase and 200 mg/d for secondary prophylaxis. Because of the high cryptococcal burden and the fungistatic activity of fluconazole, the use of low dosage should be strongly discouraged.

Finally, regarding the issue of discontinuation of antifungal therapy after highly active antiretroviral therapy-induced immune recovery, contrary to what de Souza says, a negative serum cryptococcal antigen is not specifically required. As shown in Table 1, in the studies so far published on discontinuation of secondary prophylaxis for cryptococcosis, approximately half of the patients had a positive serum cryptococcal antigen detectable in serum.²⁻¹⁰

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Section of Infectious and Tropical Diseases
University of Milan, Italy


References
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Serum Cryptococcal Antigen Detectable at Discontinuation: Positive/Total (%)</th>
<th>Median CD4/μL at Prophylaxis Discontinuation (Range)</th>
<th>Median Duration (mo) of HAART</th>
<th>Incidence per 100 Person/Years (95% CI)</th>
<th>Median Time (mo) of Follow-up</th>
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<td>0 (0-0.20)</td>
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</table>

Ag = antigen; HAART = highly active antiretroviral therapy; NR = not reported; OBS = observational study; RCT = randomized controlled trial; CI = confidence interval.

*Group of patients discontinuing prophylaxis (22 continued prophylaxis).

**Mean time.
LETTER

The Reply:

I thank Antinori for his pertinent comments. I agree that a negative serum cryptococcal antigen is not specifically required when discontinuing antifungal therapy after highly active antiretroviral therapy-induced immunorecovery. It has been shown that secondary prophylaxis can be discontinued in patients with an increase in CD4 counts greater than 100 cells/μL and an undetectable human immunodeficiency virus RNA level for at least 3 months and after 2 years of suppressive therapy.\(^1,2\) It is known that serum cryptococcal antigen is not helpful in management because changes in titer do not correlate with clinical response.\(^3,4\) However, a recent report showed that a serum cryptococcal antigen titer of 1:512 or greater at any time during follow-up was associated with a 3.5-fold increased rate of cryptococcosis relapse.\(^5\)

I also agree that the dose of fluconazole should be 400 to 800 mg per day during the consolidation phase and 200 to 400 mg per day for secondary prophylaxis in patients with normal renal function. However, this is not true in patients with a creatinine clearance of 50 mL/min or less, such as the one reported, when the dose should be reduced by 50%.\(^6\)

References


Chest Pain: Do Gestures Help in the Diagnosis?

To the Editor:

We read with interest the study by Marcus et al assessing the utility of gestures in patients with chest pain. It is indeed a thought-provoking study forcing us to reassess the validity of traditionally taught facts. However, there are a few points that we believe are worth pointing out.

Firstly, contrary to what the authors mention, a similar study was reported in the British Medical Journal in 1995. They studied 203 patients consecutively admitted to a Coronary Care Unit and recorded how they placed their hands on their chest to describe their chest pain—whether they had a clenched fist over the chest, a flat hand over the sternum, or both flat hands drawn from the center of the chest outwards. They then did a chart review a year later to find out how many of those patients actually had a cardiac cause for their pain. Their study reported that the designated hand movements had a sensitivity of 80%, specificity of 49%, a positive predictive value of 77%, and a negative predictive value of 53%.

Secondly, it is unclear from the author’s protocol when exactly the patients were interviewed, that is, whether they were interviewed in the emergency department or after the patients were moved to the medical floor. The authors do acknowledge that the interview was performed 1 day after the most recent episode of chest pain. In our experience as training physicians, we have noticed that the history we extract from the patient is substantially different from that extracted by an attending physician. Although this might just be our inexperience, it is possible that patients get biased when they are repeatedly asked the same questions, some of which may be leading. On an average, before the patient actually speaks to a cardiologist, he has narrated his story to at least 2 emergency physicians, a medicine resident, and perhaps 2 or 3 nurses. Angina, by definition, is diagnosed on history, making it difficult to accurately qualify this subjective parameter.

Finally, the authors mention that 2% of patients with unstable angina and myocardial infarctions are discharged erroneously from the hospital. Clearly, this is 2% too many and despite data to suggest the poor correlation of these signs with myocardial ischemia or infarction, physicians will find it difficult to discharge patients without adequate work-up if they describe their chest pain with gestures as described.

Nevertheless, we must commend the authors for their study. It reminds us of a phrase we were often told in medical school: “You are not here to worship what is already known, but to question it.”

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References
The Reply:

We thank Iyer and Mehta for their thoughtful comments regarding our study.\(^1\) We were indeed not aware of the article published in the *British Medical Journal* and appreciate their bringing this to light.\(^2\) It is interesting that the test characteristics for somewhat similar gestures appeared to be quite comparable to our findings. However, there are some important differences. First, they did not assess the “Pointing Sign” to exclude ischemic chest pain, which, in our study, yielded the best test characteristics. Second, although the general message was similar, the details of the methods and results are not provided, and, unlike our study, their primary outcome was not limited to an acute myocardial infarction (or elevated cardiac biomarkers such as creatinine kinase or troponin alone). Regardless, the 2 studies appear to agree that the test characteristics of the Levine and “Palm” Signs are suboptimal at best.

The patients in our study were interviewed at various times and at various places. As noted in the letter, on average this was 1 day after admission. The delay was simply related to the practical limitations of performing the study and, in general, the patient was interviewed by study personnel as soon as was feasible. Although we measured the time of interview since admission, we did not record exactly where the patient was at the time—as the inclusion criteria required that the patient be admitted for chest discomfort, the majority were interviewed on the wards. However, given intermittent bed shortages and emergency department “hold overs,” they were at times interviewed in the emergency department. We agree that previous interviews performed as part of the patients’ clinical care may have introduced some bias (potentially either away or toward the null hypothesis in this case).

Regarding the statement about the 2% of patients with unstable angina that are inappropriately discharged: we agree that these signs, including the “Pointing Sign,” should not be used alone in making the decision to admit or discharge a patient from the emergency department. However, we do hope that the findings of our study will help add to the growing evidence base involving the common history and physical examination, ideally providing some degree of meaningful guidance in incorporating data and judgment while practicing the art of medicine.

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doi:10.1016/j.amjmed.2007.03.018

Reference
Perioperative Cardiac Assessment of Orthopedic Surgery Patients

To the Editor:

We read with great interest the study by Salerno et al addressing the sometimes difficult issue of preoperative cardiac evaluation in the orthopedic surgery population. In our practice, it has been our experience that the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines often prove impractical in the evaluation of these patients. Both the poor functional capacity caused by joint disease and the urgent nature of surgery with hip fractures cited in the study limit the utility of the ACC/AHA approach.

Therefore, we were surprised to see the conclusion that the ACC/AHA guidelines accurately predict risk. In only 49% of the patients in whom testing was recommended was it actually performed. Aside from showing the difficulty applying the guidelines in practice, this makes it difficult to know exactly how well the ACC/AHA approach would have predicted risk because so many patients with intermediate predictors have their risk stratification tied to cardiac stress test results. If one is to rigidly apply the ACC/AHA methodology, a full 22% of patients would have required preoperative cardiac stress testing. By our calculations, the event rate in the population in whom further cardiac testing was indicated—by definition a high-risk group—was 8.1%. Compared with the overall event rate of 5.7% and the event rate of 4.9% in the group in whom testing was not indicated, this is a relatively marginal improvement. We believe the Revised Cardiac Risk Index (RCRI) has proven to be a superior tool for risk stratifying these patients, especially because of its lack of reliance on functional status. The data provided by Salerno et al bear this out. Only 7% of the patient population was in the high-risk category (≥2 risk factors) as defined by the RCRI. The RCRI proved to be a much better predictor of risk in its high-risk group, because the event rate in this group was approximately 23%. Further, the event rate in the low-risk groups (although higher than predicted in the original publication of the RCRI) was 4.5%, very similar to the low-risk group as defined by the ACC/AHA guidelines. We therefore think the ACC/AHA approach, in addition to being difficult to apply, is not a terribly accurate predictor of risk. As new guidelines are expected soon from the ACC/AHA, we hope to see less reliance on functional capacity as a means of predicting risk in this population. For now at least, the RCRI is in our opinion a better risk-stratifying tool in this population.

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References
The Reply:

We appreciate the interest Thoelke and Gutjahar had in our article studying cardiac risk assessment in patients preparing for orthopedic surgery. Our intent was to point out that the 2002 American College of Cardiology/American Heart Association (ACC/AHA) guidelines were an accurate tool in identifying low-risk orthopedic surgery patients (as specified in the clinical significance inset on the second page of the article) and a useful tool in describing risk in other patients. We demonstrated that patients without ACC/AHA clinical predictors of risk had no major perioperative cardiac events to support this conclusion. It is regrettable that the abstract did not carry the more specific wording that the clinical inset did. We disagree that the revised cardiac risk index (RCRI) is a panacea for risk stratification in orthopedic surgery patients. In fact, 74% of major cardiac events in our study occurred in patients with RCRI index scores of 0 and 1. Drs. Thoelke and Gutjahar echo our sentiments in the article that an over-reliance on noninvasive cardiac testing occurs in the preoperative evaluation of orthopedic surgery patients, often with little impact on patient management. We still strongly feel that a philosophic shift from preoperative noninvasive testing to bedside risk stratification and beta blockade is indicated. We hope any new ACC/AHA preoperative assessment guidelines focus on a strategy where the lowest-risk patients undergoing the least risky surgeries could proceed to the operating room, and the intermediate risk ones could receive perioperative beta blockade and careful postoperative monitoring without noninvasive cardiac testing. It is our hope that this article might stimulate interest in a randomized, controlled trial to validate such an approach. We think the highest risk patients deserve careful collaboration among the surgeon, cardiology consultant, and hospitalist for optimal planning of preoperative testing and management. These patients were not sufficiently represented in our study to recommend a specific evidence-based management strategy.

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doi:10.1016/j.amjmed.2007.06.025
LETTER

A Caveat in the Management of Acute Gout

To the Editor:

We applaud Keith and Gilliland’s review on their update in the management of gout.1 They rightly point out that a majority of the patients are cared for by primary care physicians and that errors in selecting the most appropriate medication and proper dose are common, especially with regard to colchicine.1 However, they recommend commencing colchicine at a dose of 0.6 mg every hour until pain and inflammation are alleviated, gastrointestinal side effects develop, or a maximum of 10 tablets in 24 hours is reached,1 which is 6 mg. We question the rationale behind this dose suggestion and would like a clarification on what evidence we have for recommending such a high dose within the first 24 hours.

There has been only 1 double-blind, placebo-controlled study on colchicine in acute gout in which gastrointestinal side effects occurred before the relief of pain.2 This has particular inference, especially when Morris et al3 demonstrated significant side effects in a series of patients and recommended a low-dose colchicine regimen that was effective, yet less toxic. The optimum dose of colchicine is still elusive,4 and the high-dose colchicine regimen has been controversial and created interesting debate in the literature.5-7 Of note, multiorgan failure was recently reported with colchicine therapy per se.8

Indeed, with the emergence of cardiovascular side effects associated with cyclooxygenase inhibitors and in view of the fact that most patients will present initially to the non-specialist, there is a need for a reappraisal of the plausible dose of colchicine in the management of acute gout.9

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doi:10.1016/j.ajmmed.2007.03.023

References

Competing Interests: All 3 authors have been involved with and encountered patients who have been prescribed colchicine at frequent intervals per current recommendations for acute gout resulting in serious side effects.
LETTER

The Reply:

We appreciate the comments from Varughese et al regarding the use of colchicine in acute gout. We sought to provide a maximum acceptable dose for providers who choose colchicine for their patients.1 As they correctly point out, colchicine has a narrow therapeutic index, and higher doses are associated with increased toxicity.

Colchicine has long been used in the treatment of gout. Its continued use is likely following the publication of guidelines selecting colchicine as a first-line drug for the treatment of gout.2 However, few data are available to guide optimal colchicine dosing.

In the only randomized, placebo-controlled trial of colchicine for acute gout, the mean cumulative colchicine dose was 6.7 mg.3 Colchicine was stopped when toxicity occurred. Although effective for relieving gout symptoms, colchicine caused diarrhea in all patients receiving active treatment.

Expert opinions regarding optimal colchicine dose vary. Recommended cumulative colchicine doses range from approximately 2 mg in the first 3 hours4 to 8 mg in the first 24 hours.5 The maximum dose we describe falls within this range and agrees with dosing guidelines provided in drug compendia.6,7

Most patients develop side effects before reaching a cumulative dose of 6 mg colchicine. Lower-dose regimens appear effective with reduced toxicity.8 Pending further study, colchicine can be used safely and effectively in gout. However, to avoid dangerous toxicity, we emphasize that colchicine should be discontinued when side effects occur.

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doi:10.1016/j.amjmed.2007.06.026

References
LETTERS

Factors Influencing Patient Choice of Colon Imaging Tests

To the Editor:

I read with great interest the findings of Bosworth et al from their prospective comparison of patient experience with colon imaging tests.1 Although their study used the numeric rating scale (NRS) similar to that of Steine and Kim et al for the assessment of pain, their representation of the scale is different.2,3 For Steine and Kim et al, lower scores indicate little or no pain, and higher ones indicate extreme pain. Bosworth et al used the 5-point NRS where lower scores indicate agreement, higher scores indicate disagreement, and middle scores indicate neutrality. Interpreting these types of numeric responses in the context of pain can be difficult for the subjects and confound study results. It may even pose a greater challenge to the cognitively impaired elderly patients who might have been part of this study.4 The presence of pain can be assessed by a “yes” or “no” response and the severity of pain by a progressive rating scale. In neither situation is there a place for a “neutral” score.

In addition, the same bowel preparation was used for both computed tomographic colonography and colonoscopy. However, the data presented in Tables 4 and 5 indicate that subjects were asked about the unpleasantness of the preparation as if it were different for the 2 procedures.

Bosworth et al postulated that pain and discomfort played a greater role than other variables in the acceptability of various colon imaging tests. In contrast, Kim et al found that other factors, including comfort and dignity, were more important to the patients.3 Preference for a particular imaging modality is not only influenced by personal experience but also by the amount of information given to the patient, as demonstrated by Angtuaco et al.5 In summary, the acceptance of a test procedure depends on the test-related outcome that is most important to the patient and the depth of information provided by the caregiver.

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doi:10.1016/j.amjmed.2006.10.020

References
BRIEF OBSERVATION

Hospitalist Performance of Cardiac Hand-Carried Ultrasound After Focused Training

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ABSTRACT

PURPOSE: Because the training that noncardiologists require to perform cardiac hand-carried ultrasound has not been defined, we studied how well hospitalists perform hand-carried echocardiography after limited training.

METHODS: Ten hospitalists completed a focused training program that included performing an average of 35 hand-carried echocardiograms. Hospitalists’ echocardiograms were compared with gold-standard conventional echocardiograms, and hospitalists were compared with 5 certified echocardiography technicians in their ability to acquire, measure, and interpret hand-carried ultrasound images and with 6 senior cardiology fellows in their ability to interpret echocardiograms.

RESULTS: Echocardiography technicians had significantly higher performance scores for image acquisition, measurement, and interpretation than hospitalists. Senior cardiology fellows outperformed hospitalists in most aspects of image interpretation. For hospitalists, learning image acquisition was more difficult than image interpretation.

CONCLUSIONS: Hospitalists can learn aspects of hand-carried echocardiography, but after 35 training echocardiograms cannot replicate the quality of conventional echocardiography. Whether the lower performance skills are important will depend on the clinical context of hand-carried echocardiography performed by hospitalists. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Echocardiogram; Hand-carried ultrasound; Hospitalist

Echocardiography can provide valuable information not available to physicians through the physical examination alone. Hand-carried ultrasound devices provide excellent image quality and have become more widespread, raising questions about the level of training required by noncardiologists to use hand-carried ultrasound competently. One study suggested that internal medicine residents might acquire an acceptable level of skill in hand-carried echocardiography after performing 20 to 40 studies, but to our knowledge the training requirements for internists have not been established.

Conventional echocardiography involves 2 distinct operational phases. A technician acquires the images, and then a cardiologist interprets them. In the present study, hospitalists received limited training in both aspects of echocardiography using a hand-carried device, and their competence was assessed relative to that of certified echocardiography technicians and cardiology fellows using conventional echocardiography as a reference standard. Hospitalists were studied because the many applications of diagnostic ultrasound for inpatient medicine make it a potentially important skill for this group of internists to acquire.

METHODS

Study Populations

Hospitalists and certified echocardiography technicians gave informed consent to participate in the study and completed a Johns Hopkins University training program on human...
investigation before participating. Six John Hopkins University third-year cardiology fellows served as controls for the interpretation skill experiment.

All adult patients admitted to the medical service at Johns Hopkins Bayview Medical Center were eligible to participate if they were scheduled to have a conventional echocardiogram within 24 hours of the hand-carried ultrasound and provided informed, written consent. The Johns Hopkins University School of Medicine Institutional Review Board approved the study protocol.

**Training of Hospitalists**

Hospitalists were introduced to echocardiography by the research echocardiography technician and by online resources. Each hospitalist then performed 5 training echocardiograms, during which the research technician taught them to obtain and interpret 2-dimensional and Doppler images (aortic stenosis was assessed qualitatively, based only on 2-dimensional views) using a hand-carried device (SonoSite Elite, 2.6 kg; SonoSite Inc, Bothell, Wash). Hospitalists also spent 6 hours interpreting conventional echocardiograms with a cardiologist.

**Hand-Carried Echocardiograms**

Hospitalists and echocardiography technicians performed hand-carried echocardiograms on eligible inpatients and recorded 6 cardiac measurements and 7 diagnostic interpretations (Tables 2 and 3). Hospitalists were encouraged to function independently, but the research technician remained at the bedside to give additional training if requested. Subsequent analyses were adjusted for assisted components.

One expert cardiologist (EPS) reviewed all the hand-carried and conventional echocardiograms, grading the quality of image acquisition and recording the same as Table 1.

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</table>

CI = confidence interval.

*All variables are scaled from 0 to 100, with 100 indicating perfect agreement with the conventional echocardiogram. For components of image acquisition graded on a 4-category scale ranging from “adequate” to “grossly inadequate,” the model estimates the probability of a rating being no worse than “slightly inadequate.” Image acquisition index is the mean of the 10 components of image acquisition (indented). E/A ratio refers to the early peak transmitral flow to late transmitral flow velocity ratio assessed via pulsed-wave Doppler. Doppler index is the mean of aortic regurgitation, mitral regurgitation, and E/A ratio from the acquisition skills and combined skills (Table 3) variables. Scanning index is the mean of all other variables in the acquisition skills and combined skills variable groups.

†This column contains the linear model estimate of hospitalist performance at 35 training studies.

‡The difference between the value achieved by the echocardiography technicians and that achieved by the hospitalists after 35 training studies.
sessments on the same scales used by the hospitalists. Comparisons with gold-standard conventional echocardiography were converted into performance scores from 0 to 100. A score of 100 indicated perfect agreement between hand-carried and conventional echocardiogram. For analyses, the performance scores were case-weighted using the frequency distribution of echocardiographic abnormality in this study. This gave greater weight to the less frequent outcomes and thus avoided rewarding the rote selection of the most commonly occurring outcome.

Interpretation Study: Hospitalists Versus Cardiology Fellows

Hospitalists and cardiology fellows viewed selected hand-carried echocardiogram tapes and recorded their interpretations. The viewing session took place 4 to 7 months after the hospitalists finished performing hand-carried echocardiograms.

Statistics

The SAS Institute’s (Cary, NC) Version 8.02 was used in all analyses. Because the hospitalists’ performance scores improved as a function of the number of echocardiograms done, it was not appropriate to compare the mean performance of hospitalists and echocardiography technicians directly. To solve this problem we used linear models (regression for continuous variables and logit for discrete variables) to estimate hospitalist performance after 35 hand-carried echocardiograms. All confidence intervals are 95% and 2 sided.

Table 2 Measurement Skills: Hospitalists Compared with Echocardiography Technicians Using Hand-Carried Ultrasound*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hospitalist Hand-Carried Ultrasound Relative to Conventional Echocardiogram†</th>
<th>Echocardiography Technician Relative to Conventional Echocardiogram</th>
<th>Difference Between Echocardiography Technician and Hospitalist‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
</tr>
<tr>
<td>Measurement index</td>
<td>80.2</td>
<td>(88.5-91.2)</td>
<td>89.9</td>
</tr>
<tr>
<td>Aortic root size</td>
<td>84.8</td>
<td>(87.9-92.9)</td>
<td>90.4</td>
</tr>
<tr>
<td>Diastolic left ventricular size</td>
<td>88.1</td>
<td>(87.7-92.3)</td>
<td>94.6</td>
</tr>
<tr>
<td>Left atrium size</td>
<td>82.1</td>
<td>(87.7-92.1)</td>
<td>90.0</td>
</tr>
<tr>
<td>Septum thickness</td>
<td>79.9</td>
<td>(85.3-90.1)</td>
<td>87.7</td>
</tr>
<tr>
<td>Posterior wall thickness</td>
<td>75.9</td>
<td>(84.4-90.6)</td>
<td>87.5</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*All variables represent 100 minus the percent difference from the gold-standard conventional echocardiogram. Thus, a score of 100 indicates perfect agreement with the conventional echocardiogram. Measurement index is the mean of the 6 measurement variables (indented).
†This column contains the linear model estimate of hospitalist performance at 35 training studies.
‡The difference between the value achieved by the echocardiography technicians and that achieved by the hospitalists after 35 training studies.

Table 3 Combined Skills: Hospitalists Compared with Echocardiography Technicians

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hospitalist Hand-Carried Ultrasound Relative to Conventional Echocardiogram*</th>
<th>Echocardiography Technician Relative to Conventional Echocardiogram</th>
<th>Difference Between Echocardiography Technician and Hospitalist†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
</tr>
<tr>
<td>Combined skills index</td>
<td>78.9</td>
<td>(89.2-93.3)</td>
<td>91.3</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>90.7</td>
<td>(99.8-93.7)</td>
<td>96.7</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>93.7</td>
<td>(100-100)</td>
<td>100.0</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>91.4</td>
<td>(100-100)</td>
<td>100.0</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>84.7</td>
<td>(99.8-93.7)</td>
<td>96.7</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>85.1</td>
<td>(100-100)</td>
<td>100.0</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>70.5</td>
<td>(93.6-82.5)</td>
<td>88.0</td>
</tr>
<tr>
<td>Vegetations</td>
<td>66.3</td>
<td>(95.3-85.1)</td>
<td>90.2</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*This column contains the linear model estimate of hospitalist performance at 35 training studies. For variables assessed on a 4-category scale ranging from “normal” to “severely abnormal,” the model estimates the probability that an assessment was within 1 scale point of matching that of the expert cardiologist. For the variables assessed on a 2-category scale (is E/A for E/A ratio and are vegetations present or absent), the model estimates the probability that an assessment matches that of the expert cardiologist. Combined skills index is the mean of the 7 diagnostic interpretation variables (indented).
†The difference between the value achieved by the echocardiography technicians and that achieved by the hospitalists after 35 training studies.
RESULTS

Study Populations

There were 10 hospitalists, all internists with 0 to 9 years of experience after residency. Some had limited previous experience with echocardiography. The hospitalists performed a total of 354 supervised echocardiograms (mean 35.4, range 28-50). The 5 echocardiography technician controls averaged 10.6 years of experience and performed 92 hand-carried echocardiograms (mean 18.4, range 10-52).

Image Acquisition Skills

Table 1 shows the skill of hospitalists in image acquisition with hand-carried ultrasound compared with that of the echocardiography technicians. These results represent the difference between the probability (multiplied by 100) that the echocardiography technicians produced images judged “adequate” or “slightly inadequate” by the expert cardiologist and the probability that hospitalists were so judged. For example, the echocardiography technicians were 18.4% (confidence interval 13.7-24.0) more likely to have been judged no worse than “slightly inadequate” than hospitalists in overall image acquisition. Hospitalists’ average image acquisition never equaled that of the echocardiography technicians.

Echocardiographic Measurements

Table 2 shows how hospitalists compared with echocardiography technicians in making cardiac measurements. Echocardiography technicians outperformed hospitalists for all variables.

Combined Skills

Table 3 shows how hospitalists compared with echocardiography technicians in performing the “combined skills” of image acquisition and interpretation. Hospitalists did significantly worse in each category of combined skills compared with the echocardiography technicians. Table 3 also shows that echocardiography technician performance virtually matched the assessments obtained by the expert cardiologist.

Image Interpretation

Table 4 shows that hospitalist and cardiology fellow performance in interpreting recorded echocardiograms was not significantly different for 3 diagnoses (including mitral regurgitation and E/A ratio), but hospitalists had lower scores for the other 4 outcome variables (including left ventricular function).

DISCUSSION

The level of training required for internists to achieve competency in cardiac hand-carried ultrasound has not been precisely determined. The limited level of training used in our study does not allow hospitalists to equal the skill level of certified echocardiography technicians in acquiring, measuring, or interpreting hand-carried ultrasound images. Also, hospitalists, having performed a mean of 35.4 training sonograms, are not as skilled as senior cardiology fellows at interpreting recorded echocardiograms.

Previous studies have examined the ability of briefly trained medical residents4,5 and medical students2,6 to learn
how to perform aspects of cardiac hand-carried ultrasound. All previous studies, as did the current one, found that learners could develop proficiency with some aspects of cardiac hand-carried ultrasound but do not achieve the accuracy of gold-standard conventional echocardiography.\[4,5\] Alexander et al.\[5\] for instance, showed that 20 medicine residents trained for 3 hours could detect major cardiac abnormalities with a sensitivity that ranged from 29% to 82%, depending on the type of cardiac abnormality examined.

The current study adds to what is known about training in cardiac hand-carried ultrasound in several ways. First, to our knowledge, this is the first study to evaluate training in hospitalists, who constitute the most rapidly growing group of physicians in the United States and work in a setting in which hand-carried ultrasound might be used often. Second, the current study is the first to dissect and evaluate the different tasks required to perform basic echocardiography, namely, image acquisition, measurements, and interpretation. Our study demonstrates that hospitalists did not develop equal proficiency in these different skills. For example, hospitalists came closer to matching controls in measuring and interpreting images than they did in acquiring the images, which indicates that learning image acquisition was more difficult. Third, the current study quantitates the difference in performance between hospitalists and real-world control groups, making it easier to understand the meaning of the discrepancy between hospitalist-performed and conventional echocardiography.

The question of how much training is enough to qualify physicians to carry out any diagnostic procedure depends on the clinical context in which the examination is intended to take place. We did not begin this study believing that hospitalist-performed hand-carried echocardiography could or should replace conventional echocardiography. Rather, we believe that hand-carried ultrasound could supplement the standard history and physical examination, and thereby expand the internist’s “black bag.” One possibility would be for hand-carried echocardiography to be treated similarly to electrocardiography, allowing noncardiologists to obtain and use information at the bedside with follow-up testing or expert interpretation as the clinical situation demands.

**CONCLUSIONS**

After focused training, hospitalists cannot perform hand-carried echocardiography with the skill of echocardiography technicians. However, there are no normative standards by which we can decide whether the skills acquired with this limited training are sufficient. Thus, it remains unknown whether those skills if put into clinical practice, as we have suggested, would result in net clinical benefit to patients. Our study did not address the question of whether more timely and accurate diagnostic assessments at the bedside, when conventional echocardiography is unavailable, would compensate for the increased rate of errors. Until that question is answered, it is our view that future efforts to train noncardiologists in hand-carried echocardiography should concentrate on teaching fewer skills and focus on determining clinically important abnormalities, such as left ventricular dysfunction, that may be difficult to assess on the basis of physical examination alone.

**ACKNOWLEDGMENTS**

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**References**

Physicians Should Be Civic Professionals, Not Just Knowledge Workers

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Medicine has the potential to bring more to patient care—and to physician development—than ever before. However, current trends in US medicine are teaching today’s medical students, residents, fellows, and physicians the wrong lessons. These trends include consequences of turning away patients who lack adequate insurance or the means to pay for their care; scientists selling findings from publicly funded research to securities analysts or traders; and news of scientific fraud or of academic health centers agreeing to large settlements for billing excesses or fraudulent billing. Because academic medicine also instills a physician’s values during training, when today’s physicians-in-training observe such trends, unprofessional values are encouraged.

The US medical community must counter these negative trends to achieve the fullest potential for patients and the medical profession. This commentary develops the notion that US medicine in general—and academic medicine in particular—should cultivate a civic form of professionalism rather than “knowledge workers.” Indeed, a few elements of what is traditionally understood as professionalism may be expendable, such as an over-insistence on the principle of professional autonomy if “autonomy” means that the physician must always be in charge. In fact, physicians are now expected to work well with others on health care teams, often in quite diverse roles.

What distinguishes civic professionalism, according to William M. Sullivan, is a focus on service and the public good. Sullivan argues that “the professions are vital reminders that human welfare ultimately depends upon cultivation of values such as care and responsibility, which cannot be produced by self-interest alone.” He defines civic professionals as “focusing on the quality of their craft and the inventiveness of their practice” to “provide an alternative model of what work can be: a contribution to public value, as well as a source of motivation and deep personal satisfaction.” Eliot Freidson has called for a similarly “reborn” type of professionalism.

KNOWLEDGE WORKERS, PROFESSIONALS, AND MARKET FORCES

It is crucial that medical professionalism not be eclipsed by the trend to consider physicians as typical knowledge workers. This phrase comes from sociologist Peter Drucker, a scientist who wrote extensively about the development, organization, and management of work. According to Drucker, postindustrial society places increasing value on acquiring, organizing, and applying the most highly valued commodity: knowledge. While professionalism is declining, a new type of workforce is emerging to serve new types of knowledge industries, services, and organizations. Knowledge workers are relatively independent, self-directed, and untied to traditional agrarian, guild, or corporate structures. They are mobile, entrepreneurial, and range from programmers and engineers to consultants in a variety of fields. Knowledge workers tend to be continual learners who adapt to new knowledge and to novel employment and
Economists Smith, Jeremy Bentham, and John Stuart Mill considered individualism and self-interest responsible for market forces promoting greater community interest. Often, however, this interest did not come to pass; therefore, Brandeis and 19th century moral philosophers, such as Emile Durkheim, argued that business should emulate traditional professions (law, clergy, magistracy, and medicine) to solve the social problems resulting from the unbridled individualism and self-interest of the “Robber Barons.” These individuals saw professionalism as a way—even in business—to let strong individualism lead to greater social good, limiting the excesses of unbridled market forces.

This notion has again become prominent in the spirited debate about Duncan Foley’s Adam’s Fallacy: A Guide to Economic Theology. The book criticizes Smith’s assumption that the pursuit of self-interest necessarily leads to social good. Foley calls uncritical acceptance of the fallacy “economic theology.” The book’s tenets have stirred many debates, including one of the Internet’s most trafficked economics blogs: University of California, Berkeley, Professor of Economics Brad DeLong’s semi-daily journal. Foley cites the “chronic crisis of health care in advanced capitalist societies [as] Adam’s Fallacy in microcosm.” He argues that “commodity logic,” which penetrates more and more of human life, would have an unfortunate parallel if physicians became commodities (knowledge workers) rather than true professionals.

Some commentators and influential policy makers advocate letting the “medical marketplace” work and seeing what happens. However, market forces tend to be inefficient in medicine, typically promoting more care than optimal.

### The Future of Medical Professionalism: Accounting and Sarbanes-Oxley

For several decades, medicine has experienced rapid changes to the professional and practice environment. As a result, the future of medical professionalism may be at risk. Change has uncovered and created major stresses throughout the medical profession and the health care system. While the pace of change may have slowed recently, the impacts are still reverberating and more change is certain. To be sure, the medical profession faces challenges: the reimbursement system is un-
fair and almost perverse, with high demands for visits that are too short; the proportion of college graduates who apply to US medical schools has decreased; \(^{23}\) patients—especially the poor and disenfranchised minorities—have less access to health care, \(^{24}\) with emergency rooms becoming the safety net for general medical care; \(^{25}\) and, as the Institute of Medicine (IOM) identified, the medical system suffers from quality chasms and safety problems. \(^{26}\)

However, rather than focusing on how medical professionalism is suffering, the prospects and the rationale for medical professionalism should be discussed in the context of substantial gains and almost certain continued growth of the medical knowledge base. To achieve the promise that all this knowledge offers, the medical profession will need truly civic medical professionals and more effective self-regulation.

There are highly publicized examples of individual physicians making unethical choices that run contrary to expected professional ethics. Recently, some physicians were reported to have “sold” information about unpublished drug trials to hedge fund managers. \(^{27}\) Some medical schools are forced to adopt burdensome compliance programs as part of settlement agreements related to charges of billing fraud. These are hardly examples of a profession that is effectively regulating itself.

Like medicine, accounting is a profession that has not always regulated itself as well as it should. Arthur Andersen, one of the world’s largest accounting firms, neglected its professional responsibilities to society and was found guilty of obstructing justice in the Enron scandal. More significant than the firm’s resultant loss of clients and effective dissolution was the transformation of the entire accounting profession, which the government has regulated since the Sarbanes-Oxley Act of 2003. \(^{28}\) Could medicine also lose the privilege of self-regulation?

The Enron case and the near demise of accounting as a self-regulated profession illustrate the importance of distinguishing a nonprofessional knowledge worker and a knowledge worker who is also a civic professional. In modern post-industrial society, where knowledge is the most highly valued commodity, and especially for medicine, where knowledge is expanding rapidly and will predictably do so even more rapidly, medical professionals must aspire to produce and sustain physicians who are not only knowledge workers but also truly civic professionals.

**KNOWLEDGE TURNS: OPPORTUNITIES AND CHALLENGES**

In 2005, Andrew Grove, former chairman of the board of Intel Corporation, offered a compelling view of what he called “knowledge turns.” \(^{29}\) He wrote that both the health care and microchip industries are based on science and populated by extremely dedicated and well-trained individuals striving to use the results of this science. Granted, important differences between the 2 industries exist in complexity, safety, and legal and ethical concerns; however, they both depend on developing research results and turning them into widely available products and services, called a “knowledge turn” in electronics and “translating research into practice” in medicine. According to Grove, the number of transistors that can be included on a microchip has doubled annually (per Moore’s law) over the past 40 years, eclipsing the rate of progress made in the war on cancer during the same time. Grove traces this discrepancy to the microchip industry’s recognition of the importance of rapid knowledge turns, whereas the same cannot be said for health care.

Today, medicine—especially academic medicine—is in the midst of implementing changes that will speed up knowledge turns:

- The National Institutes of Health is devoting specific amounts of its budget to improving translation—that is, the National Institutes of Health Roadmap Initiatives, which are designed to identify medical research science proposals that address current and anticipated scientific challenges and have the potential to contribute “extraordinary contributions to medical research.” \(^{30}\)
- Creation of a functional, nationwide system of interoperable electronic health records, which will revolutionize how physicians practice and how patients receive care, enabling them to more effectively take care of themselves.
- Realization of the IOM vision of what a new health system might look like, as described in *Crossing the Quality Chasm: A New Health System for the 21st Century*. \(^{31}\) The IOM report called for replacing current systems of care with new ones to meet 6 aims that are not currently being met: safety, timeliness, efficiency, effectiveness, equity, and patient-centered care. IOM also described 5 essential competencies for clinicians: provide patient-centered care; work in interdisciplinary teams; employ evidence-based practice; apply quality improvement; and utilize informatics. \(^{32}\)

Some clinical microsystems are already working to achieve this vision of a new health care system for the 21st century by aspiring to design and deliver care based on 10 rules: \(^{33}\)

1. Care is based on continuous healing.
2. Care is customized according to patient needs and values.
3. Patients control their own care.
4. Knowledge is shared and information flows freely.
5. Decision-making is evidence-based.
6. Safety is a system priority.
7. Transparency is necessary.
8. Needs are anticipated.
9. Waste is continuously decreased.
10. Cooperation among clinicians is a priority.

All of these initiatives are worthwhile, but massive, endeavors. It seems farfetched to imagine they could be accomplished by cadres of nonprofessional knowledge workers. However, civic professionals could certainly adopt these elements as an inspirational vision.

RESURGENT INTEREST IN MEDICAL PROFESSIONALISM

Although medicine has much to offer, including the promise of vast improvements, the well-publicized lapses in professional conduct and failure to provide quality patient care causes frustration and complexity in the health care system. Fortunately, this situation has resulted in a resurgence of interest in and advocacy for redefining, reviving, and advancing medical professionalism. One example, Project Professionalism, has developed a new physician charter endorsed by the American Board of Internal Medicine Foundation, American College of Physicians Foundation, and European Federation of Internal Medicine. According to the charter, “Unprofessional behavior and attitudes on the part of some physicians have eroded medicine’s historically respected position.”

The best response to this situation—both for the medical profession and for the society in which physicians work and live—is to embrace professionalism, ideally civic professionalism. Physicians can act as civic professionals by “placing the interest of patients above those of the physician, setting and maintaining standards of competence and integrity, and providing expert advice to society on matters of health,” with “the principles and responsibilities of medical professionalism . . . clearly understood by both the profession and society.”

The physician charter articulates three fundamental principles for both individual physicians and the entire profession that will maintain integrity and the public trust: patient welfare, patient autonomy, and social justice. The charter states, “Market forces, societal pressures, and administrative exigencies must not compromise the physician’s dedication to serving the interest of the patient. Altruism contributes to the trust that is central to the physician-patient relationship,” and ends with the admonition that “physicians must reaffirm their active dedication to . . . not only their (our) personal commitment to the welfare of (our) patients but also collective efforts to improve the system for the welfare of society.”

CIVIC PROFESSIONALISM AND US MEDICINE

Physicians must embrace civic professionalism as a basis for renewal of medicine. It is absolutely critical to the character, quality, and future of good health care and to the research, education, and training on which medicine is founded. US medicine has long displayed exceptional entrepreneurial and business acumen. Physicians should expand this spirit to embrace the public good more consciously. One publication recently called for “exceptional” health professionalism as the way to “get the physician right.”

Medical schools, and especially departments of internal medicine, must develop programs to train and graduate civic (or “exceptional”) medical professionals. Academic medicine and professional organizations can and should take a leadership role in promoting an inspirational vision of civic professionalism. For example, physicians should readily admit when self-regulation has failed and respond by developing more effective self-regulation, whether in science, practice, or, especially, business practices. Merely being knowledge workers is not part of an inspirational vision for the future of medicine. The enterprise of medical education can include exposure to ideas such as civic professionalism, the IOM’s vision for a new health care system, and the knowledge revolution, along with training experiences that exemplify these ideas. In so doing, medical education can become more relevant to serving the needs of patients and society.

ACKNOWLEDGMENT

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References