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We Can Reduce US Health Care Costs

The primary reason that the US needs health care reform is that we pay more for health care than any other country in the world; yet our health outcomes are below that of other western nations.[1] Our health outcomes are suboptimal because millions of Americans have limited access to ongoing primary and preventive care because they can't afford our health insurance.

REDUCING ADMINISTRATIVE COSTS

We spend more than a third of our health care dollars on overhead and administration: billing, advertising, profits, and bonuses for health care executives.[2,3] Administrative costs in countries such as Canada that have a single payer (non-profit national health insurance) are half as much as in the US.[2] If we had a single payer instead of hundreds of insurers with thousands of different plans, we would save 15% of our health care costs. Fifteen per cent of trillions adds up!

A Price Waterhouse Coopers study reported that our complex, fragmented health care delivery system wastes $210 billion per year on unnecessary billing and administrative costs.[4] The ultimate solution to our excessive health care costs is national health insurance: Medicare for all[5]; but that won't happen–at least not in the very near future. What can we do to decrease health care costs now?

FOCUS ON PREVENTIVE CARE

We need to change our focus from disease management to prevention and health promotion. To change our focus to prevention we need more primary care physicians, family physicians, and general internists. Multiple studies have shown that generalists practice more cost-effective medicine than specialists and that their patients have better health outcomes.[6-8]

Due to poor planning, currently we have an overall shortage of physicians in the US.[9] The number of medical students recently has increased, but we have an even greater problem. The number of US MD graduates choosing primary care careers keeps decreasing. In the 2009 National Residency Match, only 7% of graduates chose family practice, and 19% chose internal medicine.[10] Only a minority of those choosing internal medicine will become general internists; the majority will become subspecialists or hospitalists. Hauer et al reported that only 2% of US senior MD medical students planned to have a career in general internal medicine.[11]

One reason that medical students enter specialties is that the average educational debt of the class of 2008 MD graduates was $150,000.[12] This influences many graduates to enter specialties that pay, on average, twice as much as primary care so that they can pay off their educational debt.[13]

To influence more physicians to choose primary care we need to pay off their educational debt if they choose and remain in primary care. In addition, they should receive an annual stipend for each Medicare patient for whom they coordinate care and provide a medical home. These stipends added to their fee for service income should provide an income comparable to the average specialist. This would be an excellent investment for Medicare. If each primary care physician can avoid 1 unnecessary hospitalization or even 1 expensive but unnecessary test for each patient, Medicare will come out far ahead!

To be effective in prevention, primary care physicians must have certain skills that our current medical school curriculum does not provide adequately. We offer minimal training in nutrition, prescribed exercise, stress reduction techniques, and other effective therapies for certain conditions, for example, acupuncture for specific chronic pain syndromes.

ELIMINATE UNNECESSARY TESTS AND PROCEDURES

In addition to training a new cadre of adult generalists with expertise in prevention, we must ensure that all physicians (specialists and generalists) practice cost-effective medicine. At the present time, physicians vary tremendously in their use of expensive diagnostic tests and treatments. The average cost of treating a Medicare patient in some parts of the country is twice as expensive as in other areas.[14] The most expensive cities have more hospitalizations, and physician visits and their physicians order more expensive diagnostic tests and procedures. There is no evidence that the more expensive treatment benefits patients.[14] Much of the excessive treatment and unnecessary testing occurs at

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the end of life. We must encourage all citizens to have living wills to avoid unwanted procedures at the end of life.

Many unnecessary tests are performed to prevent malpractice suits. Kessler and McClellan, in 1996, estimated the annual cost of defensive medicine to be as much as $50 billion per year.[15] It must be much higher at present. We need malpractice reform including limits on awards for pain and suffering. Our current system of paying millions of dollars to patients and their attorneys when malpractice is documented does not prevent malpractice. We need to require retraining of physicians who are shown to practice substandard medicine. We need to suspend or deny participation in Medicare for repeat offenders.

In addition, we need to increase research funding for projects that will help to determine which diagnostic tests and procedures actually benefit specific patients. This research will increase the number of evidence-based practice guidelines. Medicare should not pay for procedures that do not benefit patients. This is not rationing–it is common sense.

CONTROLLING THE COSTS OF PRESCRIPTION DRUGS

Our government must control the prices of prescription drugs as is done in nearly every other nation. Drug companies can charge whatever they wish in the US. Citizens of other nations pay 20% to 40% less for prescription drugs compared with what Americans pay.[16]

Millions of Americans have chronic conditions that require life-long medications. If their insurance doesn't pay for them, or if they fall into Medicare's donut hole[17] and cannot afford prescribed medicines, many patients stop taking their medications. The result is increased emergency room visits and hospitalizations and a further increase in our health care costs.[18]

Some authorities have suggested that if we decrease the profits of drug companies they will stop developing new drugs. Given that drug companies spend more than twice as much for marketing and advertising as they do for research[19] this is a very unlikely outcome.

In summary, we must reduce the cost of health care in the US. We can do this by developing a health care system that emphasizes prevention rather than disease management. To do this we must encourage more physicians to be adult generalists and we must provide them with new skills.[20] Furthermore, we must insure that all physicians have cost-effective practice patterns that avoid unnecessary tests and procedures and that all citizens adopt living wills. As a nation, we need to have better control over the cost of prescription drugs.

Finally, at some point in the future, we should adopt a policy of national health insurance, Medicare for all.

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Reexamining the Physician Scholar–Professional Organization Relationship

Physician faculty at most medical schools are expected to establish a "national reputation," often in part through scholarly contributions to national nonprofit professional organizations. Yet, those who generate most of their income through clinical work and teaching (ie, clinician scholars, clinician educators) find it increasingly difficult to volunteer their time and effort to these organizations compared with their historical colleagues. Those receiving salaries, fixed or based on billings/collections or work relative value units, have increasingly limited discretionary time off-site, and protected time on-site, for such endeavors. Travel issues (connecting, delayed and canceled flights, fewer travel options) add further to the cost of committee and meeting work. Employer-provided travel funding is a fraction of its former level, having totally disappeared at many institutions, whereas support from healthcare-associated industry has been banned or severely limited by some employers as an apparent conflict of interest, leaving the physician scholars to provide their own out-of-pocket travel support for many such activities. Colleagues have less uncommitted time to provide coverage of clinical duties during off-site meetings. Simultaneously, the physician contributor's responsibilities per activity have mushroomed by the need to address a host of regulatory and quality requirements (securing copyright releases, adhering to standardized formatting, preparing educational goals and hand-outs, composing assessment questions, validating statistics, and reviewing and rewriting test questions).

The net result finds a few hours of inexpensive 1980s commitment has become many days of 2009 work and considerable personal financial expense. Junior faculty, paying educational loans and supporting young children, are particularly hesitant to make such commitments despite a mandate to establish national reputations.

Nonprofit professional organizations also suffer under growing financial pressures. Although some may provide nominal honoraria for such work, many are unable to even fully reimburse travel and per diem expenses. The largely uncompensated labor (writing, expert opinion and review, presentations) provided to such organizations by physician scholars frequently comprise the very products (continuing medical education products, certification courses, examination) by which the organizations are financially sustained. Information checking, assuring freedom from commercial bias, vetting of ideas and presentations done by individuals and committees, and a host of other necessary activities would be unsustainable if the work of physician volunteers were fully compensated at a competitive market rate. Continued productivity of professional nonprofit organizations is dependent on the continued contributions of outside physician scholars.

Through the present torrential academic and financial climate change, the need for such scholarly products has never been greater. Medicine increasingly strives to define and measure competence, while keeping growing numbers of health care providers updated on the explosive growth in scientific/clinical knowledge and expanding regulatory and statutory requirements for health care delivery. It follows that those who live and work daily on the cutting edge of their professional fields will be sought to fulfill these needs for expertise. But how can the cost—in time, effort, and dollars—be made more affordable, so those willing and capable can continue to contribute in this environment? As is the case with most complex issues, responsibilities are broadly borne and solutions will require cooperation from all stakeholders.

Professional organizations must take the lead. Full use of web-based technologies (virtual meetings) can provide much of the interaction of face-to-face conferences without the expense and time of interstate travel. Shorter, more focused physical meetings used only for those issues truly requiring such interactions should be considered. Flexible scheduling to include weekend meetings would reduce the need for physicians to cancel income-generating clinical activities at home, while meetings held in geographically centralized locations or at airport hotels and conference facilities could reduce overall meeting time and associated costs. Continuing education credit should be provided for

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participation in these projects as an additional compensation. Administrative support for the work (eg, performing literature searches, obtaining copyright releases, formatting goals and objectives, preparing slides and formatted graphics) should be provided by the organization as a routine business expense. Whenever possible, compensation should be increased to fully cover travel expenses and some honoraria to defray the income sacrificed by the participating faculty. Organizations also could consider forming a consortium to maximize their bargaining position for low-cost hotels and travel.

Medical schools and teaching hospitals also need to contribute. Referring physicians, as much customers of tertiary academic medical centers as the patients they send, often consider it advantageous to refer their complex patients to nationally recognized experts, conveying the reputation of such experts to their patients. Indeed, national scholarly recognition is often used by health care organizations to advertise the quality of experts at their hospitals and clinics. Academic institutions also can specifically identify these scholarly activities as meeting some promotion, tenure, or compensation criteria, placing them more on par with service toward other traditional academic missions, perhaps developing a schema of "relative value" for national activities with teaching, research, clinical care, and administration; such a change would increase the return-on-investment for the physicians' national work.

The consumers of these products—test takers seeking certification, practitioners wanting to learn the latest treatments—need to acknowledge the value of the physician scholar and the scholarly products they produce. Whenever possible, consumers should support those nonprofit organizations which give them the best educational value for their dollar, avoiding the lure of popular tourist sites and gourmet meals that too often drive their selections.

Finally, the physician faculty themselves must be part of the solution. Physicians typically enter the health care field out of a perceived responsibility to contribute more to society than possible through most other professions. Work with national organizations is a force multiplier, enlarging the impact of each effort to help more patients (through fellow providers) than possible through direct clinical care alone. In short, contributing to continuing medical education activities, board and other certification examinations, and committee and advocacy work for nonprofit organizations is simply an important part of being an academic physician.

Where to start? Perhaps beginning with small steps: by nonprofit professional organizations to reduce the cost to faculty contributors on whom they depend; by medical school and hospital employers to make it a bit easier for those willing and so gifted to make the greater contributions; by the consumers to reward quality in the products they purchase; and by both established and younger physician scholars to make the extra sacrifice to do more.

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Thank You, Thank You, Thank You

The machinery that makes ***The American Journal of Medicine*** (*AJM*) function is powered by many different individuals performing a variety of tasks. Without its long list of employees and volunteers, the *Journal* could not function. I am writing this editorial to thank the individuals who have made *AJM* what it is today, and what it will become in the future. The order in which these expressions of appreciation appear in this essay should not be construed as any indication of the importance of the individual or the group named. They are all equally important in the success of the *Journal*. To use a sports analogy, a baseball team needs a second baseman just as much as it needs a center fielder.

The American Journal of Medicine has been extraordinarily fortunate to have outstanding administrative, publishing, and computer personnel in Tucson, New York City, Philadelphia, San Diego, Amsterdam, and Oxford, UK. These individuals function smoothly as a team and guarantee our ability to produce a high quality issue each month. We are sponsored by one of the premier professional societies in the United States, the Association of Professors of Medicine, whose members are the chiefs of medicine in every medical school in the US and Canada.

Our associate editors, subspecialty editors, and editorial board are the intellectual backbone of the *Journal*. The importance of their advice, suggestions, and scholarly efforts in producing and reviewing material on behalf of the *Journal* cannot be overestimated. In a similar vein, committed, conscientious reviewers are essential to the publication process. The *AJM* is fortunate in having a large cohort of dedicated reviewers, some of whom we designate as elite reviewers because they have performed 8 or more quality reviews for us during the last few years. As a reward for such diligent and essential service, a number of these elite reviewers are invited each year to join the editorial board of the *AJM*.

I am sometimes asked by residents, fellows, and junior faculty, what benefit accrues to an individual from reviewing manuscripts for the *AJM*. My answer is: there are a number of potential benefits associated with reviewing. First, the reviewer sharpens her/his critical sense during the review process. Secondly, the reviewer is kept abreast of the latest scientific developments in the field even before they become public knowledge. Thirdly, young faculty members can list their reviewing activities on their curriculum vitae as scholarly activity, and this may help with promotion and tenure decisions. For example, I was recently asked by one of our elite reviewers to write a letter supporting his promotion package from assistant to associate professor at a prestigious East Coast medical school. I was pleased to write this letter and the promotion was approved. We subsequently invited this individual to join our editorial board as another sign of our appreciation for his dedicated efforts on behalf of the *AJM*. Finally, when one reviews manuscripts for the *AJM* the reviewer joins the *AJM* family, which includes some of the very best minds in contemporary clinical medicine. Knowing that one is a part of this elite group of outstanding medical intellectuals is by itself highly rewarding.

So, as we enter the first months of 2010, let me express my sincerest and deeply held gratitude to everyone who makes the *AJM* possible. It is literally true that "we could not do this without your help." I personally want to say thank you to each and every individual who helps us make ***The American Journal of Medicine*** a success. As always, feel free to comment on our blog at http://amjmed.blogspot.com.

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REVIEW

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Atrial Fibrillation in Heart Failure: A Comprehensive Review

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ABSTRACT

Chronic heart failure and atrial fibrillation are 2 major disorders that are closely linked. Their coexistence is associated with adverse prognosis. Both share several common predisposing conditions, but their interaction involves complex ultrastructural, electrophysiologic, and neurohormonal processes that go beyond mere sharing of mutual risk factors. Rate control approach remains the standard therapy for atrial fibrillation in heart failure because current strategies at rhythm control have so far failed to positively impact mortality and morbidity. This is largely because of the shortcomings of current pharmacologic anti-arrhythmic agents. Surgical and catheter-based therapies are promising, but long-term data are lacking. The role of non-anti-arrhythmic therapeutic agents also is being explored. Further progress toward improved understanding the complex relationship between atrial fibrillation and heart failure should improve management strategies.

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KEYWORDS: Arrhythmia; Atrial fibrillation; Cardiomyopathy; Heart failure

Chronic heart failure and atrial fibrillation are major cardiovascular disorders that are frequently associated with each other. They have common risk factors, and each complicates the course of the other. Both are associated with significant morbidity and mortality, creating a serious public health burden. A closer understanding of the intricate relationship between these 2 disorders would certainly improve the approach to their management.

EPIDEMIOLOGY

Chronic heart failure afflicts 5.3 million adult Americans with an equal sex distribution. It is associated with over a million hospitalizations and 3.4 million outpatient visits annually, with total costs estimated at $35 billion. The lifetime risk of developing heart failure is 1 in 5 after age 40 years,[1] with an annual mortality of 20%.

Atrial fibrillation, the most common clinically significant arrhythmia, has a prevalence of over 2.2 million in the United States. It accounts for nearly a half million hospitalizations yearly, at an estimated cost of $7312 per discharge.[2] The lifetime risk of developing atrial fibrillation is 1 in 4 after age 40 years,[3] and based on Framingham data, atrial fibrillation accounts for 14% of early deaths within the first 4 months of its diagnosis in patients with heart failure.[4]

With a steady incidence of both atrial fibrillation and chronic heart failure in the setting of an aging global population where more and more people survive to an age where these conditions occur with increased frequency, the prevalence of heart failure and atrial fibrillation will continue to increase to epidemic proportions.

PREDICTORS OF ATRIAL FIBRILLATION IN CHRONIC HEART FAILURE

In the Framingham Study, heart failure was the strongest predictor for the development of atrial fibrillation, with a

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nearly 5-fold risk in men and 6-fold in women.[5] The prevalence of atrial fibrillation in patients with preexisting heart failure is associated with increasing heart failure severity. In chronic heart failure clinical trials, the prevalence of atrial fibrillation was 4% in functional class I patients,[6] 10%-27% in those with functional class II-III,[7-10] and 50% in those with functional class IV.[11]

In a registry of heart failure patients in everyday clinical practice,[12] the overall prevalence of atrial fibrillation was 21%. Prevalence of atrial fibrillation increased with age, up 29% in patients over 70 years compared with 15% in those younger than 70 years. Nonischemic cardiomyopathy was associated with a 3-fold probability of atrial fibrillation compared with ischemic etiologies. Atrial fibrillation was more prevalent among heart failure patients with preserved systolic function, where diastolic dysfunction, hypertension, or valvular defects are presumed to be the primary etiologies of the heart failure.

CLINICAL SIGNIFICANCE

- Atrial fibrillation and chronic heart failure frequently coexist because of common risk factors and closely linked pathophysiological processes.
- Pharmacologic rate-control strategy remains the standard of care, mainly because of the limitations of the current anti-arrhythmic agents used in rhythm control therapy.
- Nonpharmacologic approaches to therapy using invasive and catheter-based modalities are showing promise in the treatment of atrial fibrillation in heart failure.

PATHOPHYSIOLOGIC INTERACTION

Chronic heart failure and atrial fibrillation are associated with common predisposing conditions such as hypertension, diabetes, coronary artery disease, and valvular heart disease. Recent data reveal complex cellular, extracellular, neurohormonal, and electrophysiologic processes that allow significant interaction between these 2 conditions that go beyond the mere sharing of mutual risk factors.

Chronic Heart Failure Predisposes to Atrial Fibrillation

Heart failure induces changes in the atrial structure and physiology that promote and maintain development of arrhythmias. Increased atrial volume and pressure in heart failure results in mechanical stretching of the atrium. In animal studies, this tissue stretch is associated with heightened atrial irritability and increased frequency of sustained and nonsustained atrial tachyarrhythmias by shortening the atrial refractory period, prolonging the atrial conduction times, and increasing inter-atrial conduction blocks.[13,14] Increased intra-atrial pressure in heart failure can intensify the rate and organization of wavelet foci that perpetuate atrial fibrillation.[15]

Neurohormonal changes that accompany heart failure, including activation of the renin-angiotensin-aldosterone system (RAAS), also contribute to the development and maintenance of atrial fibrillation. Patients with heart failure have a higher level of catecholamines, which is associated with rapid ventricular response. Increased angiotensin II expression in heart failure promotes atrial interstitial fibrosis and structural remodeling that create areas of slowed conduction and heterogeneity in repolarization, serving as substrates for atrial fibrillation generation.[16] Activation of the sympathetic nervous system causes abnormalities of atrial action potentials and automaticity that can trigger arrhythmias as well.[17]

In the failing atrium, ion channel remodeling and calcium dysregulation at the cellular level have been shown to enhance arrhythmogenesis. Heart failure causes profound abnormalities in calcium handling and regulatory proteins within the atrial cardiomyocyte that promotes triggered activity in atrial fibrillation.[18] The atrial cellular electrophysiological remodeling seen in heart failure, responsible for arrhythmogenic afterdepolarizations and action potential alterations, is distinct from that caused by atrial tachycardia.[19]

Atrial Fibrillation Predisposes to Chronic Heart Failure

Chronic or incessant atrial tachyarrhythmia is known to produce a reversible type of severe biventricular systolic dysfunction, termed "tachycardia-induced cardiomyopathy."[20] In animal models, the severity of heart failure progresses with increasing heart rates and duration of tachycardia.[21] High heart rates and recurrent tachycardia, as seen in atrial fibrillation, reduces myocardial compliance and impedes ventricular filling, resulting in shortened filling times and rapidly progressive heart failure. Ultrastructural changes that occur in this setting include cytoskeletal alterations (increased actins and tubulins), disruption of matrix metalloproteinases (gelatinase, collagenase, and stromolysin), and depletion of high energy stores. Abnormal calcium handling also occurs, along with reduction in myofibrillar calcium ATPase, sodium-potassium ATPase, and cardiac glycoside binding activities. The remodeling process results in neurohormonal derangements that include increased epinephrine and norepinephrine levels. Rate or rhythm control results in reversal of cardiac dysfunction, but recurrence of the tachyarrhythmia causes abrupt decline in left ventricular function and increases risk of sudden death.[22] Even with normalization of ejection fraction, negative remodeling and ventricular dilatation may persist after treatment of tachycardia-induced cardiomyopathy.[23]

Atrial systole can contribute up to 25% of the cardiac output, and even up to 50% in patients with preexisting valvular disease or ventricular dysfunction.[24,25] The onset of atrial fibrillation produces adverse hemodynamic effects, including reductions in cardiac output, peak oxygen uptake, and exercise tolerance. Atrial fibrillation may reduce cardiac output by several mechanisms, including loss of the atrial contribution to left ventricular filling, valvular regurgitation, and increased ventricular rate, leading to inadequate left ventricular filling time. Left ventricle ejection fraction and stroke volume significantly improve immediately after cardioversion as a result of enhanced left ventricular diastolic filling from increased cycle length and restoration of the atrial booster pump function.[26-28] Irregular ventricular response in itself has been shown to decrease cardiac output, increase pulmonary capillary wedge pressure, and increase right atrial pressure, independent of heart rate.[29]

PROGNOSIS

Even with optimal medical therapy for heart failure, the onset of atrial fibrillation is often accompanied by cardiac decompensation as well as functional class deterioration. Peak oxygen consumption and cardiac index markedly decrease, while the severity of valvular regurgitation and cardiac chamber dimensions increase shortly after the onset of atrial fibrillation.[30] Whether atrial fibrillation directly affects prognosis or is merely a marker for heart failure severity is still under debate.

In patients with asymptomatic and symptomatic heart failure, the Studies of Left Ventricular Dysfunction (SOLVD) trial showed that atrial fibrillation was independently and significantly associated with all-cause mortality, mostly from deaths due to progressive pump failure.[31] The Candesartan in Heart failure-Assessment of Reduction in Mortality (CHARM) trial, which enrolled heart failure patients with either low or preserved systolic function, showed that atrial fibrillation was associated with increased risk of mortality and cardiovascular morbidity regardless of ejection fraction.[32]

These studies, along with many others, have demonstrated adverse outcomes associated with atrial fibrillation in patients with heart failure. However, there are other trials that refute such prognostic effect. Analysis of data from the Vasodilator-Heart Failure Trial (V-HeFT) concluded that in patients with mild to moderate heart failure, atrial fibrillation did not increase cumulative mortality, sudden death, hospitalization rate, or major cardiovascular morbidity.[10] Data from the Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME-II) also showed that after adjustment for other variables such as age, ejection fraction, New York Heart Association class, renal function, and blood pressure, the presence or the development of atrial fibrillation was no longer independently related to an adverse outcome in patients with moderate to severe heart failure.[33] Post hoc analysis of the Carvedilol Or Metoprolol European Trial (COMET) showed that while the prognostic value of preexisting atrial fibrillation diminished after adjustment for other variables in patients with heart failure, the onset of new atrial fibrillation remained an independent predictor of subsequent all-cause mortality in patients with sinus rhythm at baseline.[34]

THERAPEUTIC APPROACHES

Beta-blockers are first-line agents common to the management of both atrial fibrillation and heart failure. Bisoprolol, metoprolol succinate, and carvedilol have been shown to have significant mortality benefit in heart failure[35] and also are effective for rate-control in atrial fibrillation as well. Anticoagulation is the cornerstone of therapy for stroke prophylaxis in atrial fibrillation, and atrial fibrillation is the primary indication for anticoagulation in heart failure. In addition, patients with heart failure require warfarin therapy in the presence of previous thromboembolic events, left ventricle thrombus, extensive ischemic regional wall motion abnormalities, and symptomatic heart failure with ejection fraction $<35\%$. Digoxin is another agent common to both atrial fibrillation and heart failure therapies, although it is not considered a first-line agent in either condition.[36] Digoxin is given to patients with systolic dysfunction (ejection fraction $\leq 40\%$) who are symptomatic despite treatment with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. In patients with atrial fibrillation who are unable to tolerate beta-blockers and other rate-modulating agents, digoxin remains a viable option for rate control.

Rhythm versus Rate Control

The major clinical trials on atrial fibrillation therapy (Table) have shown that pharmacologic rhythm control is not superior to rate control in terms of morbidity and mortality.[37-40] Under-represented in these trials, however, were patients with heart failure who are thought to benefit the most from

Table Comparison of Outcomes with Rate Control and Rhythm Control Strategies in the Major Atrial Fibrillation Studies

	Rate Control	Rhythm Control	*P* Value
AFFIRM[37]			
Death	25.9%	26.7%	.08
Major adverse events	32.7%	32%	NS
RACE[38]			
Death	7%	6.8%	NS
Major adverse events	17.2%	22.6%	NS
HOT CAFE[39]			
Death	1%	2.9%	NS
Major adverse events	8%	31%	.05
STAF[40]			
Death	8%	4%	NS
Major adverse events	10%	9%	NS

AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; NS = not significant; RACE = Rate-Control Efficacy in Permanent Atrial Fibrillation study; HOT CAFE = Polish How to Treat Chronic Atrial Fibrillation study; STAF = Strategies of Treatment of Atrial Fibrillation study.

the hemodynamic improvement associated with conversion to sinus rhythm. Subgroup analysis of patients with heart failure in the Rate-Control Efficacy in Permanent Atrial Fibrillation (RACE) study pointed towards a favorable outcome if sinus rhythm was maintained after cardioversion from atrial fibrillation.[41]

In the Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy (CHF-STAT),[7] the subgroup of heart failure patients with atrial fibrillation who converted to sinus rhythm with amiodarone treatment had significantly lower mortality than those who remained in atrial fibrillation. The same result was seen in a substudy of the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND), where patients with atrial fibrillation and heart failure who maintained sinus rhythm with dofetilide treatment had improved survival.[8] In a small prospective study, the CAFE-II trial found that restoration of sinus rhythm with amiodarone was associated with significant improvement in cardiac function and quality of life compared with rate control strategy.[42]

The landmark Atrial Fibrillation in Congestive Heart Failure (AF-CHF) trial,[43] however, showed no mortality or morbidity benefit of rhythm control over rate control (Figure). This was a large multicenter prospective randomized trial that compared current strategies for rhythm control for atrial fibrillation, specifically in patients with heart failure. Like the previous trials in the general atrial fibrillation population, the AF-CHF study found no clear evidence to recommend a routine rhythm control approach in patients with atrial fibrillation and heart failure. It further implied that the negative prognostic features associated with heart failure make atrial fibrillation more likely, but atrial fibrillation per se may not have an independent effect on outcomes. The different result seen in the AF-CHF trial compared with the previous studies might be explained by improved overall heart failure therapy in the AF-CHF trial, including a higher frequency of beta-blocker use (88%).

A notable observation in these studies is the suboptimal efficacy of pharmacologic agents in maintaining sinus rhythm (conversion to sinus rhythm in only 66% in CAFE-II, 51% in Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy, and 44% in Danish Investigations of Arrhythmia and Mortality on Dofetilide, with 58% atrial fibrillation recurrence in AF-CHF). The toxicity of anti-arrhythmic drugs increases morbidity, and this may have reduced the overall benefit of rhythm control in the AF-CHF study. Anti-arrhythmic drug therapy, especially Class I agents like quinidine and disopyramide, increases the risk of death from cardiac and arrhythmic etiologies in the setting of heart failure.[44] Although safer agents for atrial fibrillation like amiodarone, dofetilide, and azimilide do not increase mortality in patients with heart failure,[45] they are still associated with increased morbidity, as reflected by higher hospitalization rates due to anti-arrhythmic-related toxicity.[43]

The experimental agent dronedarone, a derivative of amiodarone with shorter half-life and devoid of iodine moiety, showed great promise in significantly reducing toxicity of anti-arrhythmic therapy in atrial fibrillation. The American-Australian Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS), and the European Trial In Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) confirmed dronedarone's superior safety profile in atrial fibrillation (albeit lower efficacy) compared with amiodarone.[46] In patients with advanced heart failure, however, the Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA)

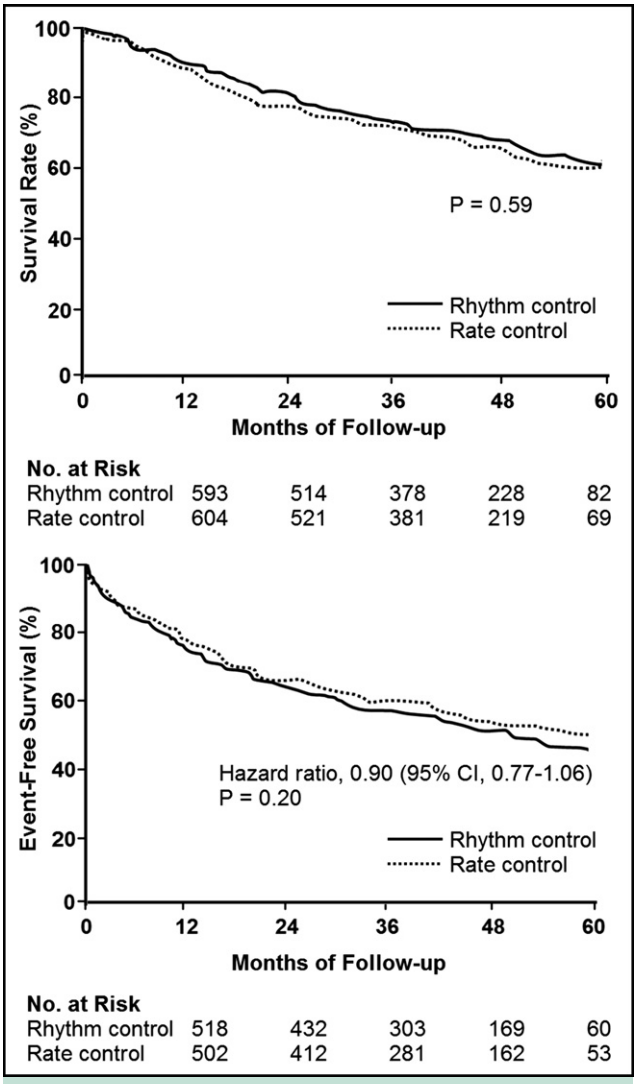

Figure Kaplan–Meier estimates of death from cardiovascular causes (**upper graph**) and probability of the composite outcome of death from cardiovascular causes, stroke, or worsening heart failure (**lower graph**) among 1376 patients with atrial fibrillation and congestive heart failure who were followed for a mean of 37 months in the Atrial Fibrillation in Congestive Heart Failure trial.[43] CI = confidence interval. Reprinted with permission from: Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667-2677.[43]

found that dronedarone was associated with deterioration of clinical status and increased mortality, prompting the early termination of the study.[47] On the other hand, the (ATHENA) trial (a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg twice a day for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter) found that dronedarone therapy was associated with reduction in cardiovascular events and mortality in patients with atrial fibrillation, 21% of whom had heart failure with functional class II or III symptoms. The authors speculated that dronedarone possibly increases cardiovascular mortality among patients with advanced and recently decompensated heart failure, but reduces cardiovascular mortality in patients with less severe heart failure.[48]

The lack of benefit of rhythm control over rate control strategies does not necessarily equate to lack of benefit of restoration of atrial fibrillation to sinus rhythm in heart failure. With a disappointing track record of current drug-based rhythm control strategies, attention is now focusing towards nonpharmacologic therapies in the management of atrial fibrillation in heart failure.

Surgical Rhythm Control

The Cox maze surgical procedure involves placing multiple incisions within the left and right atrial myocardium, primarily involving the structures around which reentry can develop to interrupt potential reentry pathways. The procedure has an excellent long-term efficacy, with nearly 90% rate of freedom from atrial fibrillation at 10 years and 94% 10-year survival. Major perioperative complications, however, occur in 13% of cases, with a 1.4% early operative mortality rate.[49] Although generally avoided in patients with heart failure, it has been shown to be safe and effective in patients with heart failure, resulting in significant improvement in ejection fraction, functional class, and symptoms.[50]

Catheter-based Ablation

As safer and less invasive alternatives to surgical approaches, catheter-based ablation techniques for rhythm control have been rapidly gaining popularity. Left atrial catheter ablation, intended to isolate the pulmonary veins where arrhythmogenic foci may originate, has been shown to be safe and effective in patients with atrial fibrillation. In a prospective study of patients with resistant atrial fibrillation and coexisting systolic heart failure, electrical isolation of the pulmonary veins by radiofrequency ablation resulted in significant improvement in cardiac function, symptoms, exercise capacity, and quality of life. Up to 78% of these patients with heart failure and atrial fibrillation were in sinus rhythm at 1-year follow-up. Complications were infrequent and occurred in $<1\%$ of cases.[51]

In patients with atrial fibrillation and heart failure, the progression of atrial fibrillation in the pulmonary vein antrum isolation vs atrioventrocular node ablation with biventricular pacing for treatment of atrial fibrillation in patients with congestive heart failure (PABA-CHF)[52] trial reported maintenance of sinus rhythm 6 months after catheter-based pulmonary vein isolation in 88% of patients receiving antiarrhythmic drugs and in 71% of patients not on any antiarrhythmic agent. No procedure-related deaths occurred, although 10% of patients had major complications, like pulmonary vein stenosis, pericardial effusion, and pulmonary edema. Compared with atrioventricular node ablation with biventricular pacing (a form of nonpharmacologic rate control), rhythm control with pulmonary vein isolation was associated with significantly improved exercise tolerance, cardiac function, and quality of life. Whether or not ablation techniques for atrial fibrillation will have a favorable impact on mortality, or whether the morbidity benefits continue in the long term for patients with heart failure is yet to be determined.

Non-anti-arrhythmic Therapy

Even with improved surgical and catheter ablation techniques, the substrates for atrial arrhythmogenesis in heart failure (eg, increased atrial load, dilatation, local conduction disturbances, and fibrosis) may become irreversible, making nonpharmacologic strategies for rhythm control not much more effective than anti-arrhythmic agents in atrial fibrillation. Beyond just rhythm or rate control, treatment of atrial fibrillation in heart failure also has started focusing on these substrates as possible therapeutic targets.

Statins are implicated in lowering the rates of atrial fibrillation independent of its cholesterol-lowering effect. Statins potentially have anti-ischemic, antioxidant, anti-arrhythmic, and anti-inflammatory properties that exert a stabilizing effect on the cardiac membrane and prevent atrial remodeling. Fish oils are thought to reduce arrhythmias through the same anti-inflammatory and membrane-stabilizing effects.[53] In patients with heart failure, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico - Heart Failure (GISSI-HF)[54] trial showed that fish oil is superior to placebo and statin in reducing mortality and hospitalization, although specific data on atrial fibrillation is lacking.

Atrial extracellular matrix fibrosis, induced by altered neurohormonal processes and RAAS activation in heart failure, is being increasingly recognized as an important factor in arrhythmogenesis. In animal models, ACE inhibitors significantly reduced atrial fibrosis in atrial fibrillation and heart failure, an effect that was not demonstrated with vasodilators.[16] Retrospective clinical studies on RAAS blockade in heart failure showed significant reduction in incidence of atrial fibrillation and improved outcomes with both ACE inhibitor and angiotensin-receptor blocker treatments, presumably by retarding atrial fibrosis through neurohormonal modulation.[55] True benefits also could be secondary to improvement in hemodynamics and cardiac performance. Several studies have reported the efficacy of ACE inhibitors and angiotensin-receptor blockers in preventing atrial fibrillation, and a meta-analysis of these trials

found that the greatest reduction in atrial fibrillation was in patients with heart failure.[56] The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-I) is currently evaluating in a large double-blind, placebo-controlled study the effect of the angiotensin-receptor blocker irbesartan on clinical outcomes in patients with atrial fibrillation.[57] Preliminary results show that irbesartan therapy reduced hospitalization from heart failure by 14% in patients with atrial fibrillation.[58]

Another deleterious neurohormonal response evoked in atrial fibrillation and heart failure is abnormal sympathetic activation. Beta-blocker therapy effectively blunts such maladaptive adrenergic response, and this mechanism is thought to significantly contribute to its beneficial effects in atrial fibrillation and heart failure, in addition to rate control and prevention of arrhythmias.[59] In patients with atrial fibrillation and heart failure, the use of beta-blockers was associated with a 42% reduction in mortality.[60]

CONCLUSION

Atrial fibrillation and chronic heart failure frequently coexist because of common risk factors and closely linked pathophysiologic processes. Their association is correlated with adverse prognosis. Rate-control strategy remains the standard of care because rhythm control therapy has yielded mixed results in patients with atrial fibrillation and heart failure. This is primarily because of the limitations of current anti-arrhythmic agents that are not that effective in maintaining sinus rhythm and also are associated with significant toxicities. Invasive and catheter-based treatment modalities are promising, but their long-term efficacy and cost-effectiveness are yet to be ascertained. Recent advances in understanding the complex relationship between atrial fibrillation and heart failure are paving the way towards better therapeutic strategies, both pharmacologic and nonpharmacologic. Although a number of questions still remain unanswered, it is hoped that a steady progress towards this endeavor would ultimately provide the clinicians with the most appropriate therapeutic strategy.

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REVIEW

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Primary Care of the Transplant Patient

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ABSTRACT

A total of 153,245 patients are living with a solid organ transplant in the US. In addition, patients are experiencing high 5-year survival rates after transplantation. Thus, primary care physicians will be caring for transplanted patients. The aim of this review is to update primary care physicians on chronic diseases, screening for malignancy, immunizations, and contraception in the transplant patient. Several studies on the treatment of hypertension and hyperlipidemia demonstrate that most agents used to treat the general population also can be used to treat transplant recipients. Little information exists on the medical management of diabetes in the transplant population, but experts in the area believe that the treatment of diabetes should be similar. Transplant recipients are at increased risk for all malignancies. Aggressive screening should be employed for all cancers with a proven screening benefit. Killed immunizations are safe for the transplant population, but live virus vaccines should be avoided. Women of childbearing age should be counseled about the impact of immunosuppressants on the efficacy and side effects of contraception.

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KEYWORDS: General internal medicine; Primary care; Transplantation

The 2006 annual report of the Scientific Registry of Transplant Recipients shows that by the end of 2004 there were 153,245 individuals living with a transplant in the US. In 2005, 16,072 individuals received a kidney transplant and 6000 received a liver transplant. Over 2000 individuals received a heart and 1400 received a lung transplant in the same year. As of 2005, there were over 89,000 individuals waiting for transplantation.[1] The survival rate for transplant recipients is high. Unadjusted 5-year survival rates for living donor renal and liver transplant recipients are 90% and 77%, respectively, while heart recipients' 5-year survival is 74%.[1] Because so many transplant recipients survive beyond the initial postoperative period, they are presenting to primary care offices in increasing numbers. Primary care physicians need to be prepared to evaluate and treat transplant recipients.

The primary care physician has the potential to play a major role in the prevention of illness and death for the transplant population. Among transplant recipients who have survived for at least 3 years after transplant, the cause of death is malignancy for 24% and complications of cardiovascular disease for 21%.[2] A large component of the primary care physician's activities revolve around early detection of malignancy and prevention of cardiovascular disorders. Thus, primary care physicians need to be experts in the special attributes of malignancy and vascular disease in transplant patients.

The goal of this review is to assist the general internist or family physician to provide primary care for transplant recipients. Initially, the immunosuppressants commonly used in transplant medicine are reviewed. The care of hypertension, hyperlipidemia, and diabetes is then discussed. Lastly, screening for malignancies, contraception care, and proper immunization practices are reviewed.

THE IMMUNOSUPPRESSANTS

Primary care physicians should have a working knowledge of the common immunosuppressants employed for the solid organ transplant population. These medicines have the potential for multiple side effects as well as interactions with medicines commonly prescribed in a primary care practice.

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The immunosuppressants used in transplant medicine include corticosteroids, cyclosporine, tacrolimus (FK506), sirolimus, azathioprine, and mycophenolate mofetil. A thorough discussion of the impact of corticosteroids on primary care practice is beyond the scope of this article and has been addressed previously.[3-7] Cyclosporine and tacrolimus are the most common immunosuppressants used in transplant medicine.[8-10] These calcineurin inhibitors and sirolimus are metabolized through the cytochrome P450 system, causing interactions with many medications employed in primary care. Medications that are metabolized through the same system (Tables 1, 2) can accelerate or decelerate the metabolism of these immunosuppressants, leading to either toxic or sub-therapeutic levels. Azathioprine and the newer immunosuppressant mycophenolate mofetil are purine synthesis inhibitors. They are not metabolized through the cytochrome P450 system and do not have as many problems with interactions.[11]

CLINICAL SIGNIFICANCE

- Primary care physicians provide long-term care for organ transplant recipients.
- Most antihypertensive and lipid-lowering therapies can be used in the transplant recipient.
- Aggressive screening should be employed for all cancers with a proven screening benefit.
- Live virus vaccines should be avoided, but killed vaccines are safe.
- Women of child-bearing age should be counseled that immunosuppressants affect contraception.

HYPERTENSION

The prevalence of hypertension is increased in transplant recipients compared, with the general population. Among liver transplant recipients, the prevalence is 55%-85%. Renal recipients and heart recipients have a prevalence of up to 90% and 100%, respectively.[12-14]

The pathophysiology of hypertension in transplant recipients is not fully understood, but is mediated through the use of immunosuppressants. Calcineurin inhibitors are known to increase the release of endothelin, leading to constriction of the afferent renal arteriole and a decrease in the glomerular filtration rate. This results in an expansion of the intravascular volume and an associated elevation in systemic blood pressure.[13]

The National Kidney Foundation Kidney Disease Quality Outcomes Initiative and the American Society of Transplantation have published guidelines for assessment and management of hypertension in patients who are transplant recipients. The appropriate target for blood pressure control in renal and liver transplant recipients is $<130/<80$ mm Hg.[12,15]

Several randomized controlled studies address treatment of hypertension in the transplant recipient.[14,16-25] The following classes of antihypertensives have been shown to be effective in this population: calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and diuretics. No single class of drugs has been shown to be more effective. Primary care physicians should consider the following in choosing an antihypertensive regimen. First, one should consider the transplant recipient's comorbid conditions in choosing an antihypertensive regimen. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are preferred in the presence of microalbuminuria or diabetes. Second, the pathophysiology of hypertension in transplant recipients should be considered. Theoretically, calcium channel blockers would be an appropriate agent for this group of patients because of their ability to counteract afferent arteriolar vasoconstriction. Diuretics would help to reduce volume expansion. Lastly, primary care physicians should consider drugs that reduce the cost of immunosuppressants. When calcium channel blockers such as diltiazem are used, cyclosporine, tacrolimus, and sirolimus levels increase, allowing for less costly lower doses of the medications.

Table 1 Medicines that Increase the Risk of Rejection in Transplant Recipients on Calcineurin Inhibitors

Antiseizure medicines
Phenobarbitol
Phenytoin
Carbamezipine
Antimicrobials
Isoniazide
Nafcillin
Substances
Tobacco
Marijuana

HYPERLIPIDEMIA

Hyperlipidemia is a common problem among transplant patients. Six to 12 months after liver transplantation, total cholesterol increases by 20%-43%, triglycerides increase by 38%-56%, and high-density lipoprotein is reduced by 50%.[26-29] The prevalence of hyperlipidemia for renal and heart transplant recipients is 90%[30-33] and 64%, respectively.[34]

The pathophysiology of hyperlipidemia in transplant recipients is multifactorial. Major factors include pretransplant lipid levels, weight gain that commonly occurs after transplantation, diabetes mellitus, and hypothyroidism. Immunosuppressants and medications used to treat hypertension also contribute to

Table 2 Medicines that Increase the Risk of Toxicity in Transplant Recipients on Calcineurin Inhibitors

Antimicrobials
Fluconazole
Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Rifampin
Antihypertensives
Diltiazem
Verapamil
Nicardipine
Immunosuppressants
Tacrolimus
Cyclosporine
Methylprednisolone
Foods
Grapefruit

the development of hyperlipidemia. Corticosteroids increase appetite and increase secretion of very low-density lipoprotein by the liver. Cyclosporine A inhibits bile acid hydroxylase, decreasing bile acid synthesis from cholesterol and increasing circulating low-density lipoprotein levels.[26-29]

Treatment decisions in the transplant population are influenced by the increased risk of metabolic syndrome caused by immunosuppressant medicines, and the increased risk of side effects and interactions with the calcineurin inhibitors. The National Kidney Foundation Kidney Disease Quality Outcomes Initiative has published guidelines on targets for lipid lowering in the renal transplant population. In these guidelines, transplanted patients are included in the highest risk category. The guidelines recommend that evaluation for dyslipidemia should occur at initial presentation and then annually thereafter. Drug therapy is recommended for a low-density lipoprotein remaining over 100 mg/dL after 3 months of lifestyle interventions.[35] In the absence of guidelines for heart and liver transplant recipients, primary care physicians should consider placing these patients in the high risk category, and following the guidelines for renal transplant recipients.

Recommendations for lifestyle interventions for the renal transplant recipient do not differ from interventions for the general population.[35-38] Again, in the absence of guidelines about lifestyle interventions, primary care physicians should adopt recommendations made for the renal transplant population. Patients should be counseled to decrease portion sizes and to exercise to control weight and diabetes. Transplant recipients also should avoid alcohol, tobacco, and high-dose oral contraceptives, as well as drugs that increase low-density lipoproteins.

Initial drug therapy for transplant patients with an elevated low-density lipoprotein should be a statin.[35] The impact of hydroxyl-methylglutaryl (HMG) Coa reductase inhibitors on cholesterol levels in solid organ transplant recipients has been studied in numerous small studies of short duration.[39-58] These studies demonstrate that the following statins: lovastatin, pravastatin, simvastatin, cerivastatin, and atorvastatin, are tolerated well and that they are effective, even at low doses, in lowering cholesterol levels. Two studies of heart transplant recipients have further demonstrated a decreased mortality rate when statin medicine is compared with placebo.[59,60] One study of renal transplant recipients demonstrated that fluvastatin is effective at reducing cardiac deaths and nonfatal myocardial infarctions, but did not reduce the rates of interventional coronary procedures or overall mortality.[61]

No long-term studies of other classes of lipid-lowering therapies have been performed, however, small prospective studies have demonstrated modest effectiveness for gemfibrozil,[48,57] nicotinic acid,[56] and fish oil supplements.[55] One retrospective analysis of ezetimibe has demonstrated it to be safe and effective in the renal transplant population.[62] One study comparing cholestyramine with gemfibrozil and simvastatin in heart recipients demonstrated that these agents had similar efficacy, however, most patients randomized to cholestyramine had dropped out by the end of the study due to gastrointestinal side effects.[48]

Side effects of statins are similar for transplant recipients compared with the general population. Because cyclosporine A causes elevated levels of almost all statins, the primary risk in patients taking this immunosuppressant is myopathy and rhabdomyolysis.[63] Of the HMG CoA reductase inhibitors, only fluvastatin has no reported cases of rhabdomyolysis. Doses up to 80 mg daily have been shown to be safe. Fluvastatin has much less of an interaction with cyclosporine A and is metabolized primarily through the cytochrome P 2C9 system, which could account for this difference. Primary care physicians should start other statins at lower doses to avoid muscular toxicity, and dose adjustments should be performed while carefully monitoring for symptoms of muscle weakness or pain. Creatinine phosphokinase levels should be checked before and after initiation or adjustment of statin therapy. Fibric acid derivatives also are associated with a greater risk of myositis and thus, a similar monitoring strategy should be employed. Bile acid derivatives have been shown to interfere with the absorption of immunosuppressant medicine. Thus, careful monitoring of immunosuppressant levels should be performed for patients who are treated with these agents. Nicotinic acid has an increased risk of hepatotoxicity in the transplant population and is associated with an additional increased risk of diabetes, gout, and gastrointestinal discomfort, as well as flushing and itching. Thus, transplant patients on these agents should undergo close monitoring of fasting glucoses and transaminase levels.[63]

DIABETES

The prevalence of diabetes increases to 53% after liver transplantation, compared with the general population,[64-66]

and to 22%[67] after renal and 30%[68] after heart transplantation.

In the postoperative period, factors that increase the risk of diabetes include increased stress levels, the use of steroids and calcineurin inhibitors, infection, and parenteral nutrition. Obesity that develops after transplantation causes increased tissue resistance, also contributing to an increased risk of developing diabetes.[64]

There are no published guidelines addressing how to translate diabetes treatment to the transplant population. The 2009 American Diabetes Association guidelines do not include specific recommendations for this group of patients.[69] For the general diabetic population, the American Diabetes Association recommends initial treatment with metformin for obese patients. For diabetics of normal weight, a sulfonylurea is recommended. Second-line therapy is insulin. The thiazolidenedione and incretin agents are reserved for third-line therapy.[69] There are no studies on the use of these agents in the transplant population. However, the metabolism of biguanides, sulfonylureas, and insulin would not be expected to affect levels of immunosuppressants. Thus, in the absence of data, experts state that, "The management of diabetes in transplant recipients is not substantially different from its management in non-transplant patients."[65] This should include lifestyle modification such as portion control, weight loss, avoidance of simple carbohydrates, regular exercise, and avoidance of high doses of steroids and calcineurin inhibitors. New research in this area addresses the downward adjustment of calcineurin inhibitors to avoid diabetes while preventing rejection of the transplanted organ.[70]

EARLY DETECTION OF MALIGNANCY

Screening for malignancy is a central activity of primary care providers. Multiple organizations, including the United States Preventive Services Task Force, the Canadian Medical Association, and the American Cancer Society, have published guidelines on cancer screening for the general population.[71-73] These publications do not include guidelines for screening transplant populations.

Recent studies have addressed the increased risk of malignancy in the solid organ transplant population.[74-89] The entire renal transplant population of Australia was compared with patients who had chronic renal insufficiency both before and after dialysis.[84] Almost all cancers had an increased incidence after transplantation. The highest ratio of observed to expected cancer events were in cancers of the lip, eye, penis, vulva, lymphoma, and Kaposi's sarcoma. Colon, lung, breast, cervix, and ovarian cancers also were disproportionately elevated after transplantation.

Because of the increased risk of malignancy in transplant patients, it would be advisable to screen for malignancies with reliable screening strategies. In the absence of guidelines, primary care physicians should consider maintaining an aggressive screening strategy for transplant recipients.

Nonmelanoma skin cancer is one of the most common cancers in solid organ transplant recipients, with squamous cell cancer the most common sub-type.[79,85-88] This cancer is an aggressive disease in transplant recipients, with a high risk of recurrence, metastasis, and death.[85,86] The pathophysiology of squamous cell cancer is linked to high levels of immunosuppression in this population.[88,89] Primary care physicians should counsel transplant recipients to avoid sun exposure, and should perform annual complete skin examinations. Primary care physicians also should counsel their patients to apply daily sun block with an SPF of 60 or greater.[90]

IMMUNIZATIONS

Transplant recipients are at increased risk of infectious diseases in the immediate postoperative period[91] and for as long as they are on immunosuppressants. There is little information available on the safety and efficacy of immunizations in the transplant population. Although killed virus vaccines are safe for transplant recipients, live virus vaccines are contraindicated. These include vaccines against herpes zoster, measles, mumps, rubella, intra-nasal influenza, oral polio, and the yellow fever vaccines. Transplant recipients should avoid prolonged contact with family members who have been immunized with these vaccines for 2 weeks after receiving these immunizations. Killed virus vaccines that are safe for transplant recipients include vaccines against influenza, *Streptococcus pneumoniae*, tetanus, diphtheria, pertussis, and hepatitis A and B.

Although killed virus vaccines are safe for transplant recipients, the efficacy of these vaccinations is unclear. Patients receiving the trivalent influenza vaccine have been shown to sero-convert up to 50%-95% of the time.[92-94] Hepatitis A virus immunization is associated with seroconversion rates of 97% initially, that decrease precipitously after 2 years.[95,96] Recombinant Hepatitis B titers also fall 2 years after immunization,[97] and Pneumovax immunoglobulin A and immunoglobulin M levels rapidly decrease 6 months after immunization.[98,99]

Because antibody titer response to immunization is reduced and of shorter duration, booster shots are under study for the transplant population. Heart transplant recipients who have been immunized before transplantation have been shown to have a better immunoglobulin G response to pneumococcal vaccination than those who receive their first pneumococcal vaccination after transplant.[100] Similarly, a booster immunization strategy of liver transplant patients increased the percentage with therapeutic titers against influenza.[94]

Primary care physicians should ensure that patients preparing for transplantation should receive all immunizations before surgery. Booster immunizations for the flu vaccine should be considered each year, and patients should be counseled to avoid family members who are ill or who have received a live virus immunization.

CONTRACEPTION

Fertility is restored in the majority of women of childbearing age after transplantation.[101,102] Despite the return to fertility, only 49% of women were counseled about contraception, and 93% of pregnancies in one Brazilian renal transplant cohort were unplanned.[103] Compared with the general population of women in Iran, renal transplant recipients were less likely to use oral contraceptive agents.[104] One small study of liver transplant recipients has demonstrated the safety and efficacy of low-dose hormonal contraception. In this study of 15 women who were followed for 12 months after liver transplantation, no cases of pregnancy or graft rejection occurred.[105]

Primary care physicians should apply similar contraindications for oral contraceptive agents to the transplant population as are applied to the general population, including a history of thromboembolism, smokers over the age of 35 years, and those with known cardiovascular disease. Transplant recipients who have hypertension or diabetes have a relative contraindication for hormonal therapy. Low-dose oral contraceptives should be considered for this group. Barrier methods such as the diaphragm are effective but have failure rates of 18%. The increased risk of urinary tract infections associated with the diaphragm may pose a greater risk for immunocompromised women.[106] Intrauterine devices also might be associated with an increased risk of infection, and the efficacy might be impaired due to the need for an intact immune system for full contraceptive function. Decreased efficacy of the intrauterine device has been reported in this population.[107]

CONCLUSION

Primary care physicians are called upon to care for an increasing number of transplant recipients. The role of the primary care physician is critically important to the survival of this population. Attention to meticulous chronic disease management, careful screening and immunization practices can serve to reduce morbidity and mortality. Immunosuppressants affect every aspect of this care. Physicians should be aware of the impact that immunosuppressants have on primary care. A summary of the recommendations for primary care physicians is shown in Table 3. There is a tremendous need for increasing knowledge that will help primary care physicians to care for the transplant population. Future studies are needed to address the safety and efficacy of medical treatments for chronic diseases, as well as to

Table 3 Summary Recommendations for the Primary Care of Solid Organ Transplant Recipients

Medications
1. Check for possible drug interactions of all new medications prescribed.
2. Check immunosuppressant levels 48 to 72 hours after initiation of any new medication expected to affect levels.

Hypertension
1. Target blood pressure is <130/<80 mm Hg for renal and liver transplant recipients and for other transplant recipients with renal disease or other cardiac risk equivalents.
2. The choice of blood pressure agents should be influenced by comorbid conditions, the pathophysiology of hypertension in transplant recipients, and drug effects on immunosuppressant levels.

Hyperlipidemia
1. The target LDL is <100 mg/dL for renal transplant recipients.
2. In the absence of data, PCPs should consider treating other transplant recipients to a target LDL of <100 mg/dL.
3. Statins should be used as first-line therapy.
4. Special attention should be paid to the increased risk of myopathy associated with statin use in the transplant population.

Diabetes
1. Recommendations of the American Diabetic Association should be applied to the transplant population.

Malignancy
1. Transplant recipients should be considered at high risk for all malignancies.
2. PCPs should consider shorter screening intervals.
3. Annual dermatological examinations should screen for skin malignancies.
4. Sunblock with an SPF of 60 or greater should be applied daily to sun-exposed skin surfaces.
5. Patients with newly diagnosed malignancy should be considered for a reduction in immunosuppressants.

Immunizations
1. All patients preparing for transplantation should receive immunizations against tetanus, diphtheria, pertussis, *Streptococcus pneumoniae*, hepatitis A and hepatitis B.
2. After transplantation, booster immunization should be provided for influenza, tetanus, diphtheria, *Streptococcus pneumoniae*, and hepatitis A and B.

Contraception
1. Women of child-bearing age should be counseled about the need for contraception after transplantation.
2. Low-dose oral contraceptive agents should be considered for women who have diabetes, hypertension, or hyperlipidemia and do not have contraindications for their use.
3. Women should be counseled about the decrease in contraceptive efficacy of intrauterine devices after transplantation.

LDL = low-density lipoprotein; PCP = primary care physician.

address cancer screening, early detection strategies, contraception, and immunization protocols for the transplant population.

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Diabetic Retinopathy: An Update on Treatment

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ABSTRACT

Diabetic retinopathy is a progressive disease that results from vascular injury due to chronic hyperglycemia. It is the leading cause of blindness in working-age adults in the US and is usually asymptomatic until late stages. Treatment with laser photocoagulation is effective at preventing severe vision loss; thus, diabetic patients should be referred for regular screening by an ophthalmologist. New inhibitors of vascular endothelial growth factor may provide targeted nonsurgical treatment to improve vision in diabetic retinopathy.

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KEYWORDS: Antiangiogenic therapy; Diabetic retinopathy; Intravitreal injection; Laser photocoagulation; Macular edema; Neovascularization; Retina; Vascular Endothelial Growth Factor; Vitrectomy

Two patients presented with mildly blurred central vision (20/30) in their left eyes. Patient 1 (Figure 1) has had diabetes and hypertension for 10 years. Patient 2 (Figure 2) has had uncontrolled diabetes for 30 years. Figure 1 demonstrates yellow exudates near the fovea with microaneurysms and dot-blot hemorrhages. Figure 2 reveals large neovascular fronds growing into the vitreous, capillary nonperfusion in the temporal macula, and laser photocoagulation scars superotemporally.

DIAGNOSIS

Patient 1 has clinically significant macular edema and mild nonproliferative retinopathy. Focal macular laser photocoagulation is required to prevent further vision loss. Patient 2 has high-risk proliferative diabetic retinopathy and a small tractional retinal detachment. She is at high risk for severe vision loss and will require aggressive intervention with panretinal photocoagulation and possible vitrectomy.

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Diabetes mellitus is estimated to affect 23.6 million individuals in the US,[1] and most patients with type I or type II diabetes have evidence of retinopathy after 20 years.[2,3] Diabetic retinopathy is the primary cause of blindness in adults aged 20-74 years in the US, causing an estimated 12,000 to 24,000 new cases of blindness annually.[1]

The major risk factors for diabetic retinopathy are hyperglycemia and increased duration of diabetes. Other risk factors include hypertension, hyperlipidemia, pregnancy, and microalbuminuria.[3,4] All of these risk factors contribute to retinal metabolic changes and microvascular injury that result in diabetic retinopathy.

Nonproliferative diabetic retinopathy is an early stage in disease progression. Loss of retinal capillary pericytes and endothelial cells has been demonstrated early in diabetes[5] and underlies the clinical signs of nonproliferative diabetic retinopathy, which include intraretinal dot-blot hemorrhages, microaneurysms, and venous beading. Microvascular injury with infarction of small areas of the nerve fiber layer leads to puffy white patches on the retina called cotton-wool spots (Table).

Proliferative diabetic retinopathy is a later and more severe stage of the disease characterized by neovascularization. Sustained retinal ischemia causes release of vascular endothelial growth factor and insulin-like growth factor, which induce growth of new vessels on the optic disk, iris, retinal surface, and into the vitreous. The abnormal vessels are fragile and may hemorrhage into the vitreous or form

fibrous bands, causing tractional retinal detachment. Neovascularization of the iris may occlude aqueous outflow, resulting in neovascular glaucoma.

Clinically significant macular edema is the most common cause of moderate vision loss (≤20/40 vision) in all types of diabetic retinopathy. As microvascular damage weakens the blood-retinal barrier, plasma leaks from vessels into the retina; when this fluid is resorbed, lipid and lipoprotein elements are retained in the retina and are visible as yellow exudates.

The majority of severe vision loss (≤20/200 vision) in diabetic retinopathy is the result of complications from proliferative diabetic retinopathy—vitreous hemorrhage, retinal detachment, and neovascular glaucoma. Most patients with diabetic retinopathy are asymptomatic until very late stages of the disease. Symptoms, when present, may include decreased visual acuity and contrast sensitivity, new onset floaters, or dark curtain.

MANAGEMENT

Current treatment strategies for diabetic retinopathy are thought to be 90% effective in preventing severe vision loss.[6] Given the asymptomatic nature of diabetic retinopathy until its latest stages and the effectiveness of early intervention,[7] referral for regular screening by an ophthalmologist is essential. The American Academy of Ophthalmology recommends type I diabetics be examined 3-5 years after diagnosis and yearly thereafter; type II diabetics should be examined at the time of diagnosis and yearly thereafter.[6]

Primary prevention of diabetic retinopathy involves strict glycemic and blood pressure control. The Diabetes Control and Complications Trial[8] and the United Kingdom Prospective Diabetes Study[9] showed that intensive glycemic control substantially reduces the incidence and progression of diabetic retinopathy in type I and II diabetes. Blood pressure control also significantly reduces the incidence and progression of diabetic retinopathy, although the specific antihypertensive agent utilized does not appear to be significant.[10,11]

Established secondary interventions for diabetic retinopathy include pan-retinal photocoagulation, focal laser photocoagulation, and surgical vitrectomy. Pan-retinal photocoagulation applies hundreds of laser burns to the peripheral retina, reducing the amount of ischemic retina that drives angiogenesis. Pan-retinal photocoagulation has been the cornerstone of treatment for severe retinopathy since the Diabetic Retinopathy Study, which showed that it reduces the risk of severe vision loss by 50% in patients with severe diabetic retinopathy.[12]

Focal laser photocoagulation is indicated for patients with clinically significant macular edema; it targets microaneurysms near the macula, reducing the plasma leakage responsible for intraretinal swelling. The Early Treatment Diabetic Retinopathy Study showed that focal laser photocoagulation reduces the risk of moderate vision loss by 50%-70% in patients with macular edema.[7]

Vitrectomy involves surgical removal of the vitreous, blood, and fibrovascular retinal tissue. It is recommended for severe proliferative diabetic retinopathy when it is unresponsive to pan-retinal photocoagulation, associated with severe vitreous hemorrhage, or associated with traction on the macula. The Diabetic Vitrectomy Study first demonstrated the ability of early vitrectomy to preserve or restore vision in patients with severe proliferative diabetic retinop-

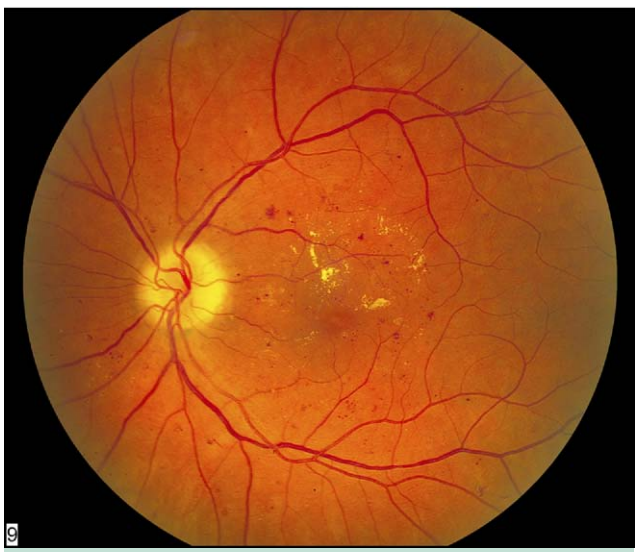

Figure 1 Fundus photograph of the left eye of a patient with nonproliferative diabetic retinopathy demonstrating microaneurysms, dot-blot intraretinal hemorrhages, and yellow exudates. (Courtesy of Peter McKay, COMT).

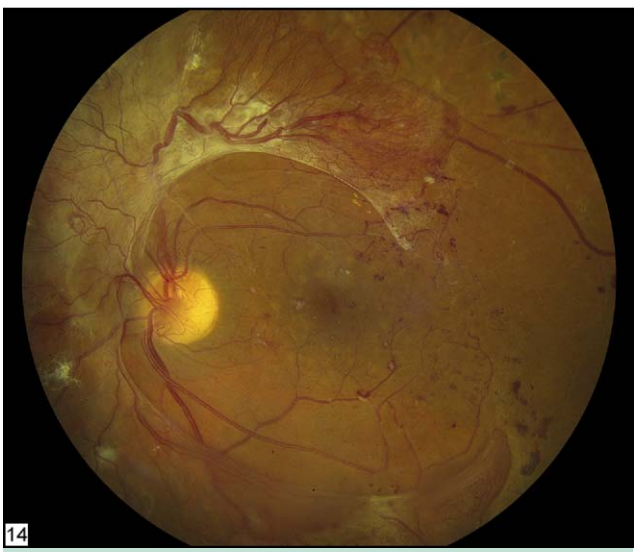

Figure 2 Fundus photograph of the left eye of a patient with proliferative diabetic retinopathy demonstrating large neovascular fronds and old laser photocoagulation scars. (Courtesy of Peter McKay, COMT).

Table Funduscopic Findings in Diabetic Retinopathy

Nonproliferative Diabetic Retinopathy	Microaneurysms; venous beading; intraretinal hemorrhages; cotton-wool spots
Proliferative diabetic retinopathy	Abnormal new vessels of the retina, optic disc, or iris; vitreous hemorrhage
Diabetic macular edema	Retinal thickening; yellow exudates

athy;[13] since this study, many advances have been made in vitreoretinal surgery.

Vascular endothelial growth factor is produced by multiple retinal cell types in response to ischemia. It is a potent promoter of vascular permeability and neovascularization, making it the primary target for emerging treatment for diabetic retinopathy. Intravitreal injection of vascular endothelial growth factor into healthy primate eyes induces changes similar to proliferative diabetic retinopathy.[14] The concentration of vascular endothelial growth factor is increased by a factor of 20 in the vitreous of patients with proliferative diabetic retinopathy, and levels subsequently fall after pan-retinal photocoagulation.[15]

Currently, 4 intravitreal inhibitors of vascular endothelial growth factor provide promising possibilities for targeted nonsurgical treatment of diabetic retinopathy. Pegaptanib (Macugen, OSI/Eyetech, Melville, NY) and bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) have been demonstrated to reduce neovascularization and improve diabetic macular edema, respectively.[16-18] Ranibizumab (Lucentis, Genentech, Inc.) and VEGF Trap-Eye (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) are currently being evaluated for treatment of macular edema.

All of the vascular endothelial growth factor antagonists appear to require repeated intravitreal injections to sustain benefits, increasing the likelihood of local complications including uveitis, cataract, retinal detachment, and endophthalmitis. Theoretical concerns about occlusion of native retinal vessels, hypertension, stroke, myocardial infarction, and thrombosis have not been demonstrated in large studies of these agents.

The central role of vascular endothelial growth factor in severe, vision-threatening diabetic retinopathy warrants further investigation to determine if inhibitors of this protein will become part of routine care of diabetic retinopathy.

Intravitreal triamcinolone acetonide also has received significant attention for the treatment of diabetic macular edema. While triamcinolone does reduce macular thickness in the short term,[19] its 3-year visual benefit was found to be inferior to standard focal macular laser, with higher rates of glaucoma and cataract.[20]

CONCLUSION

As the leading cause of new-onset blindness in the working-age population in the US, diabetic retinopathy causes a profound burden of psychologic, functional, and economic morbidity. Diabetic retinopathy progresses predictably from the early nonproliferative stage to the later proliferative stage. It is largely asymptomatic until its latest stages, emphasizing the importance of early referral by primary care providers for regular screening examinations. Application of focal macular laser and panretinal photocoagulation at appropriate disease stages reduces the risk of further vision loss. Ongoing research will determine the utility of inhibitors of vascular endothelial growth factor as an additional tool in the management of diabetic retinopathy.

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CLINICAL EFFECTIVENESS
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The Improving Continuous Cardiac Care (IC^3) Program and Outpatient Quality Improvement

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For decades, the American College of Cardiology (ACC) and the American Heart Association (AHA) have distilled clinical evidence into guidelines[1] and, recently, guidelines into performance measures.[2] Yet, there remains a significant gap between the potential for high quality health care and the quality of health care that is actually delivered to patients.[3] Although some programs, such as the ACC's National Cardiovascular Data Registries[4] and the AHA's Get with the Guidelines,[5] have demonstrated improvements in the quality of inpatient care,[6] the quality and opportunity for improvement in the outpatient setting are largely unknown. The importance of quantifying and improving care in the outpatient setting is becoming increasingly important, with the recent emphasis on reporting of postdischarge mortality and readmission rates as a reflection of inpatient hospital care. Thus, there is a compelling need to systematically measure the quality of care, as quantified by established performance measures, in the outpatient setting.

CHALLENGES IN DEVELOPING AN OUTPATIENT REGISTRY

The development of an outpatient registry faces unique challenges. Data collection for inpatient registries is typically performed retrospectively, without time constraints and often days after patient discharge.

In contrast, an outpatient registry requires the repeated acquisition of patient-level data—such as symptoms, vital signs, and medications—that are likely to change over time. The nature of these data mandate that they be captured contemporaneously to ensure accuracy and completeness of assessment during an outpatient clinical encounter. Finally, outpatient practices are typically unwilling or unable to devote significant time and personnel resources for additional data collection. Therefore, the development of a successful outpatient quality improvement registry would need to address all these factors in its design and implementation.

THE IMPROVING CONTINUOUS CARDIAC CARE PROGRAM (IC^3)

In 2007, the American College of Cardiology cited as a priority the development of an outpatient cardiac registry, thereby laying the foundation for the Improving Continuous Cardiac Care (IC^3) program (https://www.improvingcardiaccare.org). Recognizing that the IC^3 program would need to move beyond traditional inpatient registries, the ACC, in collaboration with the Mid America Heart Institute in Kansas City, Missouri, designed the IC^3 program to enable practices to both assess and improve their quality of care and to thrive in a performance-based health care system.

Conceptually, the IC^3 program collects 27 ACC/AHA Performance Measures in the outpatient setting. This is aligned with the philosophy that if a professional organization endorses a performance measure as essential for delivering high quality care, it also should provide the mechanism to systematically collect and use that measure in routine clinical care. Thus, the IC^3 program has been designed to collect, at the point of care, a variety of longitudinal patient data, including patients' symptoms, vital signs, medications, and intercurrent hospitalizations. IC^3 then converts submitted data into actionable reports at the practitioner, practice, and national levels so that benchmarking and opportunities for improvement can be identified. The IC^3 program also can use these data to report, on behalf of the practice, to payers, including Medicare and its Physician

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Authorship: Drs. Chan and Spertus had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in: interpretation of the data, drafting of the manuscript, and critical revision of this manuscript for important intellectual content.

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Quality Reporting Initiative program. Ultimately, IC^3 will become a program that will support the sharing of best practices in order to elevate performance across centers of care.

Understanding that there is heterogeneity in practice size, patient volume, use of electronic medical records (EMRs), and incentives for participation, the IC^3 program has developed multiple mechanisms for data collection that can be deployed by a practice. These include: a paper form, an online data collection site, and collaboration with EMR vendors and system integrators to collect the data elements needed to participate in IC^3. This range of data collection modalities allows practices to participate in IC^3 regardless of whether they have internet or EMR access.

IMPROVING CARE FOR OUTPATIENTS

There are several ways in which the IC^3 program may improve outpatient care for cardiac patients. First, by capturing the data components for each of the performance measures, the IC^3 program allows practices to measure their adherence to all the performance measures for each chronic cardiac condition. A list of the more than 25 performance measures for coronary artery disease, heart failure, atrial fibrillation, and hypertension is provided in the Table. Practices receive quarterly summaries of their adherence to each performance measure; as a result, gaps in the delivery of evidence-based care can be identified and corrected.

Second, practices can use their quarterly reports to compare results with other IC^3 practices around the country. As a result, practices receive not only their absolute rates of adherence for each performance measure, but also their relative performance to other practices (Figure). This information can catalyze efforts to increase adherence to evidence-based medicine. Third, practices can evaluate their performance over time, tracking whether internal quality improvement efforts increased adherence for performance measures, particularly for those where adherence had been suboptimal. Fourth, the IC^3 program allows practices to examine variations within their group and to identify individual clinicians with low adherence to evidence-based medicine. And fifth, for those practices entering data through EMRs, mechanisms for decision support may be developed to prompt clinicians to apply evidence-based medicine during each clinical encounter. For those practices without an EMR, the IC^3 data collection form itself can serve as a decision aid if used concurrently with the delivery of patient care.

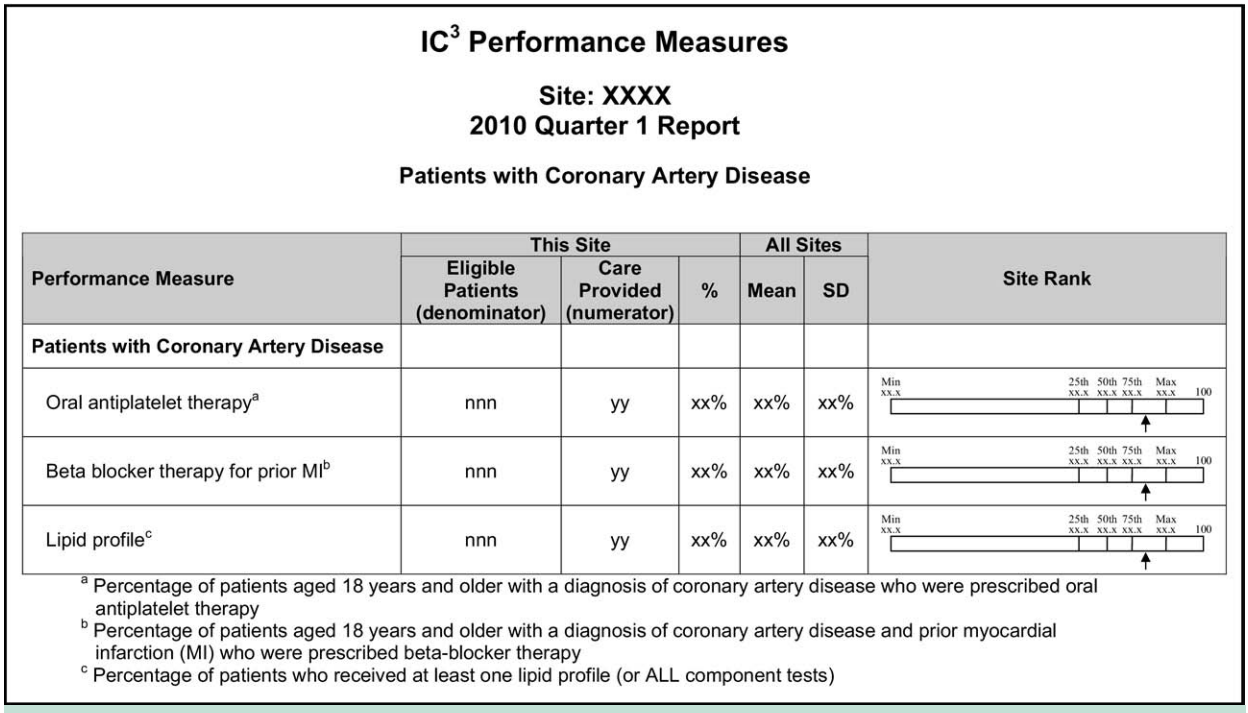
BUILDING THE ECONOMIC CASE FOR IC^3

Recognizing that the burden of data entry for IC^3 is not insignificant, the ACC has worked to make the economic case for practices to participate in IC^3. Many practices already devote substantial resources to retrospectively collect data on pay-for-performance and Physician Quality Reporting Initiative participation at year's end. Such retrospective data collection is of

Table American Heart Association and American College of Cardiology Performance Measures for Common Cardiac Conditions

Coronary artery disease	Use of beta-blocker therapy for patients with prior MI
	Use of antiplatelet therapy
	Use of ACE inhibitor or ARB therapy for patients with DM or LV dysfunction
	Annual assessment of activity level and symptoms
	Annual assessment with lipid profile
	Use of appropriate lipid-lowering therapy
	Percentage of visits with a blood pressure assessment
	Annual screening for DM
	Annual screening for cigarette smoking
	Percentage of cigarette smokers who receive smoking cessation intervention
	Percentage of patients with an MI, CABG, PCI, or cardiac valve surgery referred for outpatient cardiac rehabilitation
Heart failure	Annual assessment of LV function
	Percentage of newly diagnosed patients with initial laboratory evaluation
	Use of beta-blocker therapy in patients with LV dysfunction
	Use of ACE inhibitor or ARB therapy in patients with LV dysfunction
	Use of warfarin in patients with atrial fibrillation
	Percentage of visits with a clinical examination pertaining to volume status assessment
	Percentage of visits with a weight assessment
	Percentage of visits with a blood pressure assessment
	Annual patient education on disease management
	Percentage of visits with an assessment of activity level
	Percentage of visits with an assessment for symptoms of volume overload
Atrial fibrillation (nonvalvular only)	Annual assessment of stroke risk in patients with nonvalvular atrial fibrillation
	Warfarin use in patients with nonvalvular atrial fibrillation at high risk for stroke
	Monthly assessment of INR levels in patients on warfarin
Hypertension	Percentage of visits with a blood pressure assessment
	Percentage of visits with a documented plan for hypertension treatment if the blood pressure was elevated

MI = myocardial infarction; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DM = diabetes mellitus; LV = left ventricular; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; INR = international normalized ratio.



IC³ Performance Measures

Site: XXXX
2010 Quarter 1 Report

Patients with Coronary Artery Disease

Performance Measure	This Site			All Sites		Site Rank
	Eligible Patients (denominator)	Care Provided (numerator)	%	Mean	SD	
Patients with Coronary Artery Disease						
Oral antiplatelet therapy[a]	nnn	yy	xx%	xx%	xx%	Min xx.x 25th xx.x 50th xx.x 75th xx.x Max xx.x 100
Beta blocker therapy for prior MI[b]	nnn	yy	xx%	xx%	xx%	Min xx.x 25th xx.x 50th xx.x 75th xx.x Max xx.x 100
Lipid profile[c]	nnn	yy	xx%	xx%	xx%	Min xx.x 25th xx.x 50th xx.x 75th xx.x Max xx.x 100

[a] Percentage of patients aged 18 years and older with a diagnosis of coronary artery disease who were prescribed oral antiplatelet therapy
[b] Percentage of patients aged 18 years and older with a diagnosis of coronary artery disease and prior myocardial infarction (MI) who were prescribed beta-blocker therapy
[c] Percentage of patients who received at least one lipid profile (or ALL component tests)

Figure Mock draft of a practice's quarterly report for select performance measures. By participating in the Improving Continuous Cardiac Care (IC³) program, practices will receive quarterly reports on their adherence to each performance measure. Practices, in turn, case use these reports to identify areas of high and low performance. Additionally, they can compare their relative performance among practices throughout the US, as the quarterly reports will also report the range of adherence (minimum, median, maximum, 25th and 75th rate) for each performance measure and the practice's rate along this spectrum.

minimal utility for quality improvement because the data are already outdated by the time they are collected, retrospective processes do not provide actionable goals or comparisons with other practices, and they may be incomplete for certain performance measures.

Because the IC³ program collects data on adherence for each of the performance measures and Physician Quality Reporting Initiative items, the ACC, through the IC³ program, can provide comprehensive reporting for pay-for-performance and Physician Quality Reporting Initiative on behalf of a given practice. Therefore, the burden of entering data prospectively in IC³ can be offset by the time and resources traditionally required for retrospective data collection, while also providing added value for the use of that data, beyond merely reporting to accrediting agencies. Of course, this calculus also does not take into consideration the potential quality improvement that can be achieved with internal and external benchmarking from IC³ participation, which also could provide financial rewards to practices. To this end, the ACC is in discussion with payers who have expressed interest in learning more about the IC³ program.

CONCLUSION

While significant gains have been made to quantify and improve the quality of inpatient cardiac care, little is known about the quality of care in the outpatient setting. This is particularly concerning, given high rates of mortality and readmission for outpatients with myocardial infarction and heart failure. The IC³ program provides the infrastructure to follow the care of outpatients with cardiac disease—an effort that has unique challenges distinct from inpatient registries. By identifying gaps in the use of evidence-based medicine, tracking performance over time, and enabling contemporaneous decision support for busy clinicians, the IC³ program has the potential to transform the quality of outpatient cardiac care.

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DIAGNOSTIC DILEMMA
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Exotic Origin, Familiar Culprit

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PRESENTATION

Certain diseases are great mimickers in medicine, presenting with diverse clinical manifestations that masquerade as other entities. We present a case, which illustrates the importance of considering these diseases in the differential diagnosis of patients who present with non-specific signs and symptoms.

A 74-year-old recent Ethiopian émigré presented to our emergency department with a 7-day history of abdominal pain that had worsened over the previous 24 hours. She also complained of nausea, vomiting, and diarrhea. Her family added that she had been coughing chronically and eating poorly for several years. Notable physical exam findings included cachexia with abdominal tenderness and guarding. A computed tomography (CT) scan of the patient's abdomen revealed pneumoperitoneum, a moderate amount of ascites, and diffuse small-bowel thickening (Figure 1). A chest CT scan revealed a pneumonia involving the right upper, middle, and lower lobes and a few prominent mediastinal nodes (Figure 2).

ASSESSMENT

An emergent exploratory laparotomy revealed a moderate amount of turbid ascites and a carcinomatosis-like studding of the entire small bowel, large bowel, and mesentery. A 10-cm cecal mass with overlying necrotic omentum was identified as the cause of the bowel perforation. Two deposits also were seen on the surface of the right lobe of the liver. The surgeon electively performed a right hemicolectomy with end Brooke ileostomy.

The patient recovered well postoperatively. Her cancer antigen 125 level was found to be elevated (783 U/mL), and her carcinoembryonic antigen level was 3.4 ng/mL (reference range: 0-3.0). Final pathology of multiple specimens from the bowel revealed florid, necrotizing, granulomatous inflammation (Figure 3).

DIAGNOSIS

Human immunodeficiency virus (HIV) and tuberculin skin tests were negative, and an induced sputum sample was negative for acid fast bacilli by fluorochrome staining. Analysis of the peritoneal fluid revealed many polymorphonuclear lymphocytes but no organisms by Gram stain or culture. However, positive auramine-rhodamine stains for acid fast bacilli on portions of the patient's omentum and colon led to a diagnosis of gastrointestinal tuberculosis (TB).

Tuberculosis is a significant cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that there were 9.2 million new cases and 1.7 million deaths from TB in 2006.[1] The largest burden of the disease is in Africa and Asia.[1] In addition to the lungs, TB can involve the intestines, peritoneum, lymph nodes, and solid organs, including the liver, spleen, kidney, and pancreas. Gastrointestinal TB is one of the most common forms of extra-pulmonary TB.[2]

Gastrointestinal TB infection often occurs after reactivation of latent tuberculous foci established from hematogenous spread from a primary lung focus. It also can occur through hematogenous spread from active pulmonary or miliary TB, ingestion of bacilli from sputum or infected milk products, lymphatic spread from infected lymph nodes, or direct spread from adjacent organs, such as the Fallopian tubes and adnexa.[3] Within the gastrointestinal tract, the ileocecal area is the most common site of infection, as it is rich in lymphoid tissue and is a site of relative stasis.[3] Infection results in tubercle formation, caseous necrosis, mucosal ulceration, granuloma formation, fibrosis, and scarring.[3]

Because gastrointestinal TB might present with nonspecific signs and symptoms that mimic other conditions, such as malignancy and inflammatory bowel disease, it often presents a diagnostic challenge.[4,5] The most common clinical signs and symptoms reported in case series have been ascites, abdominal pain, abdominal distention, fever, anorexia, weight loss, and weakness.[4-11] Nausea, vomiting,

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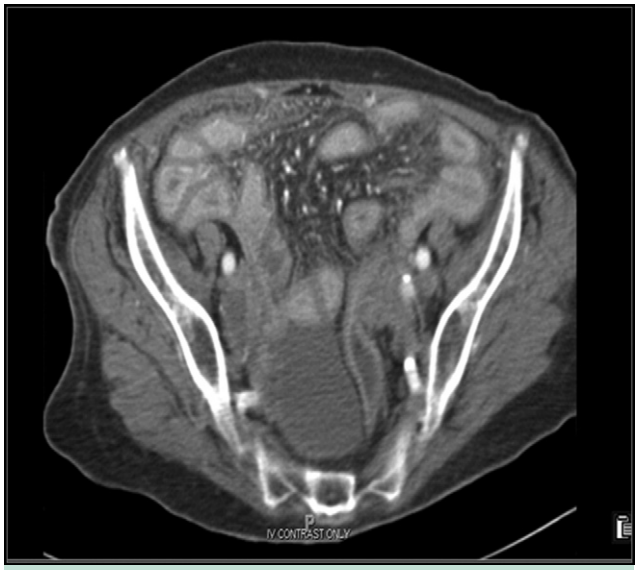

Figure 1 Abdominal CT scan revealing ascites and thickened small bowel.

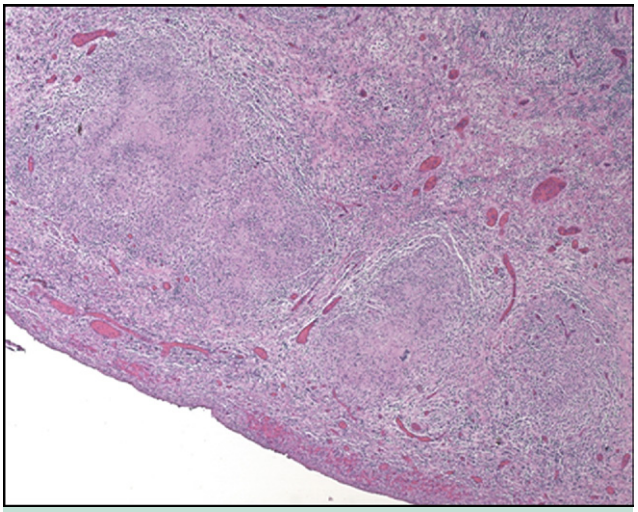

Figure 3 Surgical pathology specimens of right colon and distal ileum revealing florid, necrotizing, granulomatous inflammation.

and diarrhea also are frequently reported.[5,7] Because of the insidious nature of the disease, afflicted patients typically have symptoms for several weeks or months before presentation.[5-7,10] They might present with an acute abdomen from acute intestinal obstruction or intestinal perforation.[2,12] Common laboratory findings are anemia, an elevated erythrocyte sedimentation rate, and hypoalbuminemia.[4,9-11] Many patients have elevated cancer antigen 125 levels, which in women may lead to a misdiagnosis of ovarian cancer.[11] Indeed, Thakur et al.[13] suggest that high serum cancer antigen 125 levels in the setting of an abdominopelvic mass with or without ascites should always raise a suspicion of TB. TB skin tests are falsely negative in more than 70% of patients.[4,10,11] About 30% of patients have a history of prior TB or evidence of active TB at other sites.[4,10]

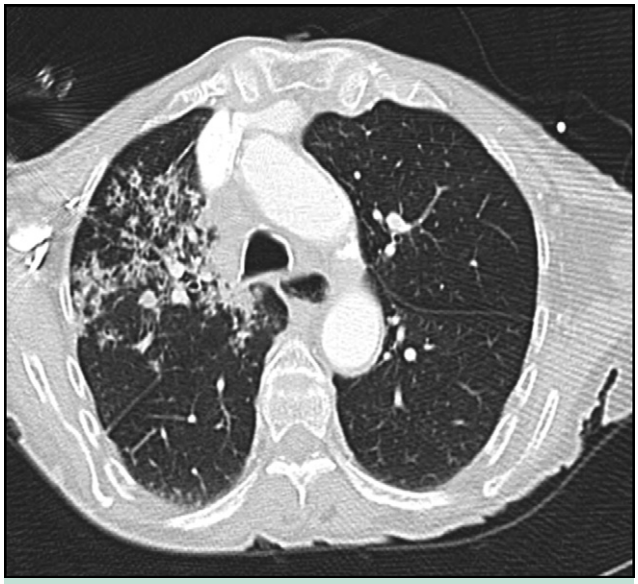

Figure 2 Chest CT scan showing a right-sided pneumonia.

Abdominal ultrasound and CT scans can aid in the diagnosis of gastrointestinal TB. These imaging techniques often reveal ascites, peritoneal thickening or nodules, bowel wall thickening, omental and mesenteric thickening, and lymphadenopathy.[4,5,8,11] Definitive diagnosis is made from histology and/or culture of specimens obtained via invasive techniques such as endoscopy, colonoscopy, laparoscopy, or laparotomy.[7,9] Findings via laparoscopy or laparotomy include ascites, diffuse involvement of the visceral and parietal peritoneum, enlarged lymph nodes, omental thickening, and small and large bowel lesions.[4,7] Histology of frozen sections typically reveals granulomatous inflammation with central caseous necrosis.[4,5] Acid-fast bacilli smears are positive in 50-60% of specimens, and cultures (which allow for drug susceptibility testing) are positive in 40-80% of specimens.[4-6] Other possible diagnostic techniques include polymerase chain reaction tests for *M. tuberculosis* in ascitic fluid obtained via paracentesis and testing of adenosine deaminase activity in ascitic fluid.[11]

MANAGEMENT

More than 80% of patients with gastrointestinal TB completely recover after 9-12 months of standard antituberculous therapy.[4,7] The standard therapy consists of 2 months of "4-drug" treatment (with rifampicin, isoniazid, pyrazinamide, and ethambutol) followed by continued rifampicin and isoniazid treatment for the remaining duration of therapy.[6]

Our patient was empirically started on 4-drug therapy with rifampin, isoniazid, pyrazinamide, and ethambutol, as well as pyridoxine. She had very poor oral intake throughout her hospitalization and required nasogastric tube place-

ment for nutritional support. Her albumin was low at 1.2 g/dL. She gradually improved clinically and was discharged to a nursing home, where she continued to show improvement. Upon discharge from the nursing home, she received 4-drug therapy under direct supervision until her return to Ethiopia about 1 month later, where she was to continue anti-TB medications for a total of 6 months prior to considering reversal of her ostomy.

This case illustrates that physicians must maintain a high degree of suspicion for the diagnosis of gastrointestinal TB in patients from endemic countries as well as in immunocompromised patients. Given the varied clinical manifestations of the disease and the fact that it may mimic other conditions, the diagnosis is often delayed or missed, leading to increased morbidity and mortality from inappropriate treatment.

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A Post-cure Complication

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PRESENTATION

Long-term drug therapy for hepatitis C virus (HCV) infection would prove to have persistent effects—both desirable and undesirable. A 29-year-old woman with chronic hepatitis C, genotype 4, was to embark on a treatment regimen of oral ribavirin, 1000 mg, once daily and subcutaneous injections of pegylated interferon alfa-2b, 80 μg, once a week. At her initial physical examination, she had a body mass index of 26 (25-29 indicates overweight). Laboratory results showed that her alanine transaminase level, at 88 IU/mL, was well above the normal reference value (<31 IU/mL). Her albumin level and prothrombin time were within the normal range. She had no other relevant medical or family history.

In the first month, the patient reported anorexia, asthenia, and a weight loss of 8.8 lb (4 kg). Therapy continued, and just before the 48-week treatment period ended, she developed signs of bilateral lipoatrophy at the interferon injection site on her abdomen (Figures 1 and 2).

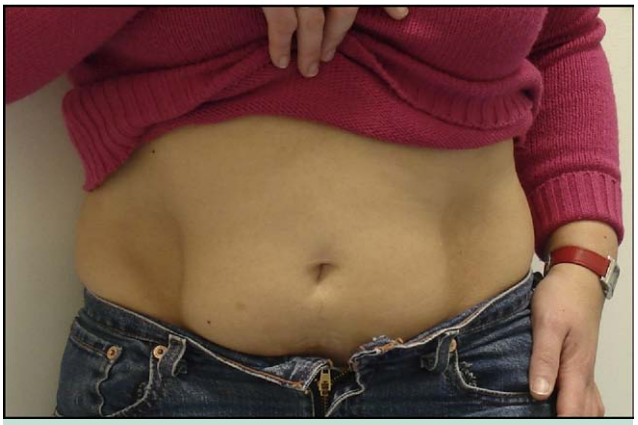

Figure 1 This is the way the patient's abdomen looked at the end of the 1-year treatment period.

ASSESSMENT

The loss of subcutaneous fat at the patient's injection site was examined by specialists in the dermatology department. They confirmed a diagnosis of bilateral lipoatrophy. Six months after interferon treatment ended, a sustained antiviral response to therapy was verified with a negative HCV-RNA test.

DIAGNOSIS

Lipoatrophy is usually secondary to an inflammatory process. In this case, it was attributed to the patient's 1-year course of interferon alfa-2b. Sometimes, differentiation between the cutaneous manifestations of hepatitis C infection and interferon therapy is not possible. A temporal relationship between the beginning of therapy and the appearance of the lesion is needed if the effect is to be ascribed to the drug.

Hepatitis C infection is a common cause of morbidity and mortality, affecting 3% of the world's population. In industrialized countries, chronic hepatitis C causes 40% of cirrhosis cases and 60% of hepatocellular carcinoma cases. It also is the leading indication for liver transplants, accounting for 30% of the surgeries. Currently, the standard regimen for chronic hepatitis C infection is subcutaneous pegylated interferon and oral ribavirin, a combination intended to produce a sustained antiviral response.[1]

Interferon therapy has been associated with a number of cutaneous complications. The most common dermatologic side effect, occurring in 15-20% of cases, is localized inflammatory skin lesions at the injection site. Progression to ulceration and necrosis, though infrequent, has been described.[2,3] The pathogenesis of progression is unknown, but a local immune-mediated inflammatory process might be involved.

Alopecia is one of the most frequently occurring cutaneous secondary reactions to interferon treatment, with a prevalence of around 10%-20%. Although the condition is gen-

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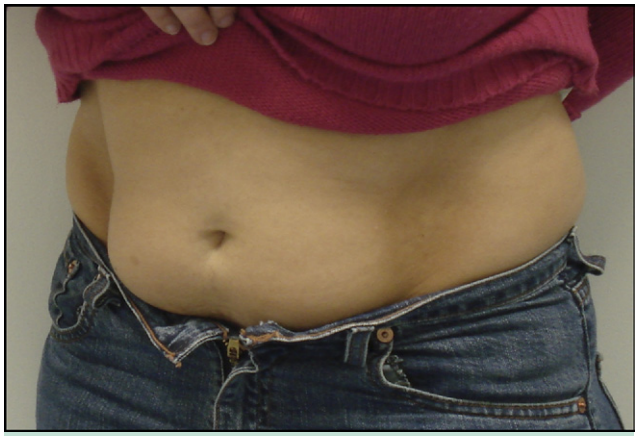

Figure 2 Another view is seen here.

erally mild, a more severe type, alopecia universalis, has been reported in a few patients. However, it was reversible once therapy was stopped.

Other complications of the skin and mucous membranes include oral pigmentation, trichomegaly, nail pigmentation, aphthous ulcers, and urticaria. It has been shown that patients with previous dermatologic diseases, such as psoriasis, seborrheic keratosis, or lichen planus, may suffer an exacerbation.[4] Overall, hospital admission is rarely required for most cutaneous and mucous membrane reactions to therapy.

Lipoatrophy secondary to subcutaneous injections has been described in conjunction with several drugs, including insulin, corticosteroids, vasopressin, antibiotics, human growth hormone, iron dextran, diphtheria-pertussis-tetanus vaccine, antihistamines, and glatiramer acetate, a treatment for multiple sclerosis.[5] Localized lipoatrophy also has been reported during treatment with interferon beta-1a and interferon beta-1b in patients with multiple sclerosis.[6] Until now, however, lipoatrophy has not been reported in patients with hepatitis C or in patients treated with interferon alfa. Although different pathogenic mechanisms have been proposed for each of these drugs, lipoatrophy most probably is the shared late or residual stage of a previous drug-induced localized panniculitis.

In some studies with glatiramer acetate, for example, biopsy of the depressed areas showed "fibrosis of the dermis and subcutis with reduction in the size of the fat lobules and minimal mononuclear infiltrates."[7] It is likely that the drug has a direct toxic effect on the adipocytes, inducing a local inflammatory response that is followed by a hypersensitivity reaction and residual lipoatrophy.

The mechanism whereby lipoatrophy lesions appear at the site of pegylated interferon injections remains to be clarified. Hypothetical explanations include stimulation of local adhesion molecules, proinflammatory chemokine expression, and a direct chemotactic effect on immune cells by interferon.[8] Why this complication seems to occur more frequently among patients with multiple sclerosis than those with hepatitis C infection is unknown.

A further point to consider is the possible pathogenic role of the polyethylene glycol molecule. Polyethylene glycol is often used as an additive in products such as topical drugs and cosmetics, and the literature refers to several cases of unwanted cutaneous side effects caused by this additive; particularly, contact dermatitis.[9]

MANAGEMENT

The patient's disfigurement persisted for several months. She was referred to a plastic surgeon for treatment that subsequently achieved good results. To our knowledge, this is the first published case of lipoatrophy after subcutaneous injection of pegylated interferon alfa in a patient with hepatitis C infection.

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Computer Calls for Cardiology Consult STAT!

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PRESENTATION

Although the electronic readouts provided by electrocardiographic systems often include an interpretation of the electrocardiogram (ECG), the clinician must not rely on this interpretation alone. In the following case, the "assistance" provided by the computer's interpretation of a routine ECG proved quite misleading.

An apparently healthy soldier on active duty presented to a bare-bones medical clinic in Iraq to undergo a routine physical exam for Airborne school. He was 23 years old, asymptomatic, and recently had passed his physical fitness test by running 2 miles in 14.5 min. He had an unremarkable medical history with no syncope or recent upper respiratory symptoms, was not taking any prescription or over-the-counter medications or supplements, and had no known medication allergies. He was a light smoker (5 pack-years), but denied any intake of alcohol or caffeine. He was 70 inches tall and weighed 147 lb (body mass index, 21). There was no history of sudden death in his family.

The soldier had never had an ECG. When one was performed as part of the standard screening for his physical exam, the medics performing the test had no reason to expect anything other than unremarkable results. They were thus alarmed and confused when the system readout proclaimed "** ** ACUTE MI ** **"!

ASSESSMENT

The soldier's ECG showed ST wave elevation in leads II, III, aVF, and V2–V6 (Figure 1), which the ECG system interpreted as evidence of an acute myocardial infarction. Although the system readout called for an immediate cardiology consultation, the patient's vital signs were completely normal, with a blood pressure of 115/72 mm Hg, heart rate of 62 beats/min, respiratory rate of 15 breaths/min, temperature of 98.2°C, and oxygen saturation on room air of 99%. A physical exam revealed no murmur, gallop, rub, thrill, displaced point of maximal intensity, jugular venous distension, lower extremity edema, crackles, or other abnormalities.

DIAGNOSIS

Although acute myocardial infarction can present with elevated ST waves, the sudden occlusion of a cardiac artery usually elevates ST waves only in the area of the blockage and rarely causes diffuse ST wave elevation such as that seen in the soldier's ECG (Figure 1). His asymptomatic presentation, normal physical exam, good functional status, and lack of atherosclerotic risk factors also suggested that the machine's diagnosis of acute myocardial infarction was incorrect.

Diffuse ST wave elevation is a typical sign of pericarditis or early repolarization. Differentiating these conditions can be difficult, but early repolarization is characterized by a shortened ST segment, an elevated J point, and concave ST-wave elevation, usually in the mid-to-lateral precordial leads.[1] The soldier's ECG demonstrated a shortened ST segment and concave ST wave elevation, suggesting early repolarization, and the absence of chest pain argued against pericarditis. In a landmark article, Ginzton and Laks described ECG changes that favor a diagnosis of early repolarization over that of pericarditis;[2] these changes include a lack of PR interval displacement and a T-wave amplitude 4 times greater than the ST-wave elevation in leads I, II, V4, V5, and V6. The demonstrable lack of PR interval displacement and the size of the T wave (4 times greater than the ST-wave elevation in leads in leads I, II, V5, and V6) in the soldier's ECG (Figure 1) confirmed the diagnosis of early repolarization.

Closer examination of the ECG revealed an irregular heart rate interpreted by the ECG system as "Sinus rhythm with AV dissociation and junctional rhythm with premature supraventricular complexes." The P waves were difficult to see in the ECG but were most obvious in leads aVR and V2.

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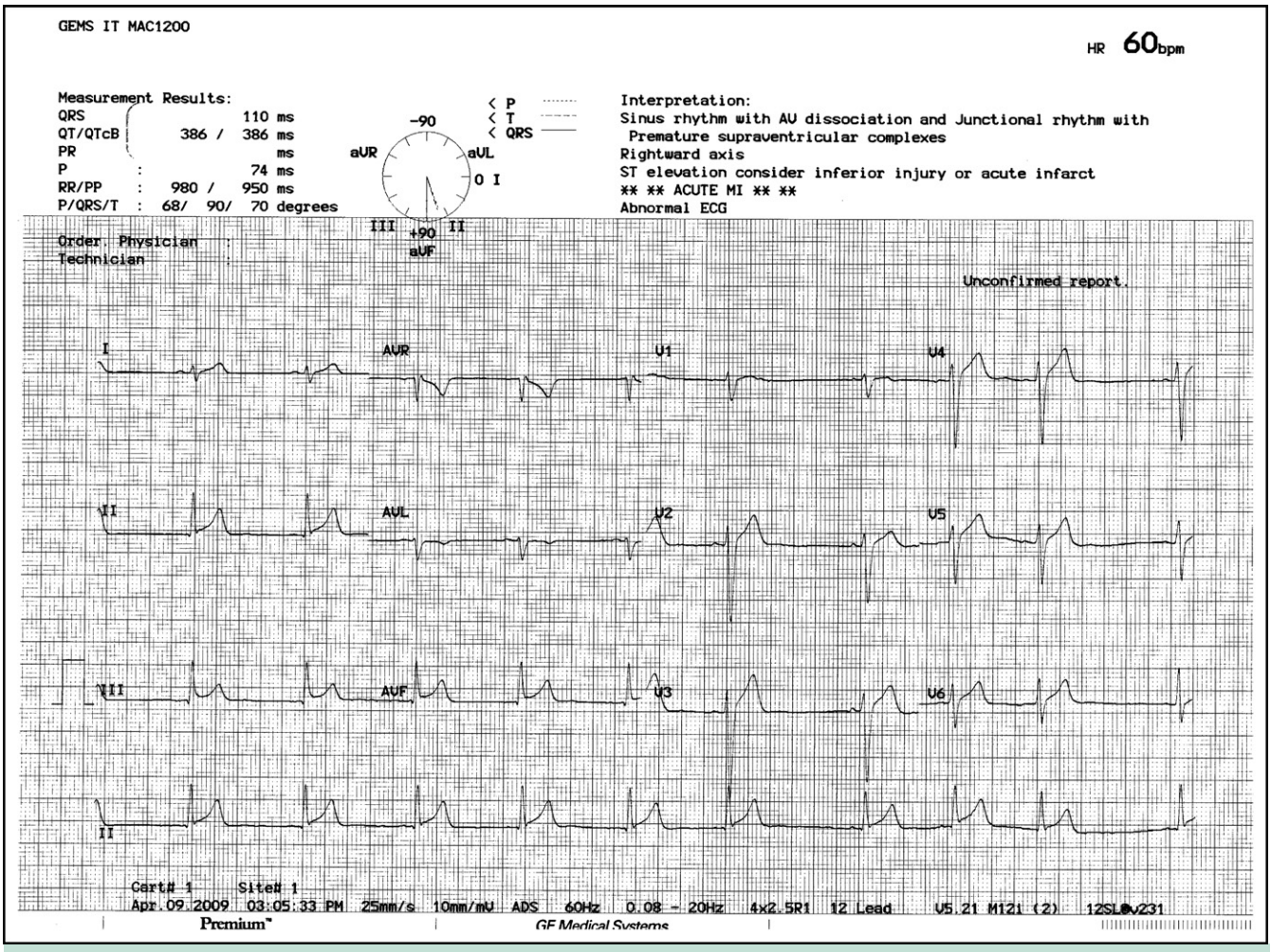

Figure 1 The asymptomatic patient's ECG displayed diffuse ST-wave elevation, irregularity, and indeterminate axis deviation.

Atrioventricular dissociation was ruled out because every QRS complex had a P wave and consistent PR interval. An ectopic atrial rhythm seemed unlikely because the P waves were upright, and the heart rate was 60 beats/min. The patient appeared to have respiratory sinus arrhythmia, a common cause of irregular rhythm in young, healthy individuals. It arises when the vagal and sympathetic nervous [system] signals to the sinoatrial node change with respiration. Quantification of this phenomenon is complex, with three separate possibilities for diagnosis.[3]

All the ECG intervals were within normal limits, but the QRS axis was indeterminate, with a value of +90° (a normal frontal plane axis is between –30° and +90°),[4] leading to a machine interpretation of "Rightward axis," a condition considered to be abnormal until proven otherwise. Some possible causes for rightward axis include left ventricular infarction, thin body habitus, and left posterior fascicular block (also called a posterior hemiblock) of the left bundle branch. The diagnostic criteria for left posterior fascicular block include a frontal plane axis of +90–180°, an rS complex in leads I and aVL, a qR complex in leads III and aVF, and a QRS duration of less than 120 ms.[4]

Although the soldier's ECG met all of the above criteria for left posterior fascicular block, this diagnosis should be made only after other causes of right axis deviation are ruled out.[5] Because almost all left posterior fascicular blocks have frontal plane axis values greater than 110°, and the patient's axis oscillated from 87° to 91°, thin body habitus appeared to be the most likely reason for the occasional indeterminate axis.

MANAGEMENT

Despite the alarming messages from the ECG machine, the soldier's ECG actually suggested good health (although new evidence suggests that early repolarization might not be a benign normal variant as originally thought[6]). He was, therefore, approved for Airborne school.

In performing routine physicals, general practitioners are expected to interpret ECGs. Although the ECG system-calculated intervals and axis can be useful, relying on the system's interpretations alone can lead to unnecessary cardiology consultation or even hospitalization. Knowledge of normal variants is thus vital for these providers.

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IMAGES IN RADIOLOGY
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Diabetes Mellitus and Confusion

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PRESENTATION

Diabetes mellitus can predispose patients to many additional health calamities. A 54-year-old Hispanic woman with a known history of diabetes presented to the emergency department with a 1-day history of confusion, fever, nausea, and vomiting. On arrival, she had a temperature of 101.1° F (38.4° C), blood pressure of 115/73 mm Hg, heart rate of 125 beats/minute, respiratory rate of 20 breaths/minute, and an oxygen saturation of 99% on room air. Her physical examination disclosed dry mucous membranes, tachycardia with regular rhythm, clear lungs, mild tenderness to palpation on the suprapubic area, and dry skin with decreased turgor. She was disoriented and unable to respond appropriately to questions.

ASSESSMENT

The initial laboratory work identified an elevated white blood cell count of 15.4×10^3 cells/mm^3; 92% were neutrophils, and 30% of these were bands. A chemistry panel showed a blood urea nitrogen concentration of 51 mg/dL, a serum creatinine concentration of 2.5 mg/dL, and a blood glucose level of 801 mg/dL. The patient's urinalysis was significant for many bacteria, 8 red blood cells per high-power field, 43 white blood cells per high-power field, and a glucose concentration of 1000 mg/dL. A plain abdominal radiograph revealed an enlarged right kidney with an air crescent along its peripheral margin (Figure 1). Retroperitoneal ultrasound confirmed the presence of air in the right kidney without evidence of obstruction. Abdominal computed tomography (CT) without contrast showed an enlarged right kidney with intraparenchymal air. It was surrounded by perinephric air that could be tracked up to the adrenal gland and down along the right lateroconal fascia (Figure 2).

DIAGNOSIS

Based on the radiographic findings, the patient was diagnosed with extensive, unilateral, Class 3A emphysematous pyelonephritis with acute nonoliguric renal impairment. This acute necrotizing infection of the kidney and surrounding tissue may cause gas formation in areas such as the renal parenchyma, collecting system, and perinephric tissue.[1] Urinary tract obstruction, most commonly due to urinary calculi, is seen in as many as 25% of reported cases. Emphysematous pyelonephritis is 5-6 times more common among females than males, but diabetes mellitus is apparently the primary predisposing factor, since a history of diabetes is noted in 70-96% of patients.[1,2]

Usually, emphysematous pyelonephritis is caused by gas-forming bacteria. The most commonly identified organism is *Escherichia coli,* followed by *Klebsiella pneumonia.*[1-5] Cases also have been attributed to *Proteus, Pseudomonas, Enterobacter, Clostridium, Aspergillus, Bacteroides*, and *Candida* species.[2,4,6-8] While pathogenesis of emphysematous pyelonephritis remains poorly understood, glucose fermentation is thought to play a major role in gas production.[3,8] Samples of gas taken from affected kidneys have yielded hydrogen and carbon dioxide, which are known products of glucose fermentation. Specifically, hydrogen gas is a product of fermentation pathways unique to *Enterobacteriaceae* organisms and anaerobes.[2,3] High glucose levels in tissue, impaired host response, urinary tract obstruction, and decreased perfusion have been postulated to influence the extent of gas production.[2,7,8]

Most patients with emphysematous pyelonephritis present with nonspecific signs and symptoms. Fever, nausea, vomiting, changes in mental status, flank, back and abdominal pain, dyspnea, acute renal function impairment, and shock are common.[2,7,8] Presence of thrombocytopenia, altered mental status, or acute renal failure on presentation are associated with a poor prognosis.[2]

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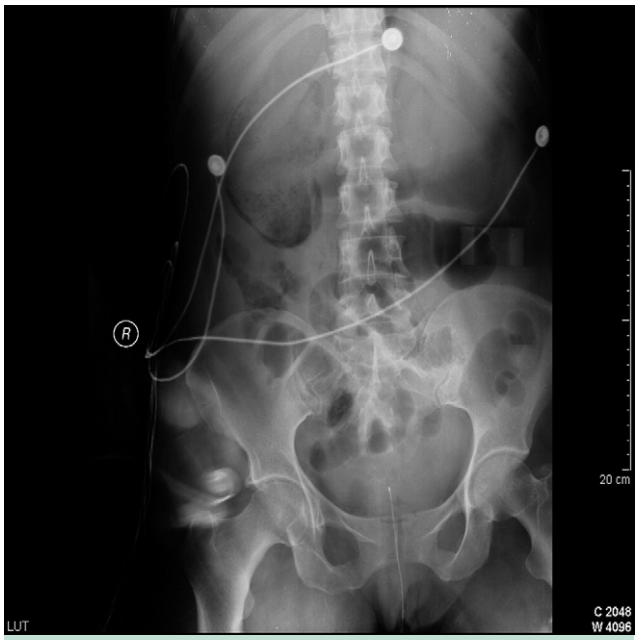

Figure 1 A radiograph of the abdomen showed an enlarged right kidney with an air crescent along the peripheral kidney outline.

Diagnosis of emphysematous pyelonephritis is established radiographically.[3,8] Although plain radiography and ultrasound can be used, CT of the abdomen is the preferred diagnostic tool. Abdominal CT defines both the extent and location of the gas and characterizes any destruction of renal parenchyma. In addition, the diagnostic sensitivity for CT is 100% in patients with emphysematous pyelonephritis, compared to 69% and 65%, for plain radiography and ultrasound, respectively.[4]

MANAGEMENT

No standard therapy has been defined for emphysematous pyelonephritis. Most treatment regimens, selected on the basis of radiologic findings and the patient's underlying condition, consist of combinations of intravenous antibiotics, percutaneous drainage, and total nephrectomy.[2,3-9] Table 1 presents the radiologic classification of emphysematous pyelonephritis used for management of our patient's case. For patients with localized disease (class 1 and 2), percutaneous drainage with antibiotic treatment is recommended initially. This treatment also is recommended for patients with extensive disease (class 3 and 4) and < 2 poor prognostic factors (ie, thrombocytopenia, acute renal impairment, altered mental status, or shock). Surgical nephrectomy is reserved for those with extensive emphysematous pyelonephritis; that is, cases with ≥ 2 poor prognostic factors, widespread intraparenchymal destruction, or inadequate response to conservative management with antibiotics and percutaneous drainage.[2]

Table 1 Classification of Emphysematous Pyelonephritis

Class	Radiologic Findings on CT
1	Gas in the collecting system
2	Gas in the renal parenchyma without extension to extrarenal space
3A	Extension of gas or abscess to perinephric space
3B	Extension of gas or abscess to pararenal space
4	Bilateral EPN or solitary kidney with EPN

CT = computed tomography; EPN = emphysematous pyelonephritis.

Overall mortality from emphysematous pyelonephritis ranges from 13-50%.[5] Medical management alone is associated with a much higher mortality rate than is medical management combined with additional percutaneous drain-

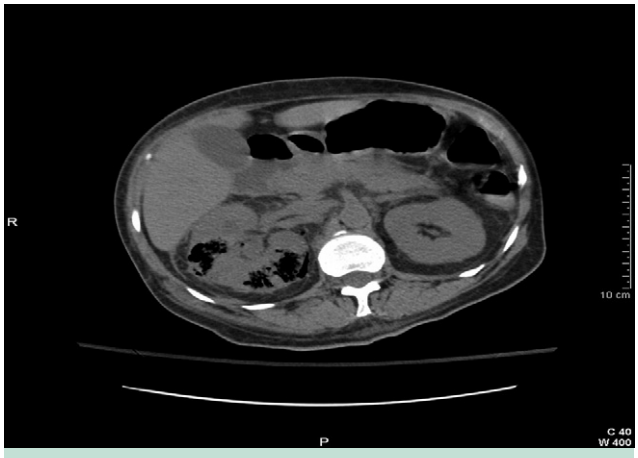

Figure 2 Computed tomography of the abdomen indicated extensive air within the right renal parenchyma (dark areas).

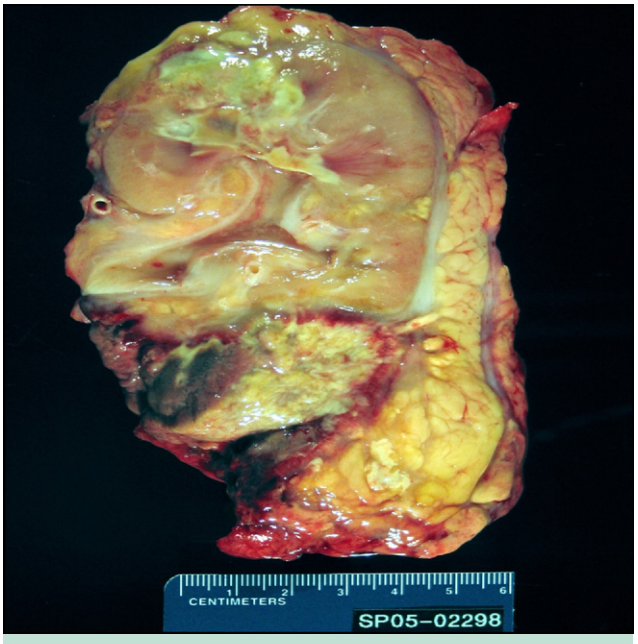

Figure 3 Evidence of necrosis can be seen at the inferior pole of the removed kidney.

age or surgical nephrectomy. Somani et al reported 13.5% mortality in patients undergoing percutaneous drainage and medical management compared with 50% in those receiving medical management alone.[4] Mortality in patients with emergency nephrectomy was reported as 25%.

Our patient was initially treated with fluid resuscitation, antibiotic therapy, and glucose control. Blood and urine cultures obtained on arrival subsequently revealed *Klebsiella pneumoniae*. Given the extent of intraparenchymal destruction, consultants from both the urology and nephrology departments recommended nephrectomy. However, the patient refused the procedure and was treated with antibiotics and percutaneous drainage.

A CT performed 2 weeks later showed persistent emphysematous pyelonephritis with multiple fluid collections in the perinephric space. When the patient was informed of the failure to respond to conservative management, she agreed to undergo surgical nephrectomy. Necrosis at the inferior pole was evident in the gross specimen of the kidney (Figure 3). Pathological findings included vascular sclerosis, glomerulosclerosis, and large areas of coagulation necrosis (Figure 4). The patient was discharged home in stable condition, and at 1-month follow-up, she was completely asymptomatic with normal renal function.

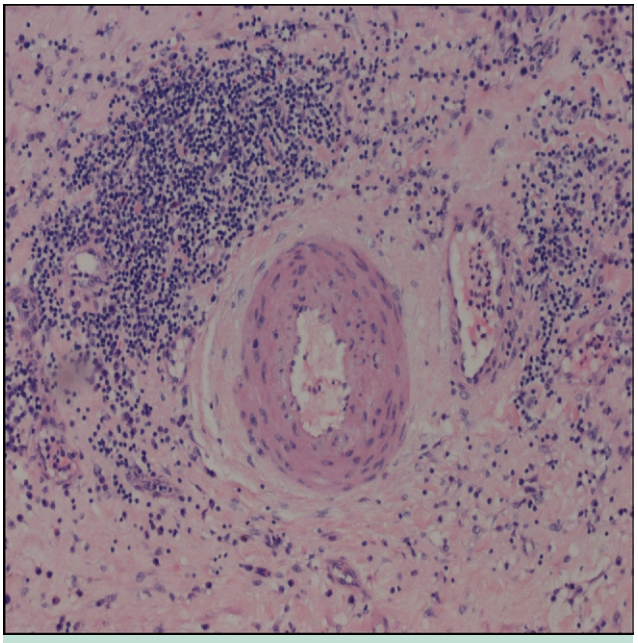

Figure 4 A histologic examination of the diseased kidney disclosed vascular sclerosis and tissue inflammation.

ACKNOWLEDGMENTS

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CLINICAL RESEARCH STUDY

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Analgesic Use and the Risk of Hearing Loss in Men

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ABSTRACT

BACKGROUND: Hearing loss is a common sensory disorder, yet prospective data on potentially modifiable risk factors are limited. Regularly used analgesics, the most commonly used drugs in the US, may be ototoxic and contribute to hearing loss.

METHODS: We examined the independent association between self-reported professionally diagnosed hearing loss and regular use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen in 26,917 men aged 40-74 years at baseline in 1986. Study participants completed detailed questionnaires at baseline and every 2 years thereafter. Incident cases of new-onset hearing loss were defined as those diagnosed after 1986. Cox proportional hazards multivariate regression was used to adjust for potential confounding factors.

RESULTS: During 369,079 person-years of follow-up, 3488 incident cases of hearing loss were reported. Regular use of each analgesic was independently associated with an increased risk of hearing loss. Multivariate-adjusted hazard ratios of hearing loss in regular users (2+ times/week) compared with men who used the specified analgesic <2 times/week were 1.12 (95% confidence interval [CI], 1.04-1.20) for aspirin, 1.21 (95% CI, 1.11-1.33) for NSAIDs, and 1.22 (95% CI, 1.07-1.39) for acetaminophen. For NSAIDs and acetaminophen, the risk increased with longer duration of regular use. The magnitude of the association was substantially higher in younger men. For men younger than age 50 years, the hazard ratio for hearing loss was 1.33 for regular aspirin use, 1.61 for NSAIDs, and 1.99 for acetaminophen.

CONCLUSIONS: Regular use of aspirin, NSAIDs, or acetaminophen increases the risk of hearing loss in men, and the impact is larger on younger individuals.

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KEYWORDS: Analgesics; Hearing loss; Prospective study

Hearing loss is the most common sensory disorder in the US and afflicts over 36 million people.[1] Data from the National Health and Nutrition Examination Survey (NHANES) demonstrate that not only is hearing loss highly prevalent among the elderly, but approximately one third of those aged 40-49 years already suffer from hearing loss.[2] The 5-year incidence of developing hearing loss in adults aged 48 years and older is 21%.[3] Even mild hearing loss can compromise the ability to understand speech in the presence of background noise or multiple speakers, leading to social isolation, depression, and poorer quality of life.[4-7]

Aspirin, acetaminophen, and ibuprofen are the 3 most commonly used drugs in the US.[8] Although 17% of the total population uses aspirin at least weekly, over 28% of men aged 45 years and above are aspirin users. Similarly, acetaminophen is used at least weekly by 23% of the population and ibuprofen is used by 17%.[8] The ototoxic effects of high doses (several grams per day) of salicylates, reversible hearing loss and tinnitus, are well documented.[9] In contrast, low-dose salicylate has been reported to protect against aminoglycoside[10] and noise-[11] induced hearing loss, possi-

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bly through an effect on the outer hair cell motor protein or inhibition of cyclooxygenage.[12] High doses of nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be ototoxic in animals and in human case reports,[13] potentially through a reduction in cochlear blood flow.[9] Pre-exposure to salicylates and NSAIDs might potentiate noise-induced hearing loss.[14,15] Acetaminophen might deplete glutathione,[16] which has been shown to protect the cochlea from noise-induced damage.[17,18] The relation between acetaminophen and hearing loss has not been studied.

Given that analgesic use might result in pathophysiologic changes in the cochlea and that regular use of these analgesics is so common, the relation of these medications and hearing loss might be an important public health issue. Therefore, we prospectively examined the association between regular analgesic use and risk of hearing loss in over 26,000 men.

CLINICAL SIGNIFICANCE

- Hearing loss is the most common sensory disorder in the US and factors other than age and noise might influence the risk of hearing loss.
- Regular use of aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs, the most commonly used drugs in the US, might increase risk of hearing loss.
- The increased risk of hearing loss associated with regular analgesic use might be greater among younger men, particularly those below age 60 years.

METHODS

Participants

The Health Professionals Follow-up Study originally enrolled 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40-75 years of age at baseline in 1986. Study participants filled out detailed questionnaires about diet, medical history, and medication use. These questionnaires have been administered every other year, and the 20-year follow-up exceeds 90%. The 2004 long-form questionnaire included a question about whether the participant had been professionally diagnosed with hearing loss, and if so, the date of diagnosis. Of the 31,496 men who returned the long-form questionnaire, 8291 (26.3%) reported a diagnosis of hearing loss. Those who reported hearing loss diagnosed before 1986 ($n = 2845$) or cancer other than nonmelanoma skin cancer (due to possible exposure to ototoxic chemotherapeutic agents) were excluded from the analysis. Recent data from NHANES demonstrate that 43% of white men aged 60-69 years exhibit low- to mid-frequency hearing loss and 93% exhibit high-frequency hearing loss.[2] Thus, because age is such a strong risk factor and the prevalence of hearing loss is so high among the elderly, we also excluded men as they reached age 75 years during follow-up. The number of men included in the analysis was 26,917.

Ascertainment of Analgesic Use

On the 1986 questionnaire and every 2 years thereafter, men were asked about regular use, defined as 2 or more times per week, of aspirin, NSAIDs, and acetaminophen. Our primary analyses examined regular analgesic use. If information on analgesic intake was missing for a time period, person-time for that participant was not included for that time period. Analgesic use assessed in this manner has been shown to be associated with a number of important outcomes in this cohort, such as colorectal cancer[19] and hypertension.[20]

Ascertainment of Outcome

The primary outcome, self-reported professionally diagnosed hearing loss, was determined based on the response to a hearing loss question on the 2004 long-form questionnaire. The question asked whether the participant had ever had professionally diagnosed hearing loss and the year of first diagnosis.

We defined incident cases as hearing loss diagnosed after 1986. Although standard pure-tone audiometry is generally considered the gold standard of hearing loss evaluation, due to the cost and logistic limitations of audiometric screening, several survey instruments have been developed to evaluate large populations. Studies that have compared the reliability of self-report to the gold standard of audiometry[21-24] demonstrate that self-reported hearing loss is a reasonably reliable measure of hearing loss.[21] For example, based on NHANES data using the definition of hearing loss to be a pure-tone average (at 500, 1000, 2000, and 4000 kHz) $\geq$25 dB in both ears, the sensitivity was 65% and the specificity was 83% in a comparison of self-report to audiometry.[2]

Ascertainment of Covariates

We selected covariates that have been purported to be risk factors for hearing loss. Covariates considered in the multivariate analysis included: age,[2] race,[2] body mass index (BMI),[25] alcohol intake,[26] folate intake,[27] physical activity,[28] smoking,[26] hypertension, diabetes,[29] cardiovascular disease,[30] elevated cholesterol,[30] and use of furosemide.[31]

Age and race were obtained from biennial questionnaires. Height and weight were obtained from the baseline questionnaire, with self-reported weight updated every 2 years. BMI was calculated as weight in kilograms divided by the square of height in meters. Information on smoking status and physical activity was updated every 2 years. Intakes of alcohol and folate were calculated from semi-quantitative food frequency questionnaires that were mailed to participants every 4 years. Information on other covariates was available from the biennial questionnaires, including diagnoses of hypertension, diabetes mellitus, cardiovascular disease, elevated cholesterol, and use of furosemide.

Questionnaire-derived information has been validated for many of the covariates by comparison with directly

measured values or detailed diaries, with correlations of 0.97 for weight,[32] 0.79 for physical activity,[33] and 0.9 for alcohol intake.[34]

Statistical Analysis

All analyses were prospective, using information on analgesic use that was collected before the diagnosis of hearing loss. For the primary analyses, the frequency of use of a particular analgesic was categorized as regular users (2 or more times per week) or nonregular users (less than twice per week). For each participant, person-time was allocated based on the response to the analgesic questions at the beginning of each follow-up period. Participants were censored at the date of diagnosis of hearing loss or cancer, age 75 years, or the date of death, whichever came first. Age- and multivariable-adjusted hazard ratios (HRs) were calculated using Cox proportional hazards regression models. Multivariable models were adjusted for potential confounders listed above as well as simultaneously for use of the other analgesic types.

To examine whether the relation between regular analgesic use and hearing loss varied by age, we performed analyses stratified by age <50 years, 50-59 years, and 60 years and older.

Secondary analyses examined the association between duration of regular analgesic use and hearing loss. Duration of regular aspirin use was categorized according to years of regular use (0, 1-4, 5-8, >8). For NSAIDs and acetaminophen, duration of regular use was categorized similarly; however, the highest categories were collapsed into a category of >4 years of regular use, as too few cases were in the categories of longer duration. We also examined whether the relation between hearing loss and regular analgesic use varied with concomitant regular use of more than one class of analgesic. Analgesic use was categorized as regular use of all 3 classes of analgesics, regular use of aspirin and NSAIDs only, NSAIDs and acetaminophen only, aspirin and acetaminophen only, aspirin only, NSAIDs only, acetaminophen only, or no regular analgesic use.

For all HRs, we calculated 95% confidence intervals (CIs). All *P* values are 2-tailed. Statistical tests were performed using SAS statistical software, version 9 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of participants at baseline according to analgesic use are shown in Table 1. Although updated information was used for the analysis, characteristics are presented from baseline to provide representative values. Regular aspirin and NSAID users were older and acetaminophen users were younger than nonregular users. Hypertension was more common among regular analgesic users. It was common for an individual to use more than one type of analgesic regularly.

During 369,079 person-years of follow-up, 3488 cases of hearing loss were reported. Regular analgesic use was independently associated with an increased risk of hearing loss for all 3 types of analgesics (Table 2). After adjusting for age, race, profession, BMI, alcohol intake, folate intake, physical activity, smoking, hypertension, diabetes, and the use of the other classes of analgesics, the multivariate HRs of hearing loss in participants who were regular users com-

Table 1 Characteristics of Men According to Analgesic Use in 1986

	Aspirin Regular Use		NSAID Regular Use		Acetaminophen Regular Use	
Variable	Yes n = 7217	No n = 19,700	Yes n = 1311	No n = 25,606	Yes n = 1439	No n = 25,478
Age, years	52.5	50.6	52.0	51.1	49.6	51.2
Race, %						
African American	0.5	0.9	0.7	0.8	0.5	0.8
Asian	0.7	1.8	0.7	1.6	1.0	1.6
Body mass index, kg/m^2	25.5	25.3	26.0	25.3	25.4	25.3
Alcohol, g/d	13	11	12	11	11	11
Folate, μg/d	493	469	484	476	497	475
Physical activity, mets/wk	21	22	23	22	18	22
Hypertension, %	21	16	21	17	20	17
Diabetes, %	2	2	2	2	1	2
Smoking never, %	45	50	40	49	43	49
Smoking past, %	46	37	52	39	39	47
Smoking current, %	8	8	8	8	9	8
Aspirin use, %	—	—	39.6	26.2	47.3	25.7
NSAID use, %	7.2	4.0	—	—	14.0	4.4
Acetaminophen use, %	9.4	3.9	15.3	4.8	—	—

mets/wk = metabolic equivalent tasks per week; NSAID = nonsteroidal anti-inflammatory drug.
Regular use is defined as at least 2 times per week.
Values are means unless otherwise specified.

Table 2 Age- and Multivariate-adjusted Hazard Ratios (95% CI) for Analgesic Use and Incident Hearing Loss

Analgesic Medication	Cases	Person-years	Age-adjusted Hazard Ratio	Multivariate Hazard Ratio*
Aspirin				
<2 per week	1769	213,831	1.0	1.0
2+ per week	1711	154,412	1.13 (1.06-1.21)	1.12 (1.04-1.20)
NSAIDs				
<2 per week	2852	320,467	1.0	1.0
2+ per week	636	48,612	1.38 (1.27-1.50)	1.21 (1.11-1.33)
Acetaminophen				
<2 per week	3214	347,362	1.0	1.0
2+ per week	274	21,717	1.32 (1.17-1.50)	1.22 (1.07-1.39)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, and race, as well as the other analgesics.

pared with participants who used the specified analgesic less than twice per week were 1.12 (95% CI, 1.04-1.20) for aspirin, 1.21 (95% CI, 1.11-1.33) for NSAIDs, and 1.22 (95% CI, 1.07-1.39) for acetaminophen. When further adjusted for history of elevated cholesterol, cardiovascular disease or use of furosemide, or after exclusion of individuals with rheumatoid arthritis or osteoarthritis, the results were materially unchanged.

For NSAIDs and acetaminophen, the risk of hearing loss increased with longer duration of regular use (Table 3). Those who used aspirin regularly for 1-4 years were 28% (95% CI, 17-40) more likely to develop hearing loss than those who did not use aspirin regularly; the risk did not increase further with longer duration of use. Those who used NSAIDs regularly for 4 or more years were 33% (95% CI, 18-49) more likely to develop hearing loss than those who did not use NSAIDs regularly. The risk of 4 or more years of regular acetaminophen use also was 33% (95% CI, 14-56) higher.

The association between hearing loss and regular use of aspirin (P, interaction = .005), NSAIDs (P, interaction = .10), and acetaminophen (P, interaction = .09) varied by age (Table 4). For each class of analgesic, the magnitude of the association tended to decrease with advancing age. For aspirin, regular users aged <50 years and those aged 50-59 years were 33% more likely to have hearing loss than were nonregular users, but there was no association among men aged 60 years and older. For NSAIDs, regular users aged <50 years were 61% more likely, those aged 50-59 years were 32% more likely, and those aged 60 years and older were 16% more likely to develop hearing loss than nonregular users of NSAIDs. For acetaminophen, regular users aged <50 years were 99% more likely, regular users aged 50-59 years were 38% more likely, and those aged 60 years and older were 16% more likely to have hearing loss than nonregular users of acetaminophen.

The association between hearing loss and concomitant use of more than one class of analgesic appeared to be

Table 3 Age and Multivariate Adjusted Hazard Ratios (95% CI) for Hearing Loss According to Duration of Analgesic Intake

Duration of Use (Years)	Cases	Person-years	Age-adjusted Hazard Ratio	Multivariate Hazard Ratio*
Aspirin				
0	1042	156,188	1.0	1.0
1-4	1122	108,177	1.35 (1.24-1.46)	1.28 (1.17-1.40)
5-8	687	56,431	1.34 (1.22-1.48)	1.30 (1.17-1.44)
>8	637	48,282	1.26 (1.14-1.40)	1.17 (1.04-1.31)
NSAIDs				
0	2409	284,706	1.0	1.0
1-4	721	59,774	1.30 (1.20-1.42)	1.23 (1.12-1.34)
>4	358	24,600	1.41 (1.26-1.57)	1.33 (1.18-1.49)
Acetaminophen				
0	2897	320,893	1.0	1.0
1-4	420	36,348	1.23 (1.11-1.36)	1.19 (1.07-1.32)
>4	171	11,838	1.39 (1.19-1.62)	1.33 (1.14-1.56)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, and race, as well as the other analgesics.

Table 4 Analgesic Use and the Age-adjusted and Multivariate* Hazard Ratios (95% CI) for Incident Hearing Loss Stratified by Age

Analgesic	Age <50 Years	Age 50-59 Years	Age 60+ Years
Aspirin			
Age-adjusted	1.32 (1.02-1.69)	1.36 (1.20-1.54)	1.03 (0.94-1.12)
Multivariate	1.33 (1.03-1.72)	1.33 (1.17-1.50)	1.02 (0.93-1.11)
NSAIDs			
Age-adjusted	1.59 (1.14-2.23)	1.35 (1.15-1.58)	1.17 (1.04-1.31)
Multivariate	1.61 (1.15-2.26)	1.32 (1.13-1.55)	1.16 (1.03-1.30)
Acetaminophen			
Age-adjusted	1.91 (1.29-2.82)	1.37 (1.09-1.73)	1.17 (0.99-1.37)
Multivariate	1.99 (1.34-2.95)	1.38 (1.09-1.74)	1.16 (0.99-1.37)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, and race, as well as the other analgesics.

approximately additive (Table 5). For the combined use of 2 analgesics, the risk was highest for use of NSAIDs and acetaminophen (HR 1.58 [95% CI, 1.16-2.16]), as compared with those who did not use any of the analgesics regularly. This risk was similar to the impact of regular use of all 3 analgesics (HR 1.60 [95% CI, 1.23-2.09]).

DISCUSSION

Regular analgesic use was independently associated with an increased risk of hearing loss. The increased risk of hearing loss seen with regular analgesic use was greatest among younger men, particularly those below age 60 years. In men aged 60 years and above, there was no relation observed between the risk of hearing loss and regular aspirin use, and the relation between regular use of NSAIDs and acetaminophen was attenuated. The risk of hearing loss increased with longer duration of analgesic use for both NSAIDs and acetaminophen.

The ototoxic effects of high-dose salicylates, reversible hearing loss and tinnitus, are well documented.[9] In animal models, salicylate administration results in abnormal outer hair cell function and decreased cochlear blood flow.[9] Salicylates induce biochemical and electrophysiological changes that alter membrane conductance of outer hair cells[35] and vasoconstriction in auditory microvasculature, possibly mediated by antiprostaglandin activity.[36]

High doses of NSAIDs also have been reported to be ototoxic in animal studies and in human case reports.[15] Similar to salicylates, NSAIDs inhibit cyclooxygenase and decrease prostaglandin activity, potentially reducing cochlear blood flow.[9]

Histopathologic studies of human temporal bones[37] and in animals show degeneration of strial microvasculature.[38] These studies suggest that vascular compromise, such as that which may result from salicylate or NSAID use, contributes to strial degeneration. Degeneration of the stria vascularis, a highly vascularized and metabolically active region of the cochlea, is a notable pathophysiologic change characteristic of age-related hearing loss[39] that may reduce the endolymphatic potential and the function of the cochlear amplifier.

The relation between acetaminophen and hearing loss has not been studied previously. Frequent use of acetaminophen has been associated with hypertension[20,40,41] and chronic renal dysfunction.[42,43] Acetaminophen use increases risk of renal function decline, potentially due to depletion of glutathione.[16] Acetaminophen also might deplete endogenous cochlear glutathione, which is present in the cochlea in substantial amounts and protects the cochlea from noise-induced damage.[17,18]

The prevalence of hearing loss increases with age.[44] After age 60 years, hearing thresholds worsen on average by

Table 5 Age- and Multivariate-adjusted Hazard Ratios (95% CI) for Concomitant Regular Use of More Than 1 Type of Analgesic and Incident Hearing Loss

Analgesic	Cases	Person-years	Age-adjusted Hazard Ratio	Multivariate Hazard Ratio*
None	1378	182,380	1.0	1.0
All 3 analgesics	60	3809	1.75 (1.35-2.26)	1.60 (1.23-2.09)
NSAIDs + acetaminophen	43	3015	1.72 (1.27-2.32)	1.58 (1.16-2.16)
Aspirin + acetaminophen	97	7769	1.44 (1.17-1.76)	1.40 (1.13-1.73)
Aspirin + NSAIDs	250	19,832	1.37 (1.20-1.57)	1.25 (1.09-1.44)

NSAID = nonsteroidal anti-inflammatory drug.
*Adjusted for age, body mass index, alcohol, physical activity, folate, smoking, hypertension, diabetes, profession, race, and all categories of analgesic use.

1 dB per year,[45] and the rate of decline might be even greater in men aged 48-59 years.[46] The magnitude of the relation between regular analgesic use and hearing loss was greatest in men younger than age 60 years. Possibly, the relative contribution of regular analgesic use to hearing loss may be greater in younger individuals before the cumulative effects of age and other factors have accrued. A similar impact of age on the relative contribution of diabetes to hearing loss was seen by Bainbridge et al.[29]

The risk of hearing loss increased with longer duration of regular use of NSAIDs and acetaminophen, but not of aspirin. However, years of use were counted from the 1986 baseline questionnaire when the mean age of participants was 51 years. Thus, those who reported 11 or more years of aspirin use were older. As the relation between analgesic use and hearing loss diminished with increasing age, this likely explains the lack of association between longer duration of aspirin use and hearing loss.

The impact of regular use of multiple analgesics appeared to be additive. This raises the possibility that the different classes of analgesics may impair auditory function through different mechanisms.

Our study has limitations. Assessment of hearing loss was based on self-report of professionally diagnosed hearing loss, and individuals who did not report hearing loss were considered not to be hearing impaired. Although standard pure-tone audiometry is generally considered the gold standard of hearing loss evaluation, self-reported hearing loss has been demonstrated to be a reliable assessment. Moreover, participants were specifically queried as to whether they had been "professionally diagnosed" with hearing loss, a more objective measure than the frequently used single question, "Do you feel you have a hearing loss?" Nevertheless, given the high prevalence of hearing loss in men of this age group,[2] there may have been misclassification of outcome.

We also did not have information on lifetime noise exposure or reasons for analgesic use. Noise is a common cause of hearing loss, and its targets overlap with those that may be compromised by analgesics. Moreover, noise exposure might increase the vulnerability to hearing loss related to age[47-49] or other causes.[50] A study of patterns of medication use in the US found that 58% of older men reported that cardiovascular prophylaxis was the most common reason for aspirin use. Other reasons for use of over-the-counter medications, of which acetaminophen, ibuprofen, and aspirin were the most common, included headache and pain.[8] We did not find any published reports relating common headache with hearing loss. Although migraine headaches might be associated with temporary hearing loss,[51] the prevalence of migraine headaches in men in the US is low (6%),[52] thus unlikely to explain our findings. Autoimmune diseases, such as rheumatoid arthritis, might cause hearing loss,[53] but these conditions are extremely rare in men and unlikely to have influenced our results. Hypertension might increase the risk of hearing loss due to changes in the cochlear microvasculature,[54] as might cardiovascular disease, such as stroke, coronary heart disease, and intermittent claudication;[30] however, we adjusted for these in our analyses and our results were not materially changed.

The present study was carried out in a population of predominantly white men, thus the results might not be generalizable to other racial groups. Although the participants in this cohort might not be representative of the adult population in the US, follow-up rates are high and information provided is reliable. The observed associations are likely to apply to other groups inasmuch as the underlying biologic and pharmacologic mechanisms are likely to be similar. However, additional studies are needed to examine these associations in women, younger men, and other racial groups.

Regular use of analgesics, specifically aspirin, NSAIDs, and acetaminophen, might increase the risk of adult hearing loss, particularly in younger individuals. Given the high prevalence of regular analgesic use and health and social implications of hearing impairment, this represents an important public health issue.

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CLINICAL RESEARCH STUDY

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Notification of Abnormal Lab Test Results in an Electronic Medical Record: Do Any Safety Concerns Remain?

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ABSTRACT

BACKGROUND: Follow-up of abnormal outpatient laboratory test results is a major patient safety concern. Electronic medical records can potentially address this concern through automated notification. We examined whether automated notifications of abnormal laboratory results (alerts) in an integrated electronic medical record resulted in timely follow-up actions.

METHODS: We studied 4 alerts: hemoglobin A1c ≥15%, positive hepatitis C antibody, prostate-specific antigen ≥15 ng/mL, and thyroid-stimulating hormone ≥15 mIU/L. An alert tracking system determined whether the alert was acknowledged (ie, provider clicked on and opened the message) within 2 weeks of transmission; acknowledged alerts were considered read. Within 30 days of result transmission, record review and provider contact determined follow-up actions (eg, patient contact, treatment). Multivariable logistic regression models analyzed predictors for lack of timely follow-up.

RESULTS: Between May and December 2008, 78,158 tests (hemoglobin A1c, hepatitis C antibody, thyroid-stimulating hormone, and prostate-specific antigen) were performed, of which 1163 (1.48%) were transmitted as alerts; 10.2% of these (119/1163) were unacknowledged. Timely follow-up was lacking in 79 (6.8%), and was statistically not different for acknowledged and unacknowledged alerts (6.4% vs 10.1%; $P = .13$). Of 1163 alerts, 202 (17.4%) arose from unnecessarily ordered (redundant) tests. Alerts for a new versus known diagnosis were more likely to lack timely follow-up (odds ratio 7.35; 95% confidence interval, 4.16-12.97), whereas alerts related to redundant tests were less likely to lack timely follow-up (odds ratio 0.24; 95% confidence interval, 0.07-0.84).

CONCLUSIONS: Safety concerns related to timely patient follow-up remain despite automated notification of non-life-threatening abnormal laboratory results in the outpatient setting.

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Outpatient care is often busy and fragmented, and therefore, follow-up of abnormal laboratory test results is prone to error.[1-10] Moreover, many laboratory test results in the outpatient setting may not be immediately life threatening and hence not verbally reported to the ordering provider. Therefore, missed laboratory results or delayed recognition of results leads to a significant potential for outpatient diagnostic errors, adverse events, and liability claims.[4,9,11-17]

Most paper-based methods of communication between laboratories and ordering physicians are especially vulnerable to failures. Automated systems notifying providers about abnormal test results in integrated electronic medical record systems offer a potential solution.[18] These systems usually communicate through "alerts" (computerized notifications of abnormal clinical information) transmitted directly to the provider's desktop, facilitating a rapid review of patient information.[15] The integrated electronic medical record used at all Veterans Affairs facilities (the Computerized Patient Record System [CPRS]) uses the View Alert system for automated notification of abnormal laboratory test results.

Abnormal result follow-up, however, will occur only if electronic communication of test results (either through alerts or direct access of test result) is reviewed and acted upon by providers. In previous work, we found that abnormal diagnostic imaging alerts may not always be reviewed by ordering practitioners, and practitioners who review them may not always act upon the transmitted results in a timely manner.[19] We thus hypothesized that a similar phenomenon would exist for abnormal laboratory results. In this study we evaluated follow-up actions on abnormal diagnostic laboratory tests transmitted as high-priority automated notifications to ordering providers in an integrated electronic medical record. We also determined predictors of lack of timely follow-up of these tests.

CLINICAL SIGNIFICANCE

- Missed abnormal laboratory results are a significant reason for outpatient diagnostic errors, adverse events, and liability claims.
- In integrated electronic medical records, automated notifications systems that "alert" providers about abnormal test results offer a potential solution.
- Almost 7% of notifications lack follow-up 30 days after transmission, suggesting that safety concerns about follow-up of abnormal outpatient laboratory test results remain even when providers are alerted through the electronic medical records.

METHODS

The study was conducted in a large multispecialty ambulatory clinic of the Michael E. DeBakey Veterans Affairs Medical Center and its 5 satellite clinics located in Southeast Texas from May to December 2008. To reliably assess follow-up actions on outpatient laboratory test alerts, we focused only on abnormal tests that generated a "high-priority" mandatory automated notification to a specified ordering provider without a concomitant verbal notification. Hence we excluded abnormal tests that:

- would be potentially life threatening and hence meet our institution's criteria for verbal notification or would result in immediate hospitalization at certain values (eg, high potassium values) or
- were not ordered through computerized provider order entry and hence ordering provider was not consistently specified or
- did not generate mandatory alerts, that is, the provider had an option to turn off the notification for a specified level of abnormality.

Four tests met our inclusion criteria: hemoglobin A1c (HbA1c) at a level ≥15%, positive hepatitis C antibody (HCV), prostate-specific antigen (PSA) at a level ≥15 ng/mL, and thyroid stimulating hormone (TSH) at a level ≥15 mIU/L.

Data Collection

While some site-specific configurations exist, many automated notification processes in CPRS are similar within the Veterans Affairs system. All Veterans Affairs health care providers receive important clinical information in a "View Alert" window of the electronic medical record screen, and life-threatening findings are communicated by telephone. As their only "inbox" for all types of CPRS notifications, providers are very dependent on the View Alert system. Providers see all of their alerts when they first log on and again when they switch among patient records. New alerts remain active in the window for 2 weeks unless acknowledged, after which they disappear. Providers are expected to click on and open the alert to review the report (considered acknowledged), after which the alert disappears from the window. The provider also might become aware of an abnormal laboratory result without clicking on the alert if they were reviewing the medical record for other purposes, hence directly accessing the result. Primary care providers assign surrogate covering providers to receive their alerts when they are out of the office.

On a daily basis we queried an Alert Tracking File of the electronic medical record to identify outpatient laboratory alerts transmitted 2 weeks earlier. We tracked acknowledgement status of alerts and extracted additional information such as patient identifiers, names of providers to whom the alert was sent, the date, and type of laboratory study. Within a week of data query, a reviewer blinded to acknowledgement status evaluated the electronic medical record using a standardized pretested data collection instrument to determine any follow-up actions such as ordering a follow-up

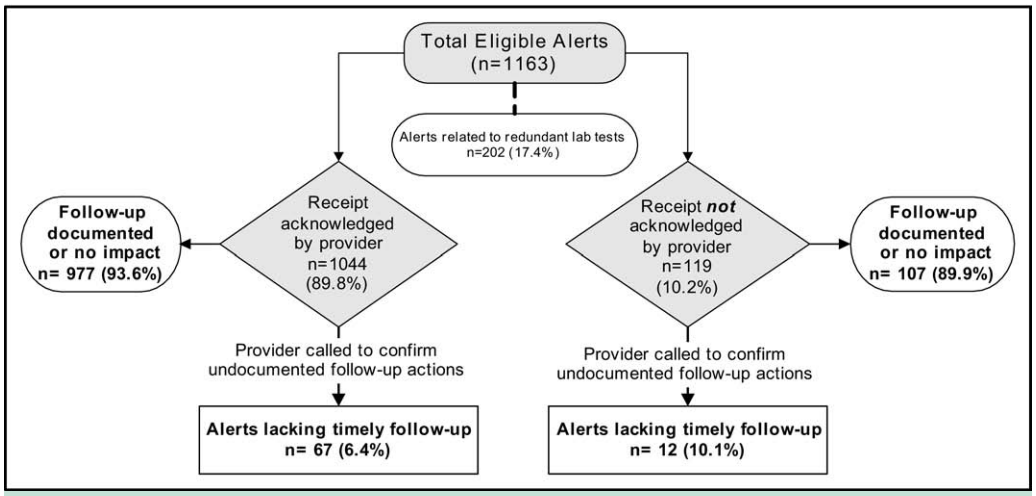

Figure Study flowchart and outcomes.

test or referral, prescribing or changing treatment, contacting the patient, or patient refusal of additional work-up. Based upon our pilot work, we unexpectedly found a fair number of abnormal tests that were clinically determined to be unnecessary. For instance, we found some tests to be redundant based on the frequency of being ordered, that is, ordered too soon after a previous test or, in cases of hepatitis C, the enzyme-linked immunosorbent assay was repeated unnecessarily despite a previous positive value. We used objective predefined explicit criteria to determine redundancy of tests.[20]

In cases of no documented follow-up, a second study investigator evaluated the medical record to confirm the findings and contacted the provider by telephone to obtain any additional evidence of undocumented follow-up or a decision to not pursue follow-up. If we could not contact any of the patient's providers or if the provider offered no additional information about follow-up, we considered the alert to *lack timely follow-up.* This determination was made approximately 30 days after alert transmission. In certain cases, we determined that calling the provider would be unnecessary or make no impact on outcome either because the alert offered no new information over what was previously documented, the patient was already receiving appropriate care for the condition, or the patient had died. These were considered as timely follow-up, however, categorized as "no-impact." Not all redundant tests were automatically considered to be of no impact. For example, a redundant positive HCV would still need follow-up if there was none documented for either the new or the previously positive test. Hence, follow-up actions on a redundant test did not make it any less redundant.

Data Analysis

In addition to descriptive data, we identified 2 groups of alerts corresponding to the 2 outcome variables in our study: alerts lacking electronic acknowledgment versus acknowledged alerts; alerts lacking timely follow-up versus those receiving timely follow-up. We compared the distribution (as proportions) of several independent variables within each group, including: ordering provider specialty (primary care, medicine subspecialties, surgery), ordering provider type (physician, trainee, and allied health professionals), redundant tests and alerts signifying a new versus known diagnosis. To assess significance, chi-squared test was used for categorical variables, and Fisher's exact test was used when chi-squared assumptions were not met. Hierarchical multivariable logistic regression models accounting for clustering of laboratory tests by providers were used to identify factors associated with the outcome variables, lack of acknowledgment, and lack of timely follow-up. Covariates with P values $<.2$ in univariate testing were tested as predictor variables. For multivariable testing, we combined specialties from univariate analysis into 3 groups: primary care, specialty care, and mental health care. The models were fit using maximum likelihood estimation, and odds ratios (OR) and 95% confidence intervals (CI) were calculated. We also described the frequencies and types of redundant test alerts.

RESULTS

Between May and December 2008, 27,092 HbA1c, 22,837 PSA, 6271 HCV, and 21,958 TSH tests were performed. A total of 1163 (1.49%) results were electronically transmitted as mandatory high-priority alerts (including 29 HbA1c $\geq$15%, 448 PSA $\geq$15 ng/mL, 433 positive HCV, and 253 TSH $\geq$15 mIU/L.). Acknowledged alerts constituted 89.8% of the total high-priority alerts (n = 1163). The Figure illustrates the outcomes of these 1163 alerts. No evidence of documented follow-up action was found in 307 (26.4%) of the alerts, however 213 (18.3% of 1163) cases were categorized as no-impact alerts. In the remaining 94 cases, we called providers to determine if, for some reason, follow-up had occurred but was not documented, or if they had addi-

Table 1 Comparison of Types of Abnormal Laboratory Test Results, Providers, Diagnosis Characteristics, and Test Characteristics for Acknowledged and Unacknowledged Alerts

	Unacknowledged n = 119		Acknowledged n = 1044		
	n	%	n	%	*P* Value
Types of abnormal laboratory test results reported					
HCV Ab (ELISA)	53	12.2%	380	87.8%	
PSA	53	11.8%	395	88.2%	
TSH	10	4.0%	243	96.0%	
Hemoglobin A1C	3	10.3%	26	89.7%	
Independent variables					
Ordering provider characteristics					
Attending physician	69	9.5%	656	90.5%	
Allied health professionals	27	7.3%	345	92.7%	
Trainees (interns, residents, fellows)	18	31.6%	39	68.4%	
Other	5	55.6%	4	44.4%	<.0001
Ordering provider specialty					
Primary care	43	5.7%	706	94.3%	
Specialty surgery	5	15.6%	27	84.4%	
Medicine subspecialties	31	14.8%	178	85.2%	
Other non-specified specialties	8	17.0%	39	83.0%	
Mental health	32	25.4%	94	74.6%	<.0001
Diagnosis characteristics					
Alerts signified newly diagnosed condition	19	7.8%	226	92.2%	
Diagnosis already known	60	9.3%	583	90.7%	.46
Considered redundant	0	0.0%	36	100.0%	.04
No impact*	35	16.4%	178	83.6%	<.001
Test not ordered by the PCP	50	11.4%	388	88.6%	.3

*No impact on outcome either because the diagnosis was not new, the patient was already receiving appropriate care for the condition, or had died.
HCV Ab = hepatitis C virus antibody; ELISA = enzyme-linked immunosorbent assay; PSA = prostate-specific antigen; TSH = thyroid-stimulating hormone; PCP = primary care provider.

tional knowledge that would affect outcome, including patient or provider decision not to pursue follow-up. Of these, 79 alerts (6.8% of total) were determined to lack timely follow-up. Two-hundred two alerts (17.4% of 1163) were considered redundant, of which 159 were considered redundant based on repetition (recent or previous test).

Acknowledgement

Table 1 shows the distribution of the 4 laboratory tests between the acknowledged and unacknowledged groups. We also show a comparison of several independent variables between the 2 groups using univariate testing. Ordering provider type and specialty were significantly different across the 2 groups. Trainees were less likely to acknowledge alerts compared with attending/staff physicians and allied health providers (physician assistants and nurse practitioners), whereas specialty services (including mental health) were less likely to acknowledge alerts compared with primary care providers ($P < .0001$ for both). In a nested logistic regression model (data not shown in Table 1), the following variables were significantly associated with lack of acknowledgment of the alert, compared with attending physicians: allied health care providers as ordering providers (OR 4.32; 95% CI, 1.21-15.52) and trainees as ordering providers (OR 8.39; 95% CI, 2.97-23.68).

Timely Follow-up

Table 2 shows the distribution of the 4 laboratory tests for the timely follow-up versus lack of timely follow-up groups. We show results of a univariate analysis comparing the several independent variables among the 79 alerts determined to lack timely follow-up versus 1084 that received timely follow-up. Statistically, there was no significant difference in rates of lack of timely follow-up between acknowledged and unacknowledged laboratory alerts (6.4% vs. 10.1%; $P = .13$). There was no significant difference in provider type, but specialty differences were significant. Redundant tests were more likely to receive follow-up ($P < .01$). Alerts for conditions signifying new diagnoses were more likely to lack timely follow-up than alerts for preexisting conditions ($P < .0001$).

In a nested logistic regression model, the following were significantly associated with lack of timely follow-up (data not shown in Table 2): redundant tests (OR 0.24; 95% CI, 0.074-0.84) with appropriately ordered tests as referent; alerts for conditions newly diagnosed, that is, diagnosis was not made until the laboratory test was done (OR 7.35; 95%

Table 2 Comparison of Types of Abnormal Laboratory Test Results, Providers, Diagnosis Characteristics, and Test Characteristics for Alerts With and Without Timely Follow-up at 30 Days

	Lack of Timely Follow-Up n = 79		Timely Follow-Up* n = 1084		
	n	%	n	%	*P* Value
Types of abnormal laboratory tests reported					
HCV Ab (ELISA)	57	13.2%	376	86.8%	
PSA	4	0.9%	444	99.1%	
TSH	16	6.3%	237	93.7%	
Hemoglobin A1C	2	6.9%	27	93.1%	
Independent variables					
Ordering provider characteristics					
Attending physician	45	6.2%	680	93.8%	
Physician assistants and nurse practitioners	28	7.5%	344	92.5%	
Trainees (interns, residents, fellows)	5	8.8%	52	91.2%	
Other	1	11.1%	8	88.9%	.67
Ordering provider specialty					
Primary care	50	6.7%	699	93.3%	
Specialty surgery	1	3.1%	31	96.9%	
Medicine subspecialties	5	2.4%	204	97.6%	
Other non-specified specialties	4	8.8%	43	91.5%	
Mental health	19	15.1%	107	84.9%	<.001
Diagnosis characteristics					
Alerts signified newly diagnosed condition	57	23.3%	188	76.7%	
Diagnosis already known	21	3.3%	622	96.7%	<.0001
Alert status					
Acknowledged	67	6.4%	977	93.6%	
Unacknowledged	12	10.1%	107	89.9%	.13
Test not ordered by the PCP	34	7.7%	404	92.2%	.30
Redundant test	4	5.1%	198	18.3%	
Appropriate test	75	94.9%	886	81.7%	<.01

*All tests with no impact considered timely follow-up.

HCV Ab = hepatitis C virus antibody; ELISA = enzyme-linked immunosorbent assay; PSA = prostate-specific antigen; TSH = thyroid-stimulating hormone; PCP = primary care provider.

CI, 4.16-12.97) with previously known diagnosis as referent; and mental health as a specialty (OR 2.82; 95% CI, 1.06-7.54) with primary care as referent.

Alerts Related to Redundant Tests

In Table 3 we list criteria to determine if an alert was related to a redundant laboratory test, and their respective frequencies (total n = 202). Because the Veterans Affairs' electronic medical record has a reminder system that prompts the ordering provider about recent orders of the same test, we further evaluated the subcategory of 159 alerts deemed redundant based on repetition. Overall, we found 28 cases where the provider ordered the test too soon after the last PSA, TSH, or HbA1c; and in 131 cases, a second HCV enzyme-linked immunosorbent assay test was ordered despite the presence of a previous positive test. In our institution the reminder is set to prompt the ordering provider about repetition when the new test is being ordered within 60 days from last TSH or PSA order or within 90 days from last HCV or HbA1c order. However, in only 11 (7%) of these 159 cases would the provider have received a computerized reminder prompting them of potential redundancy based on repetition.

DISCUSSION

We tested whether certain abnormal outpatient laboratory tests were followed-up in a timely manner in a multispecialty clinic that used an integrated electronic medical record for automated notification. We found that 6.8% of alerts lacked follow-up at 30 days, suggesting that follow-up of abnormal outpatient laboratory test results is not fail-safe even when providers are alerted about abnormal results through the electronic medical record. Of concern was the finding that there was lack of timely follow-up even when providers acknowledged notifications through the electronic medical record, which was comparable to when they did not acknowledge them. These findings are similar to our previous findings of follow-up on abnormal imaging alerts in the same electronic medical record, suggesting that this phenomenon may exist for all alerts of abnormal diagnostic test results. Unexpectedly, we found that 17% of abnormal test alerts were related to tests that we deemed

Table 3 Criteria to Determine Alerts Related to Redundant Laboratory Tests and Their Respective Frequencies (Total n = 202)

	n	%
HCV Ab (ELISA) (n = 131)*		
Known HCV ELISA positive and ongoing follow-up in hepatitis C clinic†	32	24.4%
Known HCV ELISA positive and confirmed disease by either PCR+, viral load, or treatment genotype†	104	79.4%
Known HCV ELISA positive (but no viral load, PCR, or genotype)†	29	22.1%
PSA (n = 60)*		
Documentation of patient refusal for PSA work-up already present before PSA test was ordered	37	61.7%
Similar level of PSA that already had appropriate action taken within previous 4 weeks†	21	35.0%
Patient not a candidate for screening PSA testing	10	16.7%
TSH (n = 9)		
Test repeated within 4 weeks of last adjustment†	9	100.0%
Hemoglobin A1C (n = 2)		
Test repeated within 3 months of last adjustment†	2	100.0%

*Percentages add up to more than 100 because more than one criteria for redundancy may have been met in certain cases.

†Tests deemed redundant based on repetition.

HCV Ab = hepatitis C virus antibody; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction; PSA = prostate-specific antigen; TSH = thyroid-stimulating hormone.

redundant based on predetermined criteria. Alerts related to these tests were less likely to lack timely follow-up.

Our findings have several significant implications for electronic medical record use in the future. One, it cannot be assumed that automated notification of abnormal laboratory test results within an electronic medical record and the resultant acknowledgement will translate into timely actions to address these alerts. Two, notifications of abnormal redundant tests appear to be a distracting influence on providers who are missing essential alerts for newly diagnosed conditions. Three, high-reliability tracking systems to monitor potential patient harm and outcomes are needed, which also should account for follow-up actions by providers. Currently, the only way to track follow-up actions on abnormal alerts is through medical record review, a time-consuming and expensive procedure. However, individual-level tracking of follow-up actions taken in response to abnormal test result notifications could be designed within the electronic medical record. Thus, when providers process an alert, they could be provided order sets of appropriate follow-up actions in a separate "pop-up" window (such as having a nurse call the patient, setting up a return appointment, ordering a consultation or follow-up test, or an option indicating no further action is required, such as when a patient is already in hospice care). These actions could be tracked through the electronic medical record and a reporting process could be created for clinic administrators to review and identify patients who may have truly "slipped through the cracks" without performing extensive record reviews. For instance, in cases of inaction on an abnormal laboratory test result at 2 weeks, the ordering provider or their surrogates could be informed.

We previously determined rate of lack of timely follow-up for abnormal imaging alerts in the same system and setting and found comparable results. Future work needs to confirm the extent to which these findings exist in other electronic medical record systems. Because there could be many potential reasons why busy providers in the front lines of health care delivery miss abnormal test results, a multidisciplinary approach is needed to address test result follow-up in future. For instance, an approach involving human computer interaction and informatics[3,21] that accounts for issues related to usability, organizational characteristics, technology, work-flow, and provider factors could be useful to explain why providers are unable to follow-up results despite reading them, and hence improve safety in this area.[22,23]

Computerized reminders have been shown to reduce redundant tests in the inpatient setting.[24] However, our computerized reminder system would have prompted the ordering provider only 7% of the time. Notably, in 131 cases where a positive hepatitis C test previously existed in the electronic medical record, the reminder logic was not set to prompt providers that they were ordering a repeat, redundant test. Current computerized reminder systems could be better designed to reduce test redundancy. For instance, these reminders are designed to prompt providers based only on the date of test order and not the date of the result of the last test. If the system had been configured as giving off a prompt based on both these dates, all 28 providers who unnecessarily ordered a PSA, Hba1c, or a TSH would have received a prompt. Future work is essential to better document whether the use of information technology can reduce the enormous costs associated with redundant tests, especially in the outpatient setting.[25,26]

Our study had several limitations. Because of the study population (eg, predominantly male veterans) and the unique Veterans Affairs setting, our findings may not be generalizable outside Veterans Affairs. However, with increasing emphasis on electronic medical records, the potential relevance of these findings is significant. We also lack comparable data from nonelectronic medical record-based systems and cannot comment on the effectiveness of automated notification compared with these systems. Due to the lack of similar tracking and documentation capabilities, such an evaluation study would be very difficult to carry out. Conversely, many factors, including a large sample size, multiple clinics, large number of providers (over 500 from different specialties), rigorous methods to determine follow-up, explicit criteria for determination of redundant

tests, various types of abnormal laboratory test result alerts, and an advanced integrated electronic medical record used in Veterans Affairs facilities throughout the US, all add several unique strengths to our study.

In conclusion, current systems of mandatory automated notification of abnormal laboratory test results do not guarantee timely follow-up on the abnormality in the outpatient setting. Additionally, provider acknowledgment of receipt of the test result also does not automatically result in timely follow-up. Multidisciplinary interventions involving human-computer interaction[3,21] and high-reliability tracking systems to monitor test result notification outcomes, such as follow-up actions by providers on these tests, are needed to alleviate these safety concerns.

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CLINICAL RESEARCH STUDY

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Orthostatic Syndromes Differ in Syncope Frequency

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ABSTRACT

BACKGROUND: There are conflicting opinions on whether postural tachycardia syndrome predisposes to syncope. We investigated this relationship by comparing the frequency of syncope in postural tachycardia syndrome and orthostatic hypotension.

METHODS: We queried our autonomic laboratory database of 3700 patients. Orthostatic hypotension and postural tachycardia syndrome were defined in standard fashion, except that postural tachycardia syndrome required the presence of orthostatic symptoms and a further increase in heart rate beyond 10 minutes. Syncope was defined as an abrupt decrease in blood pressure and often, heart rate, requiring termination of the tilt study. Statistical analysis utilized Fisher's exact test and Student's *t* test, as appropriate.

RESULTS: Of 810 patients referred for postural tachycardia syndrome, 185 met criteria while another 328 patients had orthostatic hypotension. Of the postural tachycardia syndrome patients, 38% had syncope on head-up tilt, compared with only 22% of those with orthostatic hypotension ($P < .0001$). In the postural tachycardia group, syncope on head-up tilt was associated with a clinical history of syncope in 90%, whereas absence of syncope on head-up tilt was associated with a clinical history of syncope in 30% ($P < .0001$). In contrast, syncope on head-up tilt did not bear any relationship to clinical history of syncope in the orthostatic hypotension group (41% vs 36%; $P = .49$).

CONCLUSION: Our results demonstrate that syncope (both tilt table and clinical) occurs far more commonly in patients who have postural tachycardia syndrome than in patients with orthostatic hypotension. These findings suggest that one should be clinically aware of the high risk of syncope in patients with postural tachycardia syndrome, and the low-pressure baroreceptor system that is implicated in postural tachycardia syndrome might confer more sensitivity to syncope than the high pressure system implicated in orthostatic hypotension.

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KEYWORDS: Dysautonomias; Orthostatic hypotension; Postural tachycardia syndrome; Syncope; Tilt table test

Postural tachycardia syndrome is a disorder characterized by orthostatic symptoms such as dizziness, lightheadedness, palpitation, and blurred vision. In addition, postural tachycardia syndrome is often accompanied by nonorthostatic symptoms such as fatigue, nausea, vomiting, constipation, diarrhea, and migraine headaches.[1] Postural tachycardia syndrome is defined as a >30 beats-per-minute increase in heart rate in the first 10 minutes of upright tilt, accompanied by orthostatic symptoms and sustained throughout the test in the absence of orthostatic hypotension. Postural tachycardia syndrome is diagnosed on the basis of clinical suspicion and usually confirmed by the tilt table test, which is the gold standard.[1]

Reflex syncope is an orthostatic disorder characterized by a brief loss of consciousness due to inadequate brain perfusion. Symptoms accompanying reflex syncope are lightheadedness, blurred vision, dizziness, weakness, sweating, and nausea,[2] similar to symptoms experienced by pos-

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tural tachycardia syndrome patients. Typical findings on tilt table test include a rapid decrease in blood pressure and, often, a decrease in heart rate resulting from inhibition of the sympathetic or activation of the parasympathetic nervous systems.[3] The duration of the decrease in heart rate and blood pressure has not been clearly defined.

Expert opinion in the field differs. Some believe that postural tachycardia syndrome predisposes to syncope, and others believe the opposite. To evaluate this disagreement, we examined the occurrence of syncope in patients with postural tachycardia syndrome, compared with patients with orthostatic hypotension with regards to frequency of syncope on tilt table test.

CLINICAL SIGNIFICANCE

- Syncope occurs with a higher frequency in patients with postural tachycardia syndrome than in patients with orthostatic hypotension.
- Tilt syncope might be a useful predictor of clinical syncope in postural tachycardia syndrome patients.
- Lack of concordance between clinical history of syncope and tilt syncope in orthostatic hypotension patients supports the view that the lack of symptoms in orthostatic hypotension patients might make a clinical diagnosis more difficult.

MATERIALS AND METHODS

Inclusion Criteria

A retrospective, Institutional Review Board-approved review of the Autonomic Laboratory database identified patients with postural tachycardia syndrome, those with orthostatic hypotension, and those with tilt-table-induced syncope in each group. All diagnoses were defined by the findings on a tilt table test, in the appropriate clinical setting. All enrolled had undergone full autonomic testing.

Postural tachycardia syndrome was defined as an increase in heart rate >30 beats per minute within the first 10 minutes of upright tilt, unaccompanied by any decrease in blood pressure. Because this criteria set is sometimes viewed as excessively inclusive, we required 2 additional inclusion criteria: the heart rate had to continue rising during the remainder of the tilt study, and orthostatic symptoms had to be present during the tilt study. Orthostatic hypotension was defined by a decrease in systolic pressure of >20 mm Hg or a decrease in diastolic blood pressure of >10 mm Hg within the first 3 minutes of upright tilt and sustained during the remainder of the tilt study. Reflex syncope was defined as a sudden decrease in blood pressure and sometimes heart rate over a period of <3 minutes on upright tilt.

To assess the clinical relevance of the occurrence or nonoccurrence of tilt syncope, we also determined the presence or absence of a clinical history of syncope in each group through review of the chart, clinical questionnaire, or referral diagnosis.

Autonomic Testing

Autonomic testing included the tilt table test, the cardiac responses to deep breathing and to the Valsalva maneuver, and the Quantitative Sudomotor Axon Reflex Test. The tilt table test consisted of 20 minutes of supine rest on a motorized tilt table before an upright tilt to 70°. Continuous blood pressure and heart rate were monitored noninvasively in the supine position for 3 minutes, and upright for 10-40 minutes. The diastolic blood pressure normally decreases <10 mm Hg, and the systolic blood pressure <20 mm Hg, and heart rate should increase <30 beats per minute.[4]

Deep breathing consists of 5 deep breaths per minute, with the heart rate variation calculated from the best 5 of 15 cycles.[4] Results are reported as the average difference between inspiration and expiration of the 5 best breaths. For the Valsalva maneuver, the subject maintains a 40-mm Hg pressure gradient with an open glottis for 15 seconds, while heart rate and blood pressure are continuously monitored. The Valsalva ratio consists of the fastest heart rate during pressure exertion (termed phase II, sympathetically mediated) divided by the lowest heart rate after pressure release (termed phase IV, parasympathetically mediated). Normal values depend on age.[5]

Sudomotor axon reflex response to the iontophoresis of acetylcholine (10% with a 2-mA current for 5 minutes, recording sweat output for 10 minutes) across the skin of the feet, calves, hands, and upper arms, was measured by standard methods.[6] Normal values vary by body site and sex and were not considered abnormal unless abnormal axon reflex response found in 2 sites were outside of the range of normal, defining the presence of an autonomic neuropathy.

Data Analysis

Fisher's exact test was used to determine the statistically significant difference between the presence of tilt syncope in postural tachycardia syndrome patients compared with that in orthostatic hypotension, and to determine the difference between other categorical values. Demographic differences (age) between groups, as well as the difference in tilt table duration before syncope between the 2 groups, was determined with an unpaired Student's *t* test.

Etiology of Orthostatic Hypotension

Patients with orthostatic hypotension were classified according to probable neuraxis localization of the underlying disorder (central, such as multiple system atrophy;

peripheral, such as diabetes; and indeterminate). The classification was based on a combination of the results of axon reflex testing and the patient's known underlying diagnosis, if there was one. Patients with 2 or more missing axon reflex responses were classified as peripheral, while patients with normal axon reflex responses were classified as central, and those with one abnormal response were classified as indeterminate. When patients were referred with a known diagnosis (about 1/3 of patients), if the known diagnosis was inconsistent with the autonomic testing diagnosis (a rare occurrence), these patients also were classified as indeterminate.

RESULTS

Demographic Characteristics

Of 3792 patients in our database, 810 patients were referred for postural tachycardia syndrome, of which 185 met the more stringent criteria for postural tachycardia syndrome set forth in the Methods section. A separate group of 328 subjects had orthostatic hypotension. Demographic characteristics and autonomic nervous system results comparing the 2 groups are described in the Table. Of the 328 orthostatic hypotension patients, etiology was classified as peripheral nervous system in 192 (59%), central in 84 (26%),

Table Demographics and Autonomic Nervous System Testing Results Comparing the 2 Groups

	All Patients		Tilt Syncope		No Tilt Syncope		
	POTS n = 185	OH n = 328	POTS n = 70	OH n = 71	POTS n = 115	OH n = 257	Statistical Analysis
Age (years)	26 ± 13	67 ± 17	25 ± 13	68 ± 15	26 ± 13	67 ± 17	POTS (all) vs OH (all), $P < .001$
Females (%)	153 (83%)	151 (46%)	58 (83%)	28 (40%)	95 (83%)	123 (48%)	POTS (all) vs OH (all), $P < .001$
Average supine SBP (mm Hg)	114 ± 14	147 ± 26	108 ± 11	142 ± 28	117 ± 14	149 ± 25	POTS(all) vs OH(all), $P < .001$ POTS: tilt syncope vs no tilt syncope, $P < .001$ OH: tilt syncope vs no tilt syncope, $P < .05$
Average supine DBP (mm Hg)	65 ± 9	78 ± 12	62 ± 7	77 ± 12	67 ± 9	78 ± 12	POTS (all) vs OH (all), $P < .001$ POTS tilt syncope vs no tilt syncope, $P < .001$
Average supine HR (beats per minute)	76 ± 13	75 ± 15	72 ± 12	72 ± 15	79 ± 13	75 ± 15	POTS tilt syncope vs no tilt syncope, $P < .01$
Average HR during HUT (beats per minute)	119 ± 15	91 ± 19	115 ± 15	90 ± 16	121 ± 14	91 ± 19	POTS (all) vs OH (all), $P < .001$ POTS tilt syncope vs no tilt syncope, $P < .05$
Peak HR during HUT (beats per minute)	134 ± 16	99 ± 21	132 ± 16	98 ± 15	136 ± 15	103 ± 59	POTS (all) vs OH (all), $P < .001$
Lowest HR during HUT (beats per minute)	67 ± 15	69 ± 15	61 ± 16	66 ± 15	71 ± 13	70 ± 15	POTS tilt syncope vs no tilt syncope, $P < .001$ OH tilt syncope vs no tilt syncope, $P < .05$
Abnormal VR, n (%)	17 (9%)	184 (56%)	9 (13%)	37 (52%)	7 (6%)	146 (57%)	POTS (all) vs OH (all), $P < .001$
Abnormal HRDB, n (%)	28 (15%)	177 (54%)	9 (13%)	35 (49%)	17 (15%)	144 (56%)	POTS (all) vs OH (all), $P < .001$
Abnormal QSART, n (%)	65 (35%)	249 (76%)	24 (34%)	58 (81%)	40 (35%)	190 (74%)	POTS (all) vs. OH (all), $P < .001$

POTS = postural tachycardia syndrome; OH = orthostatic hypotension; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; HUT = head-up tilt; VR = Valsalva ratio; HRDB = heart rate deep-breathing ratio; QSART = Quantitative Sudomotor Axon Reflex Test.

All values are expressed as percentages or reported with mean and SDs.

and indeterminate in 52 (15%). Age (66 ± 15 years central vs 65 ± 17 years peripheral) and sex were similar across these groups ($P = .6$ and $P = .9$, respectively), as was the rate of syncope (19% peripheral vs 25% central, $P = .26$). There was no difference in syncope between patients with central orthostatic hypotension (21/84) compared with patients with peripheral orthostatic hypotension (36/192, $P = .26$).

As shown in the Table, the occurrence of postural tachycardia syndrome in our laboratory database was found to be 4.78 times higher in women than in men, while the average age of the group was 26 ± 13 years. There were no significant differences in sex or age associated with syncope on tilt ($P = .96$ and .61, respectively). The sex ratio was approximately even in the orthostatic hypotension group, with an average age of 67 ± 17 years, but again, neither sex nor age were different in the subgroup with syncope ($P = .22$ and .65, respectively). However, as expected, age ($P < .0001$) and sex ($P < .0001$) differed between the postural tachycardia syndrome group and the orthostatic hypotension group.

Comparison of Syncope Frequency

The occurrence of syncope in the setting of postural tachycardia syndrome (70/185 patients, 38%) was higher than in the setting of orthostatic hypotension (71/328 patients, 22%, $P = .0001$). The difference in syncopal frequency between postural tachycardia syndrome and orthostatic hypotension could not be attributed to a difference in tilt table duration because the average duration of tilt table before syncope was significantly longer in patients with postural tachycardia syndrome (19 ± 8 minutes) than in patients with orthostatic hypotension (14 ± 8 minutes) ($P < .0004$).

To determine whether the occurrence of syncope during the tilt table test bears clinical relevance to syncope as a complaint, we also assessed the clinical history of syncope in each group. In the postural tachycardia syndrome group with syncope, 90% had a history of syncope, contrasted with only 30% in the group that did not faint ($P < .0001$). In contrast, whether a patient with orthostatic hypotension fainted or did not faint on the tilt table did not bear any relationship to the clinical history of syncope (41% vs 36%; $P = .49$).

DISCUSSION

Our study demonstrates that syncope occurs more often during the tilt table test in patients with postural tachycardia syndrome (38%) compared with patients with orthostatic hypotension (22%). Although we did not include healthy subjects, 2 previous studies indicate that the rate of syncope in postural tachycardia syndrome probably also exceeds that of healthy subjects, which ranges between 7% and 17%.[7,8] Up until this point, whether postural tachycardia syndrome predisposed to syncope was unknown. In fact, expert opinion on this subject diverged sharply, and one can construct a theoretical basis for either position. In favor of an association, one could imagine that a process affecting central venous distribution would predispose to syncope through a low pressure baroreceptor mechanism due to central hypovolemia.[9] On the other hand, chronic exposure to low blood flow could improve cerebral autoregulation[10] and modulate the autoregulatory cerebral pressure response curve to increase a postural tachycardia syndrome patient's resistance to fainting. Thus, determining the relationship between postural tachycardia syndrome and tilt-induced syncope has important pathophysiologic implications. The higher prevalence of tilt-induced syncope among patients with postural tachycardia syndrome compared with healthy controls suggests that central hypovolemia plays an important role in postural tachycardia syndrome and that changes in cerebral autoregulation are inadequate to fully compensate.

Perhaps more surprising but equally important in its physiologic meaning is the higher prevalence of tilt-induced syncope in postural tachycardia syndrome compared with orthostatic hypotension. This finding is unlikely to reflect an artifact due to tilt duration. Because orthostatic hypotension patients who fainted did so earlier in their tilt study, one would have expected to see higher frequency of fainting in orthostatic hypotension if the difference between orthostatic hypotension and postural tachycardia syndrome simply reflected tilt duration. Second, patients with postural tachycardia syndrome tended to be younger and more often female than those with orthostatic hypotension. Because syncope is far more prevalent in the younger and female population,[3] the age disparity between the orthostatic hypotension and postural tachycardia syndrome groups could, in part, explain our findings. However, a more mechanistic explanation may play an important role in this observation. Orthostatic hypotension and postural tachycardia syndrome differ in their physiology in major ways. Postural tachycardia syndrome is thought to involve central hypovolemia, an abnormality centered on the low pressure venous system.[11] In contrast, the fundamental defect in orthostatic hypotension is located in the arteriolar constriction bed on the high pressure side.[12] Thus, the higher prevalence of syncope in postural tachycardia syndrome may suggest that these 2 disorders share a common pathophysiology, and that abnormalities on the low pressure venous side are more likely to trigger syncope than abnormalities on the high pressure side, such as inadequate arteriolar constriction. One may hypothesize that the low pressure baroreceptor system present in the right atrium plays a more important pathogenic role than the high pressure carotid and aortic arch baroreceptors. This is in keeping with the findings of Hainsworth,[9] who described low body negative pressure, a procedure that primarily impacts available central volume, as a method to induce syncope in all subjects.

The absence of any significant difference in rate of syncope between patients classified as having a peripheral cause of orthostatic hypotension compared with those classified as having a central cause, suggests that the capacity of cerebral autoregulation to compensate for a decrease in pressure is not superior in patients with a peripheral cause of

orthostatic hypotension. This is not surprising, as cerebral autoregulation has previously been shown to be preserved in some central autonomic disorders.[13]

We also found concordance between the tilt syncope and clinical history of syncope in the postural tachycardia syndrome group (90%). However, the same concordance was not seen for the orthostatic hypotension group (40.8%). Even though this finding is retrospective, it is potentially significant as it might indicate that tilt syncope is a useful predictor of syncope in postural tachycardia syndrome patients but not in orthostatic hypotension. A recent study has found that a large proportion of orthostatic hypotension patients may be asymptomatic or present with symptoms atypical of orthostatic hypotension on tilt table testing.[14] The findings from this article indicate that syncope in orthostatic hypotension is more difficult to manage because of the absence of symptoms in many patients. Hence, it is possible that clinical history might not be a reliable predictor of the diagnosis of orthostatic hypotension. The lack of correlation between tilt-table-induced syncope and the historical complaint of syncope in patients with orthostatic hypotension further supports this view.

There are some limitations to this study. First, its retrospective nature could have produced some bias in the selection of patients for study. However, the very objective nature of the data collected (the presence or absence of an observed faint on a tilt table study) mitigates against a selection bias, because all patients who fainted were included in the study. Second, we did not have access to a set of our own healthy controls and used literature-based values for comparison. Although this is not ideal, it will certainly provide an estimate of fainting on a tilt table in the normal population, particularly because the values from different studies stay within a specific range.

We conclude that syncope occurs with a higher frequency in patients with postural tachycardia syndrome than in patients with orthostatic hypotension or in normal subjects. These findings suggest that one should exercise clinical caution when managing patients with postural tachycardia syndrome due to the high risk of syncope; hypovolemia imputes a higher risk of syncope than does hypotension; and postural tachycardia syndrome and reflex syncope might share a common pathophysiology.

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CLINICAL RESEARCH STUDY

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Long-term Effect of Chronic Oral Anticoagulation with Warfarin after Acute Myocardial Infarction

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ABSTRACT

BACKGROUND: Antiplatelet therapy is the principal component of the antithrombotic regimen after acute myocardial infarction. It remains unclear whether additional chronic oral anticoagulation (OAC) improves outcomes. We set out to evaluate the risk and benefit of long-term OAC after myocardial infarction.

METHODS: We pooled 10 randomized clinical trials comparing warfarin-containing regimens (OAC) with or without aspirin with non-OAC regimens with or without aspirin (No OAC) for patients with recent infarction. The primary endpoint was all-cause mortality. Other endpoints included recurrent infarction, stroke, and major bleeding. We calculated the odds ratio (OR) (fixed effect, OR <1 indicates benefit for OAC) for death and other ischemic and hemorrhagic complications at the longest interval of follow-up available.

RESULTS: Among 24,542 patients, 14,062 were assigned to OAC and 10,480 to no OAC. The patients were followed for 3-63 months, for 89,562 patient-years. Death occurred in 2424 patients (9.9%), 1279 OAC patients, and 1145 in the no OAC group, OR 0.97 (95% confidence interval [CI], 0.88-1.05), $P = .43$. Similarly, there was no effect on recurrent infarction. Stroke occurred in 578 patients (2.4%), 271 in the OAC group and 307 in the no OAC group, OR 0.75 (95% CI, 0.63-0.89), $P = .001$. There was substantially more major bleeding (OR 1.83 [95% CI, 1.50-2.23], $P < .001$) in the OAC group. Separate analyses, performed for patients (n = 11,920) randomized to aspirin versus aspirin and OAC yielded very similar results.

CONCLUSION: As compared with placebo or aspirin, OAC with or without aspirin does not reduce mortality or reinfarction, reduces stroke, but is associated with significantly more major bleeding.

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KEYWORDS: Anticoagulation; Bleeding; Death; Long-term effect; Myocardial infarction

Coronary artery disease remains the most common cause of death among adults in the United States. Anti-platelet therapy is the principal component of the antithrombotic regimen after acute myocardial infarction.[1]

There have been numerous studies over the last 4 decades attempting to address the utility of long-term oral anticoagulation (OAC) after myocardial infarction. Early studies suggested benefit in younger men only, while later ones found all patients to survive longer or to have lower rates of recurrent ischemic events, but not death.[2,3] In the last 20 years, several randomized controlled trials have been conducted to clarify the role of long-term OAC after myocardial infarction, with varying results.[4-15] They utilized different intensities of anticoagulation, starting at varying intervals from index event, and in a wide array of patients with respect to concomitant aspirin or reperfusion therapy.

As uncertainty about the benefit of OAC persists, we performed a meta-analysis of randomized clinical trials

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comparing OAC-based regimens (without or without aspirin) versus no OAC after myocardial infarction (with or without) ST-elevation, to determine whether there was any improvement in survival or other cardiovascular events in those taking OAC. We refined the analysis to evaluate the effect of OAC or placebo in addition to aspirin, which is the standard of care for patients with previous infarction.

CLINICAL SIGNIFICANCE

- Oral anticoagulation does not reduce death or reinfarction in survivors of acute myocardial infarction across a wide range of patients and intensity of therapy.
- Oral anticoagulation reduces the incidence of stroke by ~30%, independent of aspirin therapy, suggesting different mechanisms of cardiac and cerebral protection from ischemic events.
- Oral anticoagulation increases the rate of nonfatal major and minor bleeding.

METHODS

We performed a comprehensive search of OVID SR and PubMed without any language restrictions. The keywords used included warfarin, myocardial infarction, and randomized controlled trials, in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines.[16] We retrieved 66 citations, which were reviewed at the title/abstract level. The inclusion criteria were: use of chronic OAC with warfarin post infarction, randomized controlled trial, at least 30-day follow-up, and death listed as outcome. The exclusion criteria were: retrospective study or registry and use of OAC for conditions other than myocardial infarction (Figure 1). Fourteen studies were analyzed in detail. The study by Cohen at al[7] was excluded because it did not provide details about the 2 randomized arms and listed only the results comparing non-Q-wave infarction versus unstable angina. The study by Huynh et al[11] was excluded because it studied a selected group of patients with unstable angina or non-ST-segment elevation myocardial infarction, with prior coronary bypass surgery, and who were poor candidates for a revascularization procedure. The third excluded study was a subgroup analysis of the original Coumadin Aspirin Reinfarction Study (CARS).[17] The Organization to Assess Strategies for Ischemic Syndromes[5] study reported use of aspirin in 85%-87% of patients, however, the study did not report the results separately for those receiving aspirin or not. This study was excluded because it did not report specifically number of deaths, but rather the combination of death, infarction, or stroke.

The primary endpoint for each trial (except 1 trial that used all-cause mortality as endpoint[8]) was a composite of ischemic events, including death, infarction, stroke, or recurrent ischemia in various combinations. While our focus was on all-cause mortality, we examined individually each ischemic event (death, infarction, or stroke) because of the possibility of heterogeneity in response among the components of the composite endpoint. We also analyzed separately major bleeding and minor bleeding, according to the definition in each trial. Statistical analysis was performed using the weighted fixed and random effects methods for meta-analysis. After confirming that there were no substantial differences between the 2 methods, we reported only the pooled fixed-effect results. Heterogeneity was assessed using a standard

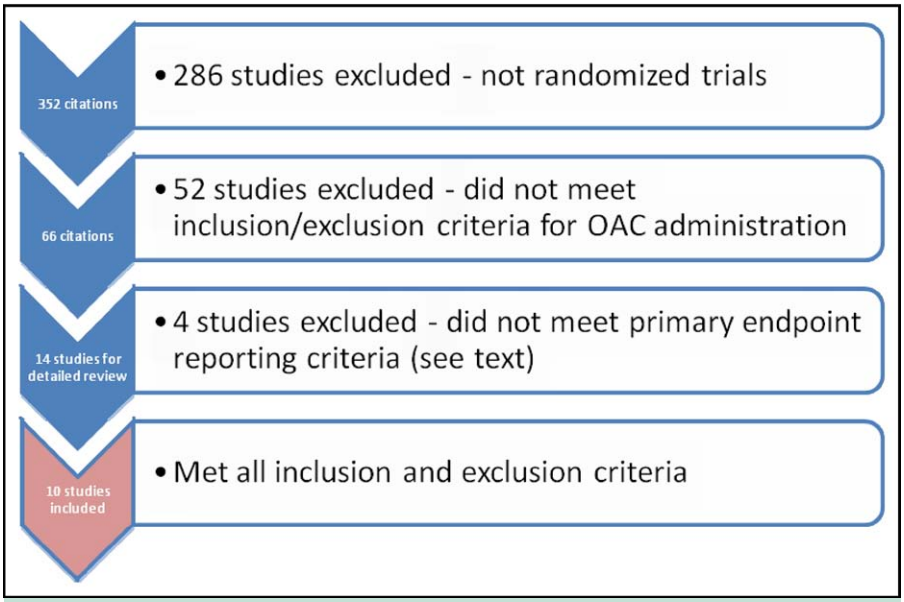

Figure 1 Study inclusion and exclusion process. OAC = oral anticoagulation.

chi-squared test (inverse variance method). For each event, the pooled result was presented as odds ratio (OR) with 95% confidence intervals. OR <1 signifies benefit for OAC-based therapy. The analyses were performed first for all patients and then only for patients randomized to aspirin versus aspirin and OAC. Statistical significance was set at $P < .05$, and all analyses were performed using STATA SE ver. 9.0 (StataCorp LP, College Station, Tex).

RESULTS

Ten studies of long-term OAC versus no OAC, with or without aspirin, were included for final analysis. Table 1 highlights the studies identified: 1 study compared OAC versus placebo, without aspirin in either arm. There were 5 studies of patients on OAC and aspirin versus aspirin alone. Four studies had 3 arms that compared OAC alone versus aspirin alone versus OAC with aspirin. For the latter group, the groups were condensed into OAC-based regimens or no OAC regimens. The baseline characteristics of patients from all the studies are listed in Table 2. The number of patients enrolled in the studies ranged from 93 to 8803. Among the 24,542 patients, 14,062 were assigned to OAC and 10,480 to no OAC. The patients were followed for 3-63 months, with 89,562 patient-years of observation. The ejection fraction was listed in only one study.[9] Reperfusion therapy was administered to 6009 patients (25%).

Table 3 lists the outcomes of patients. Death occurred in 2424 patients (9.9%), OR 0.97 (95% confidence interval [CI] 0.88-1.05), $P = .43$ ($P_{\text{heterogeneity}} = .14$) (Figure 2). All except one study reported myocardial infarction as an endpoint. A total of 2430 new infarctions occurred (9.9%), OR 0.94 (95% CI, 0.87-1.03), $P = .18$ ($P_{\text{heterogeneity}} = .001$). Stroke, reported in 7 of the 11 studies, occurred in a total of 578 patients (2.5%, Figure 3), OR 0.75 (95% CI, 0.63-0.89), $P = .001$ ($P_{\text{heterogeneity}} = .001$). In one study with angiographic follow-up, in which patients were treated with fibrinolytic therapy for their index infarction and had a patent artery at enrollment, OAC therapy added to aspirin significantly lowered rates of reocclusion and recurrent ischemic events.[6] International normalized ratio (INR) target varied from 1.5 to 4.5, depending on the adjunctive antiplatelet therapy. The actual INR was <2 in 2 studies using low-dose warfarin.[4,9] Most studies reported both major (all 10) and minor (8 studies) bleeding. The definition of major bleeding varied among the different studies. A total of 482 major bleeding events occurred (2.0%, Figure 4), OR 1.83 (95% CI, 1.50-2.23), $P < .001$ ($P_{\text{heterogeneity}} = .14$). Minor bleeding was reported in 1025 patients (4.2%), OR 3.46 (95% CI, 2.95-4.05), $P < .001$ ($P_{\text{heterogeneity}} = .001$). Odds ratios for ischemic events and major bleeding complications are summarized in Table 4. Because it is important to assess the effect of OAC on the background of obligatory aspirin background recommended in patients with previous infarction, we also analyzed the subset of patients (n = 11,920) randomized to aspirin versus aspirin and OAC. OAC did not affect mortality or reinfarction, reduced stroke by 30% (without evidence for heterogeneity), and markedly increased the odds of major bleeding (Table 5). There was no evidence for publication bias for the entire population ($P = .72$) or the aspirin background cohort ($P = .73$) by funnel plot analysis (Egger's test).

Table 1 Studies Included in the Meta-analysis

Study Design and First Author/ Study Name and Reference	Year	n
OAC vs. placebo		
WARIS[13]	1990	1214
OAC (± aspirin) vs. aspirin		
AFTER[12]	1996	1036
CHAMP[8]	2002	5059
APRICOT 2[6]	2002	274
LoWASA[9]	2004	3300
Zibaeenezhad et al[15]	2004	140
OAC vs. aspirin vs. OAC + aspirin		
ATACS[7]	1990	93
CARS[4]	1997	8803
ASPECT 2[14]	2002	993
Hurlen et al[10]	2002	3630

OAC = oral anticoagulation; WARIS = Warfarin Aspirin Re-infarction Study; AFTER = Aspirin/Anticoagulants Following Thrombolysis with Eminase in Recurrent infarction study; CHAMP = Combination Hemotherapy and Mortality Prevention study; APRICOT = Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; LoWASA = Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction study; CARS = Coumadin Aspirin Reinfarction Study; ATACS = Antithrombotic Therapy in Acute Coronary Syndromes Study; ASPECT = Aspirin and Coumadin after Acute Coronary Syndromes study.

DISCUSSION

The principal finding of our meta-analysis is that among nearly 25,000 patients with recent acute myocardial infarction followed for nearly 90,000 patient-years, OAC does not reduce the risk of all-cause death (the focus of this analysis) or reinfarction. There was a substantial reduction in the incidence of stroke (30%). OAC doubled the risk of major bleeding. There was substantial heterogeneity among the studies for some endpoints (infarction and stroke), but not for the principal efficacy and safety endpoints (all-cause mortality and major bleeding). Unlike in previous meta-analyses, we chose to examine the strategy of OAC-based versus no OAC treatments, rather than to separate the individual arms of the studies when 3 regimens were compared. These results indicate that for every 100 patients treated with warfarin after a myocardial infarction, 1 major bleeding (number needed to harm = 100) and 4 minor bleeding (number needed to harm = 25) are caused, while 1 stroke was prevented (number needed to treat = 100). An analysis geared towards a more homogenous population receiving background aspirin therapy confirmed the directionality and magnitude of these findings.

Table 2 Selected Baseline Characteristics

Study/Year	Male (%)	Age (Years)	DM (%)	HTN (%)	Previous Angina/ Infarction (%)	Time from Infarction	Lytics (%)	PTCA (%)	CABG (%)	BB (%)	Statins (%)
WARIS 1990[13]											
No OAC	77	61.6	8	35	25				4.6	48	
OAC	79	61.4	6	32	28				4.4	48	
ATACS 1990[7]											
No OAC	56	62	34	53	75			22	16	25	
OAC	62	61-63	38	48	85			21	34	25	
AFTER 1996[12]											
No OAC	77	60.3				<24 h	100				
OAC	76	60.3				<24 h	100				
CARS 1997[4]											
No OAC	76		18.		18.2	3-21 days					
OAC	85		19		18.8	3-21 days					
ASPECT-2 2002[14]											
No OAC	79		12	22	38	11 days		7	4	79	30
OAC	75		8	24	36	10-11 days		5	4	71	32
Hurlen et al 2002[10]											
No OAC	74	60.7	9		12		54	19	18		
OAC	78	59.9	8		13		54	19	16		
CHAMP 2001[8]											
No OAC	98	64	27	53	35	<28 days	30				
OAC	98	64	27	55	37	<28 days	31				
APRICOT-2 2002[6]											
No OAC	81	58	6	31	12	48 h	36				
OAC	82	57	6	23	11	48 h	44				
LoWASA 2004[9]											
No OAC	75	66	13	33	58	<42 days		2	4	84	17
OAC	72	66	13	35	59			2	4	86	17
Zibaeenezhad et al 2004[15]											
No OAC	63	58.9				5-7 days					
OAC	68	63				5-7 days					

OAC = oral anticoagulation; DM = diabetes mellitus; HTN = arterial hypertension; PTCA = percutaneous coronary transluminal angioplasty; CABG = coronary artery bypass grafting; BB = beta-blockers; WARIS = Warfarin Aspirin Re-infarction Study; ATACS = Antithrombotic Therapy in Acute Coronary Syndromes Study; AFTER = Aspirin/Anticoagulants Following Thrombolysis with Eminase in Recurrent infarction study; CARS = Coumadin Aspirin Reinfarction Study; ASPECT = Aspirin and Coumadin after Acute Coronary Syndromes study; CHAMP = Combination Hemotherapy and Mortality Prevention study; APRICOT = Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; LoWASA = Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction study.

Epidemiological data support the association between elevated concentrations of factor VII and the risk of a primary vascular thrombotic event or recurrence after one had occurred. A potential benefit might be obtained by lowering factor VII concentrations. Some had suggested therapy with a low fixed-dose warfarin, which in pilot studies lowered factor VII levels, and decreased the risk of bleeding complications compared with full anticoagulation. The Warfarin Aspirin Re-infarction Study (WARIS)[13] specifically addressed this question and found that OAC improved mortality in the setting of acute myocardial infarction compared with placebo, in the absence of aspirin therapy. However, when OAC was compared with no OAC, on aspirin background therapy, the largest trial to date, CARS,[4] did not find any difference in mortality among 8803 patients randomized to OAC alone, aspirin alone, or combination of the 2. The INR achieved in CARS was 1.2-1.5. Our meta-analysis confirms these results in a much larger cohort of patients, with a more heterogeneous level of anticoagulation.

It is well recognized that platelets play an important role in vascular thrombosis at the ruptured coronary atherosclerotic plaque, leading to acute ischemic episodes.[18] Antiplatelet strategies have contributed substantially to improve the outcome of patients with acute coronary syndromes.[1] However, some studies reinforced the doubt about the putative benefit of adding OAC to aspirin for some groups of patients. The current American College of Cardiology/American Heart Association guidelines for ST-elevation myocardial infarction recommend warfarin alone (INR 2.5 to 3.5) or warfarin with aspirin (75 to 162 mg) (INR 2.0 to 3.0) as Class IIa indication for secondary prevention.[19] Similar recommendations were promoted by the American College of Chest Physicians.[20] They distinguish between the majority of patients with recent infarction who can monitor INR and for whom warfarin is weakly indicated (Class

Table 3 Summary of Ischemic and Hemorrhagic Events

Study	n	Death	Infarction	Stroke	Major Bleeding	Minor Bleeding
WARIS[13]						
No OAC	607	20.3%	20.4%	7.2%	0.0%	4.1%
OAC	607	15.5%	13.5%	3.3%	1.3%	7.2%
ATACS[7]						
ASA	32	0.0%	3.1%	0.0%	0.0%	3.1%
OAC + ASA	61	1.6%	4.9%	0.0%	0.0%	1.6%
AFTER[12]						
ASA	519	8.9%	3.3%	0.0%	1.0%	0.0%
OAC	517	8.1%	5.0%	0.0%	2.5%	0.0%
CARS[4]						
ASA	3393	3.0%	6.8%	0.6%	1.7%	0.0%
OAC + ASA	5410	3.3%	7.2%	1.1%	2.2%	0.0%
ASPECT 2[14]						
ASA	336	4.5%	4.2%	1.5%	0.9%	4.8%
OAC + ASA	657	1.8%	3.5%	0.2%	1.5%	11.6%
Hurlen et al[10]						
ASA	1206	7.6%	9.7%	2.7%	0.7%	3.2%
OAC + ASA	2424	7.9%	6.6%	1.4%	2.5%	9.7%
CHAMP[8]						
ASA	2537	17.3%	13.1%	3.5%	2.0%	3.0%
OAC + ASA	2522	17.6%	13.3%	3.1%	3.4%	13.8%
APRICOT 2[6]						
ASA	139	0.0%	7.9%	0.0%	1.4%	1.4%
OAC + ASA	135	0.7%	2.2%	0.0%	1.5%	3.7%
LoWASA[9]						
ASA	1641	19.7%	16.3%	7.1%	1.0%	2.6%
OAC + ASA	1659	18.7%	17.1%	4.7%	2.2%	5.8%
Zibaeenezhad et al[15]						
ASA	70	8.6%	8.6%	0.0%	2.9%	2.9%
OAC + ASA	70	2.9%	5.7%	0.0%	7.1%	18.6%
Total						
No OAC	10,480	10.9%	10.7%	2.9%	1.4%	2.0%
OAC	14,062	9.1%	9.3%	1.9%	2.4%	5.8%

WARIS = Warfarin Aspirin Re-infarction Study; OAC = oral anticoagulation; ATACS = Antithrombotic Therapy in Acute Coronary Syndromes Study; ASA = aspirin; AFTER = Aspirin/Anticoagulants Following Thrombolysis with Eminase in Recurrent infarction study; CARS = Coumadin Aspirin Reinfarction Study; ASPECT = Aspirin and Coumadin after Acute Coronary Syndromes study; CHAMP = Combination Hemotherapy and Mortality Prevention study; APRICOT = Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; LoWASA = Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction study.

IIb) and those at high risk (large anterior myocardial infarction, thrombus in left ventricle) for whom warfarin is recommended for at least 3 months at moderate intensity and in addition to aspirin (Class IIA).

Rothberg et al performed a meta-analysis of studies comparing warfarin plus aspirin versus aspirin alone after myocardial infarction or acute coronary syndromes.[3] They evaluated 10 trials (5938 patients), reported until 2004, and demonstrated no benefit in mortality for OAC and aspirin versus aspirin alone, but there was significant reduction in reinfarction, revascularization, and stroke. The incidence of major bleeding was significantly higher in the OAC group (1.5% per year), as found in our updated meta-analysis. There was a 2.5-fold (95% CI, 1.7-3.7, $P < .01$) higher rate of major bleeding and 2.6-fold (95% CI, 2.0-3.3, $P < .01$) higher rate of minor bleeding. Nevertheless, the authors did recommend warfarin in patients at low or intermediate risk for bleeding, stating that the benefits may outweigh the risk of bleeding because of a significant reduction in reinfarction (from 4.1% per year to 2.2%, $P < .01$) and in thrombotic stroke (from 0.84% per year to 0.34%, $P < .01$). Three of the largest trials completed since, CARS (8803 patients),[4] Combination Hemotherapy and Mortality Prevention study (CHAMP, 5059 patients),[8] and Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction study (LoWASA, 3,300 patients),[9] are included in our analysis. These studies quadrupled the number of patients analyzed and reinforced the lack of benefit in mortality and excess of bleeding associated with OAC added to aspirin background therapy. The reduction in stroke remained highly statistically significant and clinically relevant. In these trials, one quarter to one third of patients had anterior infarction, and

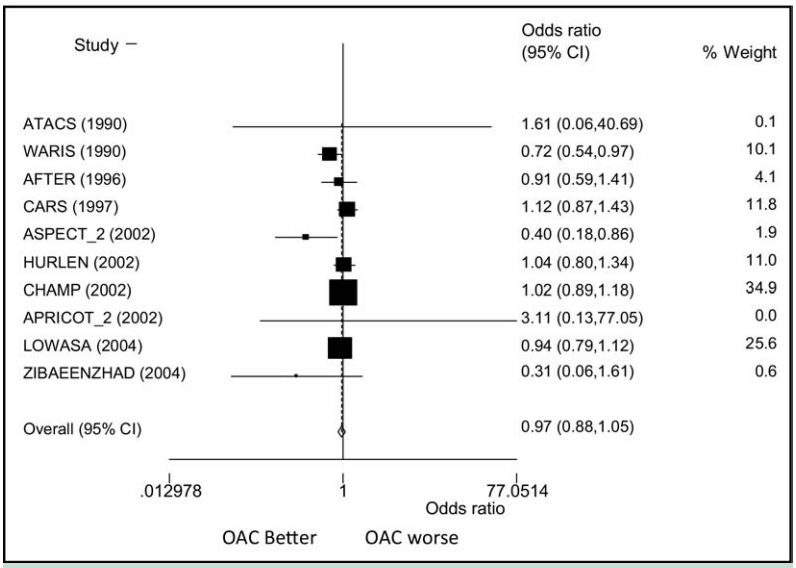

Figure 2 Forester plot of effect of long-term oral anticoagulation on mortality (point estimate proportional to number of events, odds ratio <1 indicates benefit for oral anticoagulation). OAC = oral anticoagulation; ATACS = Antithrombotic Therapy in Acute Coronary Syndromes Study; WARIS = Warfarin Aspirin Re-infarction Study; AFTER = Aspirin/Anticoagulants Following Thrombolysis with Eminase in Recurrent infarction study; CARS = Coumadin Aspirin Reinfarction Study; ASPECT = Aspirin and Coumadin after Acute Coronary Syndromes study; CHAMP = Combination Hemotherapy and Mortality Prevention study; APRICOT = Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; LoWASA = Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction study.

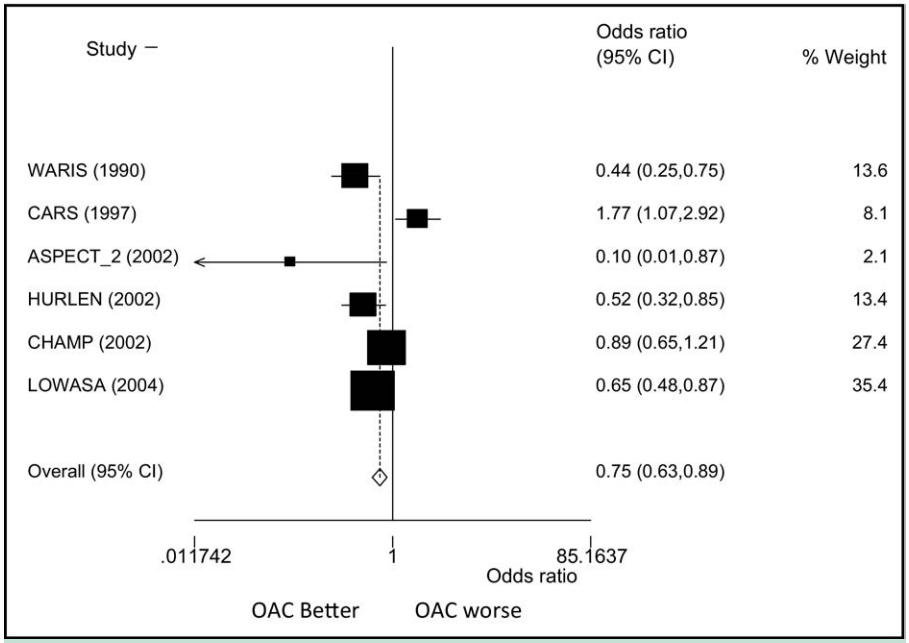

Figure 3 Forester plot of effect of long-term oral anticoagulation on nonfatal stroke (point estimate proportional to number of events, odds ratio <1 indicates benefit for oral anticoagulation). OAC = oral anticoagulation; WARIS = Warfarin Aspirin Re-infarction Study; CARS = Coumadin Aspirin Reinfarction Study; ASPECT = Aspirin and Coumadin after Acute Coronary Syndromes study; CHAMP = Combination Hemotherapy and Mortality Prevention study; LoWASA = Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction study.

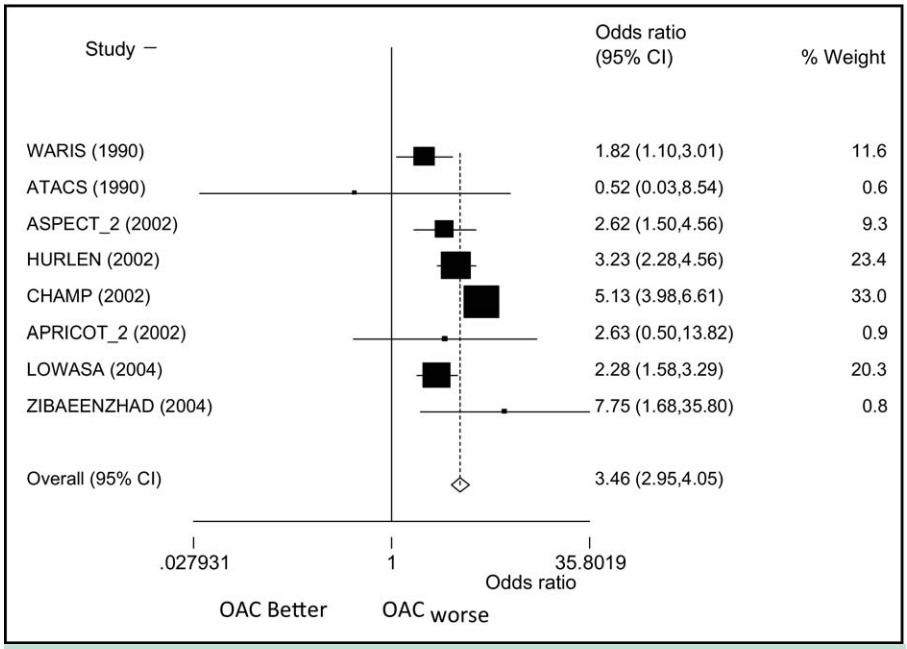

Figure 4 Forester plot of effect of long-term oral anticoagulation on nonfatal major bleeding (point estimate proportional to number of events, odds ratio >1 indicates excess with oral anticoagulation). OAC = oral anticoagulation; WARIS = Warfarin Aspirin Reinfarction Study; ATACS = Antithrombotic Therapy in Acute Coronary Syndromes Study; CARS = Coumadin Aspirin Reinfarction Study; ASPECT = Aspirin and Coumadin after Acute Coronary Syndromes study; CHAMP = Combination Hemotherapy and Mortality Prevention study; APRICOT = Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis; LoWASA = Effect of fixed low-dose warfarin added to aspirin in the long term after acute myocardial infarction study.

in 2 of them (CHAMP and LoWASA), prespecified analyses showed no evidence of benefit in patients with anterior infarction. As new studies accumulate, it appears that the benefit of OAC for cardiac protection is less and less evident, reflecting the pathophysiology of acute coronary syndromes and concomitant therapies offered to patients in more recent trials. The rupture of a stable plaque results in platelet activation and aggregation, which decreases blood flow, and possibly results in myocardial infarction. Thus, there appears to be a limited role for warfarin-like compounds, as they would not prevent the initiation of the thrombotic cascade related to the disruption of the atherosclerotic plaque. Furthermore, more modern postinfarction therapy, including statins and angiotensin-converting enzyme inhibitors, used infrequently in older trials, may decrease the potential for additional ischemic events.[21-24] Not least important is the advantage of more frequent reperfusion with pharmacological or mechanical means that decreases the likelihood of death and severe heart failure after infarction.[25] In 2006, Andreotti et al performed an updated meta-analysis of aspirin plus warfarin versus aspirin alone in patients recovering from acute coronary syndromes.[26] Their analysis focused on the combination of major adverse events (MAE), rather than death alone in our study, and

Table 4 Pooled (Fixed) Effect of OAC for Ischemic and Hemorrhagic Events (OR <1 Indicates Benefit for OAC)

Event	OR	CI	*P* Value	*P* (Heterogeneity)
Death	0.97	0.88-1.05	.43	.14
Infarction	0.94	0.87-1.03	.18	.001
Stroke	0.75	0.63-0.89	.001	.001
Major bleeding	1.83	1.50-2.23	<.001	.14

OAC = oral anticoagulation; OR = odds ratio; CI = confidence interval.

Table 5 Pooled (Fixed) Effect of OAC for Ischemic and Hemorrhagic Events (OR <1 Indicates Benefit for OAC) in 11,920 Patients Randomized to Aspirin Alone or Aspirin and OAC

Event	OR	CI	*P* Value	*P* (Heterogeneity)
Death	0.98	0.89-1.09	.74	.50
Infarction	0.93	0.83-1.04	.20	.007
Stroke	0.71	0.58-0.87	.001	.19
Major bleeding	2.03	1.56-2.64	<.001	.65

OAC = oral anticoagulation; OR = odds ratio; CI = confidence interval.

excluded studies in which aspirin was not given. They concluded that, among 25,307 patients randomized, warfarin added to aspirin did not reduce the incidence of MAE (fixed OR 0.96, $P = .30$ with considerable heterogeneity). When only studies with INR 2-3 were included, the OR was 0.73, $P < .001$ and without heterogeneity. The authors concluded that addition of intermediate-intensity warfarin to aspirin is indicated to prevent MAE in patients willing "to face the logistic hurdles" and accept the inherent bleeding risk associated with chronic OAC. Nevertheless, when mortality alone is analyzed, as is the primary focus of our analysis, there was no benefit for the combination therapy over aspirin alone, even in studies targeting INR of 2-3 (2.8% vs 2.9%).

Limitations

While our data are derived from a large cohort of patients, we did not have access to patient-specific data and could not identify subsets of patients in whom OAC may be beneficial. Specifically, we could not find evidence that subsets of patients, such as those with large anterior infarctions and those in whom thrombus was present in the left ventricle benefited from the addition of OAC. We could not reliably detect an interaction between intensity of anticoagulation and prevention of ischemic events, particularly death, and could not find a therapeutic window for which anticoagulation prevents ischemic events without affecting safety. Furthermore, because randomized clinical trials frequently represent a relatively healthier population than those treated in daily practice, it is possible that our findings underestimate the benefit of chronic OAC in patients with multiple co-morbidities.

CONCLUSION

Notwithstanding these limitations, we concluded that chronic OAC with warfarin does not reduce mortality or reinfarction after myocardial infarction, regardless of concomitant aspirin administration. There was a significantly higher rate of bleeding in patients receiving OAC, balanced by a significant protective effect for stroke. Dedicated clinical trials may be able to identify selected subsets of patients who could still benefit from OAC in the current era. These results do not exclude the possibility that carefully monitored INR at a moderate intensity may prevent the combination of ischemic events analyzed separately in this study. We see a need, based on our findings, for revisiting the American College of Cardiology/American Heart Association guidelines for postinfarction care with respect to OAC.

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CLINICAL RESEARCH STUDY

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Acute Myocardial Infarction Hospitalization in the United States, 1979 to 2005

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ABSTRACT

BACKGROUND: We reported earlier that there was no decline of acute myocardial infarction hospitalization from 1988 to 1997. We now extend these observations to document trends in acute myocardial infarction hospitalization rates and in-hospital case-fatality rates for 27 years from 1979 to 2005.

METHODS: We determined hospitalization rates for acute myocardial infarction by age and gender using data from the National Hospital Discharge Survey and US civilian population from 1979 to 2005, aggregated by 3-year groupings. We also assessed comorbid, complications, cardiac procedure use, and in-hospital case-fatality rates.

RESULTS: Age-adjusted hospitalization rate for acute myocardial infarction identified by primary International Classification of Diseases code was 215 per 100,000 people in 1979-1981 and increased to 342 in 1985-1987. Thereafter, the rate stabilized for the next decade and then declined slowly after 1996 to 242 in 2003-2005. Trends were similar for men and women, although rates for men were almost twice that of women. Hospitalization rates increased substantially with age and were the highest among those aged 85 years or more. Although median hospital stay decreased from 12 to 4 days, intensity of hospital care increased, including use of coronary angioplasty, coronary bypass, and thrombolytics therapy. During the period, reported comorbidity from diabetes and hypertension increased. Acute myocardial infarction complicated by heart failure increased, and cardiogenic shock decreased. Altogether, the in-hospital case-fatality rate declined.

CONCLUSION: During the past quarter century, hospitalization for acute myocardial infarction increased until the mid-1990s, but has declined since then. At the same time, in-hospital case-fatality rates declined steadily. This decline has been associated with more aggressive therapeutic intervention.

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KEYWORDS: Acute myocardial infarction; Hospitalization; In-hospital case-fatality

Age-adjusted mortality rates from coronary heart disease and acute myocardial infarction have declined steadily in the United States since the 1960s.[1-4] Many factors might have contributed to this decline in mortality, including control of risk factors for coronary heart disease and declining incidence and severity of disease.[5] In addition, more intensive medical care likely has contributed to this decline.[6] These factors might have influenced the incidence of acute myocardial infarction and the survival of those with the disease. We previously reported there was no decline in hospitalization for acute myocardial infarction from 1988 to 1997 in the United States.[7] We now extend our observations to document trends in acute myocardial infarction hospitalization rates for 27 years, from 1979 to 2005.

MATERIALS AND METHODS

Data Sources

The National Hospital Discharge Survey (NHDS) 1979-2005 was conducted by the National Center for Health

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Statistics, Centers for Disease Control and Prevention. The NHDS collected annual data from a sample of inpatient records acquired from a national sample of hospitals. General hospitals or children's general hospitals, and hospitals with an average length of stay of fewer than 30 days for all patients were included in the survey. Federal, military, and Department of Veterans Affairs hospitals were excluded, as were hospital units of institutions and hospitals with fewer than 6 beds staffed for patient use.

Before 1988, the NHDS sample was based on a 2-stage design. The survey was redesigned in 1988.[8] The new method of sample design used a modified 3-stage design. Although there are a number of differences between the original and new designs that have been documented, the changes do not affect the ability to conduct trend analysis.[8]

We selected the discharge records of patients aged 25 years or more within sampled hospitals using systematic random sampling. Because discharges were sampled, an individual patient might appear more than once if he/she had more than 1 hospitalization. We collected information from the hospital records related to patient characteristics, including date of birth, gender, expected primary sources of payment, discharge status (including in-hospital death), up to 7 discharge diagnoses, and number of days hospitalized. We did not analyze data for racial or ethnic groups because some hospitals did not collect information on race.[9]

Patients were defined as having an acute myocardial infarction with the primary (first listed) diagnostic code of International Classification of Diseases, Ninth Revision, Clinical Modification (Table 1). Cardiovascular comorbidity was defined by the second to seventh listed diagnostic codes of the International Classification of Diseases, Ninth Revision, Clinical Modification. These included hypertension and diabetes. Complications from acute myocardial infarction also were identified from the second to seventh listed codes, including heart failure and cardiogenic shock. Cardiac procedures performed during hospitalization were defined with International Classification of Diseases, Ninth Revision, Clinical Modification procedure code, including cardiac catheterization, coronary artery bypass graft surgery, and percutaneous transluminal coronary angioplasty. Thrombolytic therapy also was identified by procedure code (Table 1).

Statistical Analysis

To better reflect overall US hospitalizations, we estimated the number of hospitalizations and frequencies of characteristics of patients in the NHDS by taking into account the sampling weight. We calculated hospitalization rates by every 3 aggregated years from 1979 to 2005 (1979-1981, 1982-1984, . . . 2003-2005), using the estimated number of hospitalizations as the numerator and the US civilian population as the denominator. We calculated age-standardized hospitalization rates (per 100,000) using the 2000 US Standard Population. We also estimated the percentage of comorbid conditions, complications, use of revascularization procedures, and in-hospital case-fatality rates. We assessed age-specific rates and trends of these characteristics. We estimated relative percentage changes from 1979-1981 to 2003-2005 by the changes over the 2 periods divided by the first period.

CLINICAL SIGNIFICANCE

- From 1979 to 2005, the hospitalization rate for acute myocardial infarction in the United States has declined only since 1996.
- The use of cardiac reperfusion treatment for patients with acute myocardial infarction has expanded.
- Length of hospital stay has shortened.
- In-hospital case-fatality rate has declined.
- Disparities exist for these estimates by age and gender.

RESULTS

The total number of hospitalizations with the first-listed diagnosis of acute myocardial infarction was approximately 432,000 in 1979 and 681,000 in 2005, a 58% increase. Hospitalization rates were 194 and 231 per 100,000 population for 1979 and 2003, respectively. The mean (± standard deviation) age of patients was 67 ± 14 years (60% were aged ≥ 65 years), and 60% were men. Among acute myocardial infarction hospitalizations, women were older than men (71 ± 13 years vs 64 ± 13 years).

Table 1 International Classification of Diseases, Ninth Revision, Clinical Modification for Diseases and Procedures

Description	ICD-9-CM
Disease codes	
Acute myocardial infarction	410.0-410.9
Hypertension	401.0-405.9
Diabetes	250.0-250.9
Heart failure	428.0-428.9
Cardiogenic shock	785.51
Procedure codes	
Cardiac catheterization	37.21-37.23, 88.50-88.58, 89.64
Coronary artery bypass graft surgery	36.10-36.19
Percutaneous transluminal coronary angioplasty	36.01, 36.02, 36.05, 36.06
Thrombolytic therapy	99.10, 99.20

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

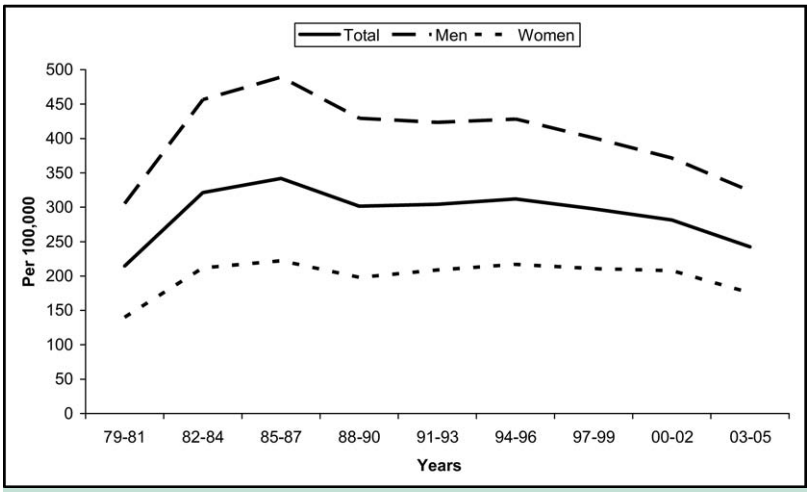

Figure 1 Trends of age-adjusted annual hospitalization rates for acute myocardial infarction, for total and by gender, NHDS, 1979-2005.

Age-adjusted Rates of Hospitalization for Acute Myocardial Infarction

During the 27-year period, the age-adjusted hospitalization rate for acute myocardial infarction was 215 per 100,000 people in 1979-1981 and increased to 342 in 1985-1987. Thereafter, the rate stabilized for the next decade before declining after 1996 to reach 242 in 2003-2005. Although the trends were similar for men and women, men had rates almost twice those of women (Figure 1).

Acute myocardial infarction hospitalization rates increased with age and were the highest among those aged 85 years or more (Figure 2). Of note is the continuously increasing hospitalization rate until 2002 among those aged 85 years or more, even though the rates declined after the period from 1994 to 1996 for all other age groups.

Characteristics of Patients with Acute Myocardial Infarction

Patient characteristics were compared between the first period (1979-1981) and the last period (2003-2005). Over the years, age at acute myocardial infarction hospitalization, percentages of women, comorbidity of hypertension and diabetes, heart failure complication, and percentage discharged to short- or long-term care facilities increased (Table 2). On the other hand, the percentage of patients with private insurance, cardiogenic shock complications, and in-hospital case-fatality decreased, as did the median length of hospital stay.

The median hospital stay decreased by 67% over the period, from 12 days in 1979-1981 to 4 days in 2003-2005 (Table 2). Women and men had the same overall median

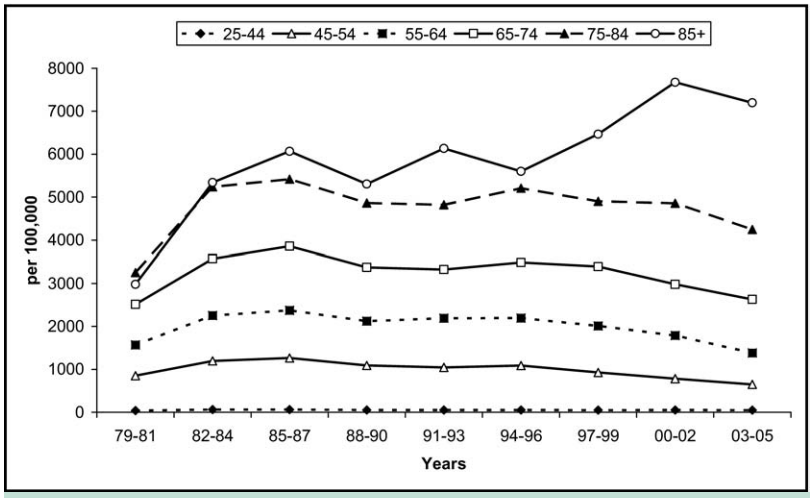

Figure 2 Acute myocardial infarction hospitalization rates by age, NHDS, 1979-2005.

Table 2 Selected Characteristics of Hospitalizations for Acute Myocardial Infarction as First-listed Diagnosis for 1979-1981 and 2003-2005: National Hospital Discharge Survey, 1979-2005

Characteristics	1979-1981	2003-2005	Relative Percent Change (%)
No. of hospitalizations	1,325,363	2,178,023	64.3
Age (mean ± SD)	64.1 ± 12.4	69.3 ± 14.5	8.1
Age group, y (%)			
25-44	5.7	5.8	1.8
45-64	40.3	30.8	−23.6
65-74	29.7	22.3	−24.9
75-84	19.1	25.3	32.5
>85	5.1	16.2	217.6
Women (%)	37.2	41.9	12.6
Source of payment (%)			
Self-pay	0.7	3.8	442.9
Medicare/Medicaid	60.1	67.0	11.3
Private, including HMO	39.2	26.2	−33.2
Others	0	3.0	2900.0
Median hospital days	12	4	−66.7
Comorbidity (%)			
Hypertension	14.1	46.8	233.8
Diabetes	14.7	23.4	58.5
Complications (%)			
Heart failure	13.0	33.4	154.2
Cardiogenic shock	3.8	1.9	−50.0
Intervention (%)			
Cardiac catheterization	4.6	46.7	915
CABG	0.5	8.2	1560.0
PTCA	0	30.0	–
Thrombolytic drugs	0	8.3	–
Discharge status (%)			
Home	69.2	56.5	−18.2
Other short-term facilities	5.2	16.4	215.4
Long-term facilities[a]	1.5	11.1	640.0
Against medical advice	0.8	0.8	0
Death	17.8	8.0	−55.1
Unknown	5.6	7.1	26.8

HMO = health maintenance organization or other managed care plan; CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

[a]Long-term care facility includes nursing home, skilled nursing facility, extended care facility, intermediate care facility, or custodial care facility.

length of stay (6 days). Median length of stay increased with age: 4 days for patients aged less than 45 years, 5 days for patients aged 55 to 64 years, and 6 days for patients aged 65 years or more.

Cardiac Procedures Performed and Thrombolytic Therapy

During this period, cardiac catheterization use among patients hospitalized with acute myocardial infarction increased from 4.6% in 1979-1981 to 46.7% in 2003-2005. Coronary artery bypass graft surgery use increased from 0.5% in 1979-1981 to a peak of 10.7% in 1994-1996 and decreased to 8.3% in 2003-2005. On the other hand, percutaneous transluminal coronary angioplasty was performed in 2.9% of cases in 1985-1987 and increased to 30% by 2003-2005. The frequency of thrombolytic therapy was first recorded in 1997-1999 at 2.1%, increased to 8.7% in 2000-2002, and then decreased slightly to 8.3% in 2003-2005. Throughout this period, a higher percentage of men received these procedures and treatment than did women (Figure 3). In addition, patients aged 25 to 64 years were more likely to receive procedures and treatment than were older patients, and those aged 85 years or more were least likely to receive these interventions (Figure 4).

In-hospital Case-fatality Rate of Acute Myocardial Infarction

The average in-hospital case-fatality rate during the entire period was 12.1%, which increased with age: 5.4% for those aged 25 to 64 years, 14.5% for those aged 65 to 84 years, and 22.9% for those aged 85 years or more. Women had a higher in-hospital case-fatality rate than men (14.9% vs 10.2%). For all age groups, the in-hospital case-fatality rate was slightly higher among women than men except among

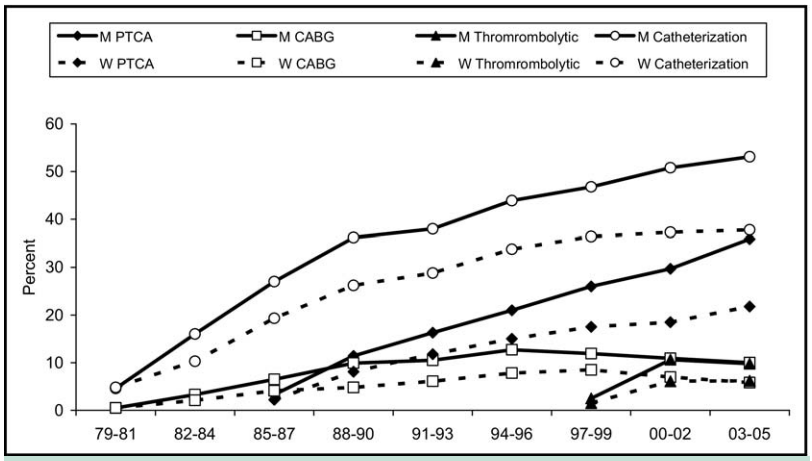

Figure 3 Use of cardiac procedures and thrombolytic drugs among patients hospitalized for acute myocardial infarction by gender, NHDS, 1979-2005. M = men; W = women; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft.

those aged 85 years or more (Figure 5). The in-hospital case-fatality rate declined in both men and women for all age groups. Age-adjusted, in-hospital case-fatality rate decreased from 24.2% to 9.4% between the periods 1979-1981 and 2003-2005.

DISCUSSION

From 1979 to 2005, acute myocardial infarction hospitalization rates increased from 194 to 231. These rates increased at first, then leveled off, and finally declined slowly. During this time, there were increases in use of cardiac catheterization, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, and thrombolytic drugs. Length of stay decreased substantially during this time, as did in-hospital case-fatality rates. In addition, disparities were noted by age and gender for hospitalization rates, use of procedures, and in-hospital case-fatality rates.

Incidence of Acute Myocardial Infarction

Although national surveillance to monitor trends in the incidence of acute myocardial infarction is lacking, population-based studies in different geographic settings have examined the incidence of acute myocardial infarction. These studies include the Worcester Heart Attack Study,[10] Framingham Heart Study,[11] Minnesota Heart Survey,[6] Corpus Christi Heart Project,[12] Rochester Epidemiology Project,[13] and Charleston Heart Study.[14] Despite the varying time periods involved in each of these studies, and differing clinical and sociodemographic characteristics of the study samples, all of these studies have observed declines in the incidence of acute myocardial infarction. Although an earlier report from the Worcester Heart Attack Study showed increases in the age-adjusted incidence rates of initial acute myocardial infarction in greater Worcester residents hospitalized between 1975 and 1981, more recent data from this study showed declines in these incidence rates through the mid[15] and late 1980s.[16]

Factors Contributing to the Observed Trends of Acute Myocardial Infarction Hospitalization

The changes in acute myocardial infarction hospitalization observed can be attributed to multiple factors, including change in incidence rates and reduction in risk of death before hospitalization, changing diagnostic criteria, hospital treatment, and data-collection methods. There is evidence that risk of death before hospitalization declined during the 1990s.[17,18] The diagnostic criteria for acute myocardial infarction early in the study period differed from those presented later in the study.[19] The introduction of the measurement of troponin levels in the early 1990s might have resulted in the admission of patients with less severe acute myocardial infarction who would previously have been diagnosed with unstable angina.[11,20,21] As a result, such patients might have had better survival than those with more severe infarctions, as diagnosed using older criteria.

Cardiogenic shock rates were 3.8% and 1.9% in 1979-1981 and 2003-2005, respectively, lower than 6.6% reported by the Worcester Heart Attack Study.[22] This could be due to the data record. Our report identified acute myocardial infarction with the primary International Classification of Diseases, Ninth Revision, Clinical Modification code, and cardiogenic shock was defined by the second to seventh codes of the International Classification of Diseases. Because cardiogenic shock is a life-threatening condition, it could be coded as primary diagnosis at discharge with NHDS. Therefore, it would not be included, because all cases reported in this article had primary diagnosis of acute myocardial infarction. In addition, the Worcester Heart Attack Study included only acute myocardial infarc-

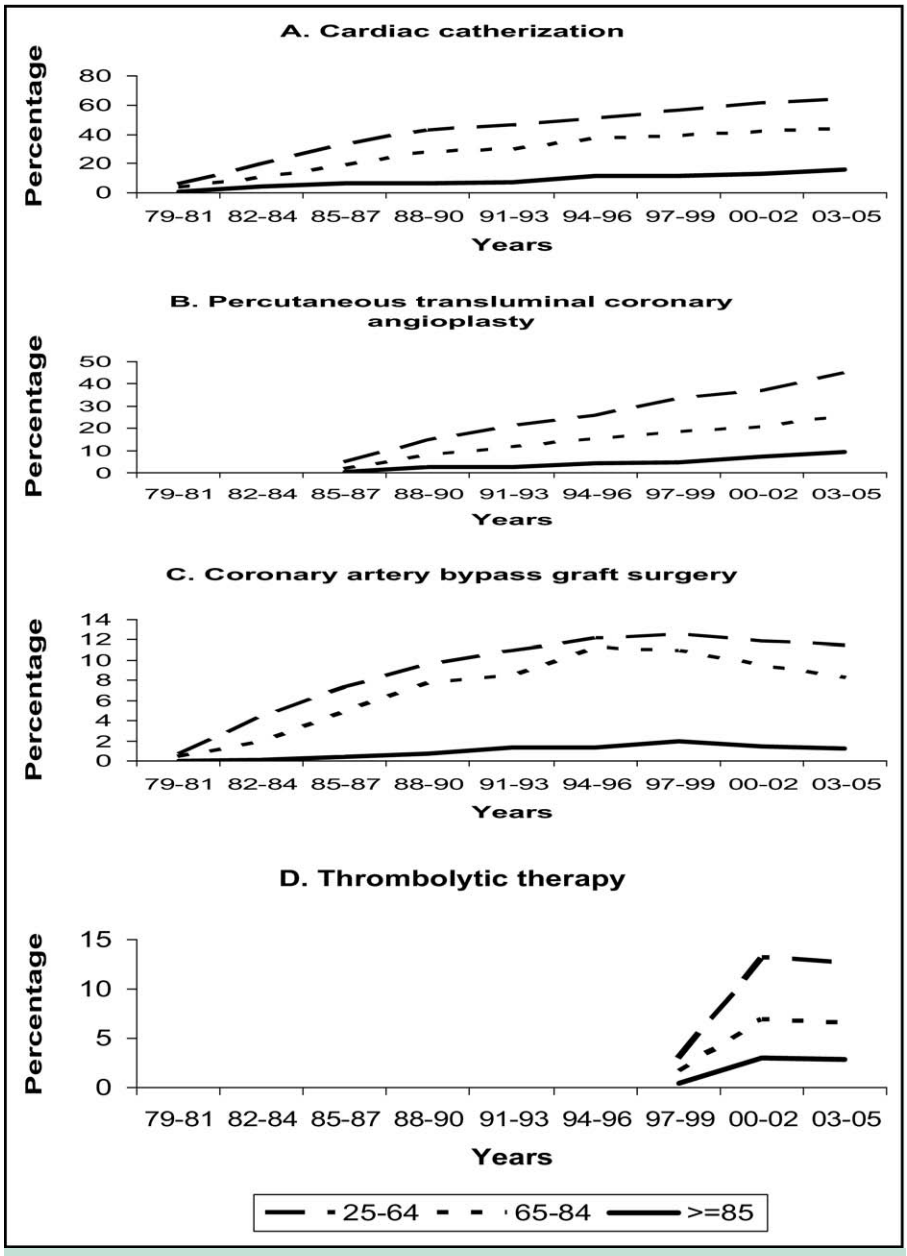

Figure 4 Use of cardiac procedures and thrombolytic drugs among patients hospitalized for acute myocardial infarction by age, NHDS, 1979-2005.

tion during the index hospitalization, and NHDS included both index hospitalization and readmission.

Furthermore, evidence-based data revealed that with the introduction of coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, and thrombolytic therapy during the past 3 decades, acute myocardial infarction hospital survival improved and length of stay shortened.[23,24] Finally, because NHDS data do not distinguish between the first and subsequent events, the incidence of first acute myocardial infarction could have declined because of improved preventive care, whereas more patients survived a first event and experienced a second or even third event with hospitalizations.

In-hospital Case-fatality Rates of Acute Myocardial Infarction Hospitalization

The decline in in-hospital case-fatality rates observed is consistent with the overall decline in age-adjusted mortality from coronary heart disease in the Framingham Heart Study and other regional studies.[1,3,6,11,25,26] This decline can be explained by both the declining incidence of myocardial infarction in the population and the improved survival of patients with myocardial infarction.[6] Recent reports from the Worcester Heart Attack Study showed that among patients hospitalized with acute myocardial infarction, the incidence of cardiogenic shock,[22] complete heart block,[27]

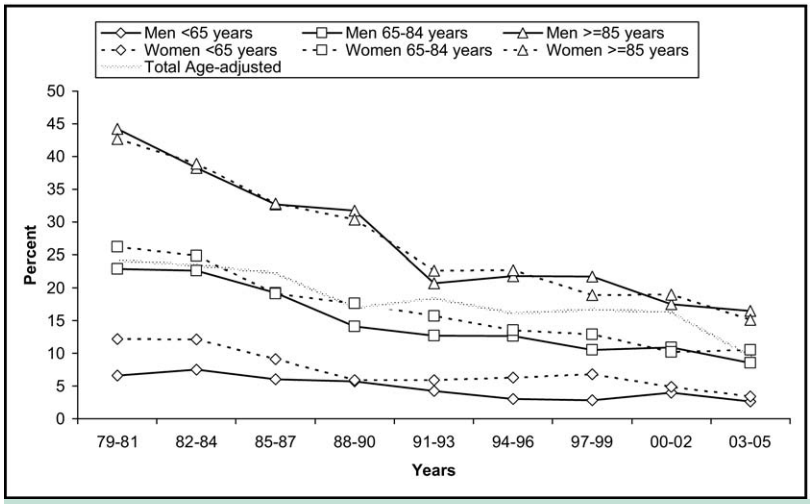

Figure 5 In-hospital case-fatality rate among patients hospitalized for acute myocardial infarction, by age and gender, NHDS, 1979-2005.

and ventricular fibrillation,[28] the major complications of acute myocardial infarction associated with fatality, all declined throughout the 30-year study period from 1975 to 2005. The reduction of these complications of acute myocardial infarction contributed to the decline of in-hospital case-fatality. Moreover, the Olmsted County Study examined indicators of myocardial infarction severity, including Killip class, electrocardiogram descriptors, and peak creatine kinase values, among patients with acute myocardial infarction and found a decline in the severity of myocardial infarction from 1983 to 1994,[29] which contributed to the decline of in-hospital case-fatality rate.

Because longer-term mortality data after hospital discharge are not readily available, it is possible that the observed decline in in-hospital case-fatality rates merely reflected the shift in mortality from in-hospital to out-of-hospital as the result of substantially reducing the length of stay from 12 to 4 days. However, this was not likely because a recent report based on the Minnesota Heart Survey showed that the progressive and substantial decrease in hospital length of stay after acute myocardial infarction in the past 2 decades was not associated with increased mortality after discharge. These decreases in length of stay were associated with increasing use of effective therapies.[30] Moreover, most deaths in-hospital among patients with acute myocardial infarction occurred within the first several days.[31]

Ford et al[32] recently estimated that approximately half of the decline in the US death rate for coronary heart disease from 1980 to 2000 was due to reductions in major risk factors, and that approximately half was due to evidence-based medical therapies. On the basis of a summary of studies published from 1975 to 1995, Heidenreich and McClellan[33] concluded that the primary reason for the decrease in early mortality from myocardial infarction seemed to be the increased use of effective treatments, including aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and coronary reperfusion.

Strengths and Limitations

Our study, which is based on National Hospital Discharge data, eliminates bias due to variations in acute care by hospital and region, and is more representative of the total US experience than previous local and regional studies. The strengths of this database include its large size, representative quality, and standardized methodology. However, major limitations of this administrative database include the inability to validate diagnoses or procedure use, assess racial or state variations, determine 30-day and postdischarge mortality, or distinguish first from subsequent hospitalizations, because our report is the number of hospital discharges rather than patients. In addition, the administrative database provides minimal clinical detail, including duration of delay in seeking medical care after the onset of acute coronary symptoms and use of medications other than thrombolytic drugs. However, these limitations should not affect the trend estimates of this study.

CONCLUSIONS

During the past quarter century, although coronary heart disease mortality has decreased, hospitalization for acute myocardial infarction has only begun to decline more recently. At the same time, there has been a trend toward more intensive acute care and vastly expanded use of invasive procedures associated with both shorter length of stay and decreasing in-hospital case-fatality rates.

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CLINICAL RESEARCH STUDY

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Higher Incidence of Mild Cognitive Impairment in Familial Hypercholesterolemia

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ABSTRACT

OBJECTIVE: Hypercholesterolemia is an *early* risk factor for Alzheimer's disease. Low-density lipoprotein (LDL) receptors might be involved in this disorder. Our objective was to determine the risk of mild cognitive impairment in a population of patients with heterozygous familial hypercholesterolemia, a condition involving LDL receptor dysfunction and lifelong hypercholesterolemia.

METHODS: By using a cohort study design, patients with familial hypercholesterolemia (N = 47) meeting inclusion criteria and comparison patients without familial hypercholesterolemia (N = 70) were consecutively selected from academic specialty and primary care clinics, respectively. All patients were older than 50 years. Those with disorders that could affect cognition, including history of stroke or transient ischemic attacks, were excluded from both groups. Thirteen standardized neuropsychologic tests were performed in all subjects. Mutational analysis was performed in patients with familial hypercholesterolemia, and brain imaging was obtained in those with familial hypercholesterolemia and mild cognitive impairment.

RESULTS: Patients with familial hypercholesterolemia showed a high incidence of mild cognitive impairment compared with those without familial hypercholesterolemia (21.3% vs 2.9%; $P = .00$). This diagnosis was unrelated to structural pathology or white matter disease. There were significant differences, independent of apolipoprotein E4 or E2 status, between those with familial hypercholesterolemia and those with no familial hypercholesterolemia in several cognitive measures, all in the direction of worse performance for those with familial hypercholesterolemia.

CONCLUSION: Because prior studies have shown that older patients with *sporadic* hypercholesterolemia do not show a higher incidence of mild cognitive impairment, the findings presented suggest that *early* exposure to elevated cholesterol or LDL receptor dysfunction may be risk factors for mild cognitive impairment.

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KEYWORDS: Alzheimer's disease; Hypercholesterolemia; Lipoprotein receptors; Mild cognitive impairment

Alzheimer's disease is a progressive neurodegenerative disorder characterized by global deterioration of cognition and behavior.[1] Development of dementia in Alzheimer's disease is usually preceded by a prodromal stage of abnormal cognitive performance known as mild cognitive impairment.[2] A major neuropathologic feature of Alzheimer's disease is the increase in insoluble amyloid fibrils composed of 40-42 amino acid peptides known as the amyloid beta protein.[3,4]

Recent studies suggest a connection between cholesterol metabolism and the pathogenesis of Alzheimer's disease.[5-9] We reported that hypercholesterolemia accelerates amyloid beta protein production in the brain of transgenic mice[7,8] and

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associates with higher levels of amyloid beta protein amyloid in the human brain.[10] On the basis of apparently controversial epidemiologic studies,[11] some investigators have argued that this relationship might be spurious. However, the discrepancies might be more apparent than real for the following reasons. Most positive studies have typically measured serum cholesterol levels early in life and then correlated these levels prospectively to development of dementia *later* in life.[10-16] In contrast, most negative reports have examined cohorts of *older* patients and for short follow-up periods, and concluded that there was no association between cognitive decline and higher cholesterolemia.[11,16] Taken together, the studies suggest that hypercholesterolemia is only an *early* (not a late) risk factor for Alzheimer's disease. In addition, the negative studies inadvertently missed gradual declines in cholesterolemia that precede by years the development of dementia in most affected patients;[15] this phenomenon could obscure abnormalities that might have occurred earlier in life. Last, subjects with the highest levels of cholesterolemia generally die of cardiovascular events at younger ages and are lost from the samples of elderly subjects (ie, comparative studies of patients with Alzheimer's disease vs controls), introducing a bias known as survivor effect.[17] The hypothesis that hypercholesterolemia represents an early risk factor for Alzheimer's disease was recently tested and substantiated by us in a neuropathologic study.[10] Hypercholesterolemia was strongly correlated with the presence of brain amyloid but only in subjects aged 40 to 55 years ($P = .00$). The differences in cholesterolemia between amyloid-bearing and amyloid-free brains disappeared as the subjects' age increased beyond 55 years. With the foregoing mechanisms in mind, one also can explain most studies negating a role for statins in Alzheimer's disease prevention because they have been conducted in samples of patients older than 65 years, failing to consider the mentioned age-related dynamics in the populations' risk.[18-26]

The aim of the current study was to determine whether patients who have familial hypercholesterolemia exhibit cognitive abnormalities. Patients with familial hypercholesterolemia offer a unique window into the role of cholesterol metabolism in cognition because the afflicted patients are exposed to hypercholesterolemia from early in life and also carry a dysfunction of low-density lipoprotein (LDL) receptors. Members of the LDL receptor family, including LDL receptors themselves, have been implicated in synaptic function and Alzheimer's disease pathogenesis.[18] There are no studies examining cognition in this population, independently of cerebrovascular disease, because statins have only been widely available since the early 1990s.

Familial hypercholesterolemia is characterized by hypercholesterolemia since birth and is caused by inherited genetic abnormalities that directly or indirectly affect the function of the LDL receptors.[19] The resulting condition carries a high risk of early-onset coronary heart disease and decreased survival if untreated.[19]

CLINICAL SIGNIFICANCE

- A high incidence of mild cognitive impairment is observed in patients with familial hypercholesterolemia.
- Early exposure to elevated cholesterol or dysfunction of lipoprotein receptors might be risk factors for mild cognitive impairment.
- Symptoms of memory deficits in patients with familial hypercholesterolemia might represent a marker of mild cognitive impairment.
- Impaired cognition is unrelated to white matter disease and independent of apolipoprotein E4 or E2 status.

METHODS

Diagnosis of Familial Hypercholesterolemia

We used the Dutch Lipid Clinic Network criteria.[20] Briefly, these criteria are based on LDL-cholesterol levels above the age- and gender-specific 95th percentiles of a reference population, vertical transmission of hypercholesterolemia, early-onset coronary heart disease in the index case or first-degree relatives, and presence of tendon xanthomas.[21] Each of these variables was scored, and an overall score was constructed to indicate the diagnostic probability of familial hypercholesterolemia (possible 3-5, probable 6-7, and certain ≥ 8). Only individuals with a score of ≥ 8 were included in the familial hypercholesterolemia group.

Patients with clinical familial hypercholesterolemia were then recruited into the Spanish Familial Hypercholesterolemia Register[22] and subjected to DNA testing for identification of LDL receptor mutations and the apolipoprotein B R3500G mutation following standard protocols. Briefly, genomic DNA was screened by a microarray system (Lipochip, Progenika Biopharma, Derio, Spain).[23,24] DNA samples from those patients in whom no mutation was identified by the microarray method were further sequenced after polymerase chain reaction amplification of the promoter region, the translated exon sequences, and the exon-intron boundaries of the LDL receptors gene. Large rearrangements were analyzed using a method based on quantitative fluorescent multiplex polymerase chain reaction. Nucleotide positions were numbered as suggested by Yamamoto and colleagues.[23] By these methods (microarray and sequencing), LDL receptor gene mutations were identified in 24 patients (~50% of patients), a proportion that is in agreement with other studies.[29,31-33]

Subjects and Design

Between August 2005 and May 2007, 47 patients with a diagnosis of familial hypercholesterolemia, aged more than 50 years, and without history of stroke or transient ischemic

attacks were recruited from 2 Lipid Clinics (University of Barcelona and the Spanish Familial Hypercholesterolemia Foundation, Madrid, Spain). Patients without familial hypercholesterolemia were recruited from the Internal Medicine Service of the University of Barcelona. None of the patients were referred to any of these clinics for cognitive problems. The patients with familial hypercholesterolemia were self-referred or referred for neurologically unrelated conditions for lipid management or to establish primary care. Patients with clinical evidence of psychiatric or neurologic disorders (including history of stroke or transient ischemic attack), any metabolic disease that could affect cognitive performance, illiteracy, history of excessive alcohol use (consumption $>$ 50 g/d), or drug abuse were excluded from the study. In addition, patients with history of hypertension, diabetes, or prior coronary artery bypass graft surgery also were excluded from both the familial hypercholesterolemia and the no-familial hypercholesterolemia groups because these conditions might adversely affect cognitive performance and potentially bias the results. Comprehensive medical histories and neurologic examinations were obtained from all participating subjects, including visual capacity, history of alcohol consumption, and administration of the Hamilton Depression Rating Scale.[24] All subjects were outpatients. Comparison subjects without familial hypercholesterolemia underwent a similar screening process as detailed above; however, the criteria for inclusion of control subjects also was conditioned on the absence of hypercholesterolemia (LDL cholesterol level $<$ 160 mg/dL). The latter was necessary to avoid inadvertent inclusion of patients with familial hypercholesterolemia into the comparison group because not all mutations associated with familial hypercholesterolemia are known and the genetic screen detects only approximately 50% of the mutations. All study participants underwent detailed neuropsychologic studies and laboratory investigations. Brain magnetic resonance imaging (MRI) was performed in all patients meeting criteria for mild cognitive impairment in the familial hypercholesterolemia group; 2 patients with mild cognitive impairment in the no-familial hypercholesterolemia group refused the MRI study. All subjects provided informed consent to a protocol approved by the institutional review boards at each location.

Clinical and Laboratory Determinations

All subjects' medical records were thoroughly reviewed, and each patient was clinically assessed for family history of early coronary heart disease ($<$55 years for men and $<$60 years for women), medication use, demographic characteristics, standard cardiovascular risk factors, and presence of tendon xanthomas.[21] Serum glucose, cholesterol, and triglycerides were measured by standard automated enzymatic procedures. LDL-cholesterol was estimated with the Friedewald equation.[25] Baseline lipid profiles were obtained from patients who had not received hypolipemic therapy for at least 4 weeks before drawing fasting glucose samples. Apolipoprotein E genotyping was performed by the polymerase chain reaction followed by restriction digestion with 5 U of *Hha I*. Digested products were separated by electrophoresis as described.[26]

Neuropsychologic Evaluation

The neuropsychologic examination was conducted by 2 experienced neuropsychologists blinded to the patients' diagnosis. We selected 13 well-established neuropsychologic instruments for screening of all cognitive domains.[27] The tests selected included the Mini-Mental State Examination, Buschke Memory Impairment Screen, semantic verbal category fluency for animals, Benton temporal orientation, clock drawing test (copy and command forms), Rey Auditory Verbal Learning test, Verbal Paired Associates, Boston Naming Test, digit span (forward and backward), Digit Symbol Substitution Test, Trail Making Test (Parts A and B), and Stroop test. Other measures incorporated in the assessment were the Global Dementia Scale and Hamilton Depression Rating Scale.

Definitions of Cognitive Abnormalities and Mild Cognitive Impairment

The diagnosis of mild cognitive impairment was made using the criteria outlined by Petersen et al,[2] recently endorsed by US[28] and European expert groups.[29] Briefly, amnestic mild cognitive impairment was defined as having a positive history of memory complaints and abnormal memory function on at least 2 neuropsychologic instruments tapping on the memory domain and normal performance on instruments tapping mainly on domains other than memory. However, patients with abnormal memory performance on 2 instruments plus *only* isolated deficits in a *single* instrument tapping on another domain also were classified as having amnestic mild cognitive impairment. Patients with mild cognitive impairment also were required to have intact activities of daily living and not to be demented. For the results to be considered abnormal, the scores were required to be less than 1.5 standard deviations of the controls. Patients were classified as affected with the multiple-domain form of mild cognitive impairment if they exhibited memory complaints and abnormal memory on neuropsychologic testing as defined above plus abnormal scores ($<$1.5 standard deviations of the controls) in at least 2 additional instruments tapping on cognitive domains other than memory. Patients with deficits in other cognitive domains as identified by poor performance on 2 instruments (tapping primarily in such domains) were considered for the diagnosis of non-amnestic mild cognitive impairment (ie, dysexecutive syndrome) (2), but these subtypes were not encountered in our cohorts.

Imaging Studies

Brain MRI was carried out in patients with mild cognitive impairment. The scans were performed by using a 1.5 Tesla Sigma apparatus (General Electric, Fairfield, Conn), according to a pre-established protocol that included coronal T1,

axial T1, fast spin echo, diffusion-T2, and Flair and coronal fast spin gradient. All scans were read by an experienced neuroradiologist.

Data Analysis

Demographics, clinical features, apolipoprotein E status, and neuropsychologic test scores were compared between familial hypercholesterolemia and control (no-familial hypercholesterolemia) groups using independent sample *t* tests for continuous variables and chi-square tests for categoric values. All tests were 2-sided using *P* less than .05 as the threshold for statistical significance. Of primary interest was the difference between familial hypercholesterolemia and no-familial hypercholesterolemia groups in the proportion of patients with mild cognitive impairment. Power calculations for the chi-square test (2-sided, alpha = 0.05, 45 patients with familial hypercholesterolemia, 70 patients with no familial hypercholesterolemia) yielded 80% power to detect a difference in mild cognitive impairment proportions of 3% in the no-familial hypercholesterolemia group (lowest reported proportion) and 20% in the familial hypercholesterolemia group.

In addition to direct familial hypercholesterolemia versus no-familial hypercholesterolemia group comparisons, factors associated with cognitive test scores were explored using separate stepwise multiple linear regression models for the Mini-Mental State Examination, Verbal Paired Associates, Rey Auditory Verbal Learning, and Trail Making Test. The dependent variable in each model was the test score, with the following independent variables allowed to enter: familial hypercholesterolemia group, age per 10 years, gender, education per 5 years, family history of premature coronary heart disease, ever tobacco use, body mass index, total cholesterol, and presence of apolipoprotein E4 and E2 alleles. SPSS software version 12.0 (SPSS Inc, Chicago, Ill) was used for all analyses.

RESULTS

Participant Characteristics

Participant characteristics are presented in Table 1.

Cognitive Function

None of the patients with familial hypercholesterolemia and mild cognitive impairment had a history of coronary events. Patients in the familial hypercholesterolemia group were significantly more likely than those in the no-familial hypercholesterolemia group to have developed mild cognitive impairment (relative risk 7.45; 95% confidence interval, 1.71-32.47). Ten subjects (21.3%) from the familial hypercholesterolemia group met criteria for mild cognitive impairment and exhibited neuropsychologic findings supporting this diagnosis. Of these patients, 7 were classified as having amnestic mild cognitive impairment and 3 were classified as having the multiple-domain form. On the other hand, only 2 subjects (2.9%) from the no-familial hypercholesterolemia group met the criteria for mild cognitive impairment (1 patient had the amnestic type, and 1 patient had the multiple-domain form).

There were significant differences between the familial hypercholesterolemia and the no-familial hypercholesterolemia groups in a number of individual cognitive measures, all in the direction of worse cognitive performance for those with familial hypercholesterolemia, as summarized in Table 2.

Factors associated with cognitive functioning were explored using stepwise linear regression separately for each

Table 1 Participant Characteristics

	FH N = 47	No FH N = 70	*P* Value
Men (No., %)	21 (44.7)	32 (45.7)	1.00
Age, y (mean, SD)	60.1 (6.7)	61.0 (7.0)	.49
Education, y (mean, SD)	10.1 (5.2)	9.7 (5.2)	.65
Family history of premature CHD (No., %)	15 (31.9)	7 (10.0)	.00
Ever smoked (No., %)	14 (29.8)	35 (50.0)	.04
Body mass index, kg/m^2 (mean, SD)	26.5 (3.5)	25.6 (3.2)	.15
Baseline glucose (mean, SD)	91.5 (8.7)	91.5 (10.3)	1.00
Mild cognitive impairment (No., %)	10 (21.3)	2 (2.9)	.00
Baseline lipid profile, mg/dL			
Total cholesterol (mean, SD)	386.3 (65.7)	214.8 (23.3)	.00
LDL cholesterol (mean, SD)	300.4 (66.9)	136.1 (17.8)	.00
HDL cholesterol (mean, SD)	60.7 (12.8)	61.7 (13.1)	.70
Triglycerides, (mean, SD)	128.2 (40.3)	84.5 (29.2)	.00
Apolipoprotein E status (FH n = 46, Comp n = 63)			
ε4 carrier (No., %)	9 (19.6)	11 (17.5)	.81
ε2 carrier (No., %)	0 (0.0)	9 (14.3)	.01

CHD = coronary heart disease; FH = familial hypercholesterolemia; SD = standard deviation; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Demographic and clinical characteristics of the study subjects.

Table 2 Neuropsychologic Test Results

Neuropsychologic Tests	FH	No FH	*P* Value
MMSE[a]	28.6 (1.6)	29.2 (1.1)	.027
Benton Temporal Orientation test	0.38 (2.0)	0.02 (0.1)	.230
Memory impairment screen	6.8 (1.6)	7.1 (1.0)	.351
Verbal category fluency	19.5 (4.8)	18.9 (4.4)	.548
Clock drawing test			
Order	9.3 (1.3)	9.9 (0.4)	.005
Copy	9.9 (0.4)	10.0 (0.2)	.102
Boston Naming Test	50.1 (6.2)	50.9 (6.7)	.528
RAVL test			
A1	4.9 (1.5)	4.8 (1.5)	.784
A2	7.2 (1.7)	7.3 (1.5)	.949
A3	8.4 (2.1)	9.1 (1.5)	.048
A4	9.4 (2.2)	10.2 (2.1)	.075
A5	10.0 (2.3)	11.2 (2.0)	.014
Total	39.9 (8.4)	42.7 (7.1)	.085
Interference	7.6 (2.9)	8.8 (2.2)	.021
Delayed recall	7.3 (2.9)	8.3 (2.4)	.076
Digit span			
Forward	5.6 (0.8)	5.8 (0.9)	.268
Backward	3.9 (1.0)	4.2 (1.0)	.271
VPA			
Easy	16.3 (2.1)	17.6 (0.9)	<.001
Difficult	6.7 (2.9)	8.9 (2.2)	<.001
Total	15.8 (3.5)	18.5 (2.7)	<.001
TMT			
Part A	50.9 (21.9)	49.2 (24.1)	.720
Part B	99.1 (39.7)	84.5 (28.4)	.053
Symbol Digit Modality	49.6 (19.5)	52.8 (20.6)	.456
Stroop test (Interference)	−2.1 (8.8)	0.1 (7.3)	.218
Global Deterioration Scale	2.13 (0.4)	1.98 (0.1)	.033
Hamilton Depression Rating Scale	2.2 (2.6)	2.8 (3.1)	.329

FH = Familial hypercholesterolemia; MMSE = Mini-Mental State Examination; RAVL = Rey Auditory Verbal Learning; TMT = Trail Making Test; VPA = Verbal Paired Associates.

Neuropsychologic assessment: standardized tests scores for FH and No-FH groups. Data are expressed as mean and SD.

[a]Corrected for age and education.

test (Table 3). Membership in the familial hypercholesterolemia group was independently associated with worse scores on the Mini-Mental State Examination ($P = .01$), Verbal Paired Associates ($P = .00$), and Rey Auditory Verbal Learning Interference ($P = .049$) tests. Cholesterol level was independently associated *only* with worse scores in the Trail Making Test Part B ($P = .01$). As expected, younger age and higher education years were independent predictors of better scores in several neuropsychologic measures. Finally, women scored significantly better than men in the Rey Auditory Verbal Learning Total ($P = .049$) and Delayed Recall ($P = .01$) tests. In the familial hypercholesterolemia group, the presence of memory complaints was associated with significantly decreased performance on neuropsychologic testing (Table 4). However, whether this clinical subjective marker of such lower performance will extend to larger samples is unknown.

Imaging Studies

Brain MRI studies were obtained from 10 patients with familial hypercholesterolemia and mild cognitive impairment and in neither of the 2 subjects with no familial hypercholesterolemia with mild cognitive impairment. None of the scans showed significant vascular lesions. A small lacunar pontine infarction was present in 2 of the patients with familial hypercholesterolemia; 1 patient had a small T2 hyperintense area in the subcortical parieto-occipital white matter. No areas of leukoaraiosis, T2 hyperintense white matter lesions (except for few minute T2 hyperintense periventricular white matter lesions in 2 patients), or other significant structural abnormalities were identified.

DISCUSSION

In this study, we found an association between familial hypercholesterolemia and mild cognitive impairment. The proportion of patients with familial hypercholesterolemia exhibiting abnormal cognitive function and meeting criteria for mild cognitive impairment (21.3%) was significantly higher than that observed in the control group (2.9%; $P = .00$) and far exceeded the age-specific prevalence predicted from either epidemiologic studies in the general population or the prevalence observed in follow-up of large cohorts with milder *sporadic* hypercholesterolemia.[2,30-32] All 10 patients from the mild cognitive impairment group had history of memory complaints, and all of them had neuropsychologic profiles meeting the criteria for mild cognitive impairment. Therefore, the clinical presence of a memory complaint seemed to be (at least in this small sample) an important marker for mild cognitive impairment. In the non-familial hypercholesterolemia control group, however, there were 4 patients with memory complaints. The diagnosis of mild cognitive impairment, however, could be confirmed in only 2 of these 4 patients in the non-familial hypercholesterolemia group by neuropsychologic examination. When comparing the familial hypercholesterolemia group with the non-familial hypercholesterolemia group, score differences were more conspicuous with the Mini-Mental State Examination ($P = .03$), clock test (order: $P = .01$), Verbal Paired Associates ($P = .00$), and Rey Auditory Verbal Learning (A3: $P = .048$; A5: $P = .01$; interference: $P = .02$). The Trail Making Test Part B was almost significant at $P = .053$. There also were significant differences in the Global Deterioration Scale ($P = .03$). Our findings cannot be explained solely by large vessel cerebrovascular disease because this possibility was excluded clinically and by imaging. We were surprised, however, by the relative lack of white matter disease in patients with mild cognitive impairment.

The term "mild cognitive impairment" is generally used to define a transitional stage between normal cognitive function and dementia.[2,39-41] Estimates of its progression rate to Alz-

Table 3 Independent Determinants of Cognitive Test Scores by Stepwise Multiple Linear Regression Analysis[a]

Cognitive Tests	Independent Variables	Regression Coefficient B	Standardized Coefficient Beta	R^2 for Model	Coefficient *P* Value
MMSE[b]	Constant	29.383	—	0.072	—
	FH group	−0.731	−0.269	—	.005
VPA	Constant	16.700	—	0.408	—
	Education per 5 y	0.709	0.221	—	.016
	FH group	−2.339	−0.355	—	<.001
RAVL					
Total (A1-A5)	Constant	35.288	—	0.304	—
	Education per 5 y	2.128	0.280	—	.004
	Gender (female)	2.979	0.192	—	.049
Interference	Constant	8.600	—	0.037	—
	FH Group	−0.991	−0.192		.049
Delayed recall	Constant	12.611	—	0.093	—
	Age per 10 y	−0.942	−0.237	—	.018
	Gender (female)	1.436	0.273	—	.006
TMT Part B	Constant	31.433	—	0.399	—
	Age per 10 y	12.274	0.240	—	.006
	Education per 5 y	−16.541	−0.471	—	<.001
	Cholesterol	0.072	0.206		.013

MMSE = Mini Mental State Examination; RAVL = Rey Auditory Verbal Learning; FH = familial hypercholesterolemia; VPA = Verbal Paired Associates; TMT = Trail Making Test.

[a]Variables allowed to enter the model were FH group, age per 10 years, gender, education per 5 years, family history of premature CHD, tobacco use, body mass index, total cholesterol, and presence of $\varepsilon 4$ and $\varepsilon 2$ alleles.

[b]Score already adjusted for age and education years.

heimer's disease range from 10% to 15% per year compared with 1% to 2% for cognitively intact subjects.[2] There are disagreements on which tests are most accurate for the diagnosis of mild cognitive impairment; however, instruments that assess learning and retention of information seem to be best as predictors for progression to Alzheimer's disease.[33]

We became interested in familial hypercholesterolemia because this condition may offer a unique window into the

Table 4 Group Statistics within the Familial Hypercholesterolemia Group: Mild Cognitive Impairment versus No Mild Cognitive Impairment

	MCI	N	Mean	SD	*P*
MMSE[a]	Normal	37	28.95	1.433	.004
	MCI	10	27.40	1.430	
VPA basal scores	Normal	37	16.8919	2.81152	.000
	MCI	10	11.7500	2.86017	
AVLT basal scores	Normal	37	42.24	7.661	.000
	MCI	10	31.10	3.635	
Interference AVLT scores	Normal	37	8.38	2.649	.000
	MCI	10	4.80	1.687	
AVLT delayed (at 20 min)	Normal	37	8.03	2.619	.000
	MCI	10	4.60	2.011	
TMT B	Normal	35	93.34	39.501	.068
	MCI	10	119.20	34.941	

FH = familial hypercholesterolemia; MCI = mild cognitive impairment; SD = standard deviation; MMSE = Mini Mental State Examination; VPA = Verbal Paired Associates; AVLT = Auditory Verbal Learning Test; TMT B = Trail Making Test Part B.

Intra-group comparison of neuropsychologic performance between patients with mild cognitive impairment and without mild cognitive impairment within the FH group analyzed by a 2-sided, 2-group independent samples *t* test for equality of means.

[a]Corrected for age and education.

role of cholesterol metabolism in cognition. Two aspects of familial hypercholesterolemia may be of particular relevance to Alzheimer's disease. The first is that patients who have this disorder are exposed to higher cholesterol levels from early in life. This is important because as mentioned, hypercholesterolemia may be an early risk factor for Alzheimer's disease.[10,15] The second feature is the involvement of LDL receptors in familial hypercholesterolemia. LDL receptors have been implicated in synaptic maintenance and Alzheimer's disease pathogenesis. Members of the LDL receptors family are involved in amyloid beta clearance[18,34] and synaptic plasticity from the brain, as supported by a growing body of literature.[18] One study showed that when an Alzheimer's disease mouse model of amyloidosis was crossed into an LDL receptor-deficient background, the mice not only developed exacerbated age-dependent cerebral beta-amyloidosis but also developed more severe behavioral abnormalities than observed in mice with LDL receptor-intact Alzheimer's disease.[34]

On the basis of the results of the current study, we propose the hypotheses that either early exposure to cholesterol or dysfunction of LDL receptors contributes to cognitive dysfunction in patients with familial hypercholesterolemia and that it is possible that similar mechanisms may be involved in mild cognitive impairment not associated with familial hypercholesterolemia. These hypotheses also might explain the apparently divergent results between our data and those from longitudinal studies of patients aged more than 65 years in whom (sporadic) hypercholesterolemia was not associated with increased risk of developing incident mild cognitive impairment. Presumably, these patients were neither exposed to high cholesterol levels early in life nor affected by LDL receptor mutations.

As in other populations with familial hypercholesterolemia who have been studied, only 50% of our patients had detectable LDL receptor mutations. Although this rate was higher among patients with familial hypercholesterolemia with mild cognitive impairment, it would be premature to make conclusions on this finding because of the small sample size. The possibility still stands, however, that in association with or independently of the lipid abnormalities, dysfunctions of LDL receptors or other unknown defects causing the familial hypercholesterolemia phenotype are linked to cognitive decline as patients grow older. The sample size in our study also was insufficient to dissect the effect of cholesterol from the effect of the LDL receptor mutations or their subtypes. Likewise, additional effects of lipoprotein E isoforms could not be fully assessed, although stepwise linear regression analysis suggested that the apolipoprotein E2 or E4 status did not affect cognitive performance (Table 3).

CONCLUSIONS

Cognitive impairment in familial hypercholesterolemia was unrecognized before this report probably because statins became widely available only in the early 1990s. Before that time, many patients with familial hypercholesterolemia would die of cardiovascular disease early before cognitive impairment could become manifest. Studies of larger samples of patients with familial hypercholesterolemia will allow further insights into the mechanisms and rates of conversion to dementia in this disorder.

ACKNOWLEDGMENTS

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CLINICAL RESEARCH STUDY

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Adoption of Once-monthly Oral Bisphosphonates and the Impact on Adherence

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ABSTRACT

BACKGROUND: The extent of the adoption of once-monthly bisphosphonates into general clinical practice is not known, nor is it known if the novel formulation improves adherence.

METHODS: We analyzed administrative claims 2003-2006 from a large employer-based health insurance database for incident use of oral bisphosphonates and stratified users by daily, weekly, and monthly dosing regimen. We measured adherence as the medication possession ratio (MPR) during the first year of therapy. We compared patient characteristics by dosing regimen and evaluated how the dosing regimen influenced the MPR.

RESULTS: We identified 61,125 incident users of bisphosphonates (n = 1034 daily, n = 56,925 weekly, n = 3166 monthly). Monthly bisphosphonate users were, on average, slightly older than the other groups (mean age 66 years for monthly users vs 65 years for weekly users or 66 years for daily users, $P < .05$) and more often lived in the North Central or South United States (76% vs 72% weekly users or 69% daily users, $P < .05$). There were no detectable differences among the dosing groups in the history of serious gastrointestinal risk, comorbidity burden, or prior osteoporotic fractures. During the first year of bisphosphonate therapy, 49% of monthly users had MPR ≥ 80% compared with 49% of weekly users (not significant) or 23% of daily users ($P < .0001$).

CONCLUSION: We found little evidence of preferential prescribing of monthly bisphosphonates to certain types of patients. Furthermore, we found no evidence of improved bisphosphonate adherence with monthly dosing relative to weekly dosing, although adherence with either weekly or monthly dosing was significantly better than with daily dosing.

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KEYWORDS: Bisphosphonates; Novel formulation; Patient compliance

In April 2005, the Food and Drug Administration approved the first once-monthly oral tablet for the treatment of a chronic disease. The once-monthly ibandronate sodium is a bisphosphonate, a class of drugs that inhibit bone resorption and are commonly prescribed for the treatment and prevention of osteoporosis in postmenopausal women.[1,2] The efficacy and safety of once-monthly bisphosphonates were demonstrated in a 1-year, double-blind study of postmenopausal women with osteoporosis whose treatment with 150 mg once-monthly ibandronate (n = 327) was shown to be noninferior to 2.5 mg daily ibandronate (n = 318) in increasing the bone mineral density in the lumbar spine.[3,4]

Previous to the monthly formulation, oral bisphosphonates were available in daily and weekly formulations, although the weekly formulation has dominated the market since its introduction in 2000. For instance, in a 2002-2003 observational cohort study, 84% of 211,319 patients were taking once-weekly bisphosphonates.[5] Once-weekly oral bisphosphonates have been associated with higher adherence over the once-daily formulations, although overall adherence has remained suboptimal in that drug class.[5-7] Between 52% and 87% of patients starting daily or weekly

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oral bisphosphonates discontinue the therapy within 1 year or do not fill enough prescriptions to cover 80% of a year of therapy.[5,8]

The extent of the adoption of once-monthly bisphosphonates into general clinical practice is not known, nor is it known if the novel formulation improves adherence. Research finds consistently that reducing the dosing demands of medications increases medication adherence, although this relationship has not been tested with once-monthly formulations.[9] In addition, recent surveys report conflicting results on patient preferences for the once-monthly formulation over the weekly, which also might influence adherence.[10,11] Furthermore, it is unclear whether prescribers channel the once-monthly bisphosphonates to certain kinds of patients, such as those with gastrointestinal disorders. The adoption patterns of these medications and the impact of a once-monthly dosing schedule on adherence is especially important because once-monthly bisphosphonate costs approximately 40% to 60% more than the generic forms of the daily and weekly oral bisphosphonates, which have been available since early 2008. The objectives of this study were to assess whether once-monthly bisphosphonates are preferentially channeled to certain patients and whether the monthly dosing schedule is associated with improvements in adherence.

CLINICAL SIGNIFICANCE

- Low adherence occurs with all oral dosing formulations of bisphosphonates (daily, weekly, and monthly).
- Merely reducing the dosing frequency of oral bisphosphonates will not improve adherence, although the worst adherence is associated with daily dosing.
- Clinicians need to reinforce the importance of adherence when starting a patient on bisphosphonates, irrespective of the dosing formulation.

MATERIALS AND METHODS

Study Population and Data Sources

This study used the 2001-2006 MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (Medstat: Ann Arbor, MI). This database contains more than 500 million claim records per year from individuals with private health care insurance. Scientific studies based on this data source have been reported in more than 75 peer-reviewed articles.[12] The data come from approximately 45 large employers who self-insure their employees and dependents. The MarketScan database offers advantages over raw administrative claims because data files undergo validity and editing procedures to ensure high-quality and consistency in fields across years.[13] The data are evaluated against population norms, previous year summaries, and validated data subsets. Outliers are flagged and reviewed for coding or processing errors. Encounter data are audited at the health plan level, and plans submitting incomplete data are excluded. Diagnostic and procedural codes are compared against validity algorithms and set to missing values if inconsistent. The encounter files contain age, sex, geographic residence, and eligibility information. The prescription claims include the national drug codes, date of purchase, quantity, days' supply, and expenditure information. The medical claims contain payment information, diagnoses, procedure codes, and type of provider. For this analysis, we pooled annual files to create a dataset of approximately 15 million people.

The study sample included individuals who were aged 50 years or older, had an osteoporosis diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification 733.xx), an incident dispensing of an oral bisphosphonate (ibandronate, alendronate, or risedronate), and least 2 years of observation. Incident use was defined as no bisphosphonate therapy for at least 12 months before initiating therapy. Individuals were excluded if they had Paget's disease (731.0) (n = 242), received transplantations (n = 321), or received an oral solution of bisphosphonates (n = 1210). The institutional review board of the University of Massachusetts Medical School approved this research.

Measures

The main study variable was dosing schedule. We calculated the dosing schedule as the day's supply divided by the metric quantity for each dispensing of the study drugs. Preliminary analyses showed evidence of prescribing outside of dosing guidelines, which made assignment by only tablet strength unreliable. We identified the modal value for each unique generic study drug dispensed to each individual, manually checked outliers for error (<0.5% of patients), and assigned individuals into mutually exclusive dosing schedules based on set thresholds. For instance, if an individual's modal dosing schedule of alendronate dispensed during the year fell within the range of 1/2 to 2 tablets daily, then that individual was assigned to a daily dosing schedule. Individuals receiving more than 1 assignment were categorized by the earliest assignment (eg, switching from weekly to monthly dosing), and all subsequent bisphosphonate use was summed into 1 medication possession ratio (MPR) value.

The dependent variable was adherence measured as MPR. We estimated the MPR as the sum of the day's supply of study medication dispensed during the year divided by the number of days in the year. Overlaps in the dispensing days of different generic drug therapies were eliminated, under the assumption that leftover supplies from earlier refills were discarded to begin the newer medication (eg, a change in therapy). The value of the day's supply was truncated if the supply extended beyond the time period of

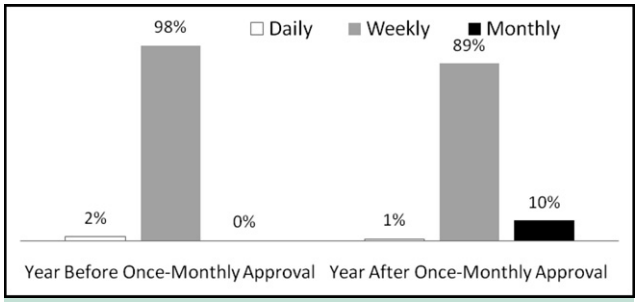

Figure 1 Adoption of once-monthly bisphosphonates by new users. The percentage of new users on daily, weekly, and monthly bisphosphonates 1 year before and 1 year after the approval of once-monthly bisphosphonates.

observation. Covariates included age; sex; geographic residence; health plan type; any pre-period bone mineral density testing; serious gastrointestinal risk;[14] osteoporotic fractures of the hip, wrist, or humerus; acute care hospitalizations; and a comorbidity risk score from the Diagnostic Cost Group Hierarchical Condition Category classification system (DxCG, Boston, MA).[15,16] The Diagnostic Cost Group Hierarchical Condition Category risk adjuster creates a single score for each person on the basis of the presence of 189 medical conditions in the diagnosis fields of claims records. Each person was assigned an index date based on the first dispensing of the incident study medication. Data from the year before the index date were used to construct pre-period measures of the covariates, most notably the comorbidity risk score.

Statistical Analysis

Bivariate statistics were used to calculate 95% confidence intervals (CIs), unadjusted *t* tests of means, and chi-square tests of frequency distributions. Stratified analyses by dosing frequency were conducted with all covariates.

RESULTS

We identified 61,125 unique individuals who initiated an oral bisphosphonate for osteoporosis (n = 1034 daily, n = 56,925 weekly, n = 3166 monthly). Approximately 4% switched dosing schedules, of which more than 93% were from weekly to monthly dosing (data not shown). Figure 1 shows that in the year before the approval of once-monthly bisphosphonate, 98% of the study population was started on a weekly formulation. However, after 1 year on the market, the once-monthly bisphosphonate was the drug of choice for 10% of new users.

Table 1 shows relatively modest differences in the characteristics of the 3 groups, except for type of health insurance. Relative to the weekly or daily users, patients receiving once-monthly bisphosphonates were, on average, slightly older (66 vs 65 or 65 years, $P < .05$), and more often female (93% vs 90% and 90%, $P < .05$). In the year before initiating therapy, once-monthly users were more likely to have had bone mineral testing (72.7% vs 65.3%, $P < .001$) and less likely to have been hospitalized than daily users (13.3% vs 14.4%, $P < .02$), but slightly less likely to have bone mineral testing (72.7% vs 74.9%, $P < .006$) than weekly users. Patients receiving once-monthly bisphosphonates more often lived in the North Central and South regions of the United

Table 1 Characteristics of Patients in Year Before Initiating Bisphosphonate Therapy by Dosing Schedule

Characteristics No. of Patients	Monthly n = 3166	Weekly N = 56,925	Daily N = 1034
Age, mean (SD)	66.0 (10.1)	65.4 (10.2)[a]	65.7 (10.4)[a]
Female sex (%)	93.1	90.1[a]	90.1[a]
Comorbidity risk score, mean (SD)	.754 (.63)	.743 (.66)	.754 (.65)
Selected diagnoses and medical care history			
Any bone mineral density testing, (%)	72.7	74.9[a]	65.3[a]
Any serious GI risk, (%)	3.7	3.2	2.5
Any osteoporotic fracture, (%)	3.3	3.7	3.8
Any hospitalization (%)	13.3	14.4	16.3[a]
Geographic residence (%)			
North East	8.7	9.5[a]	4.5[a]
North Central	38.9	37.8[a]	35.2[a]
South	37.6	34.2[a]	34.1[a]
West	14.5	18.5[a]	26.0[a]
Type of health plan (%)			
Comprehensive	49.9	44.6[a]	36.2[a]
Health maintenance organization	0.1	0.0	12.5[a]
Point-of-service	42.8	46.3[a]	7.8[a]
Preferred provider organization	6.6	7.8[a]	43.6[a]

SD = standard deviation; GI = gastrointestinal.
[a] $P < .05$ relative to monthly users.

States (76.5% vs 72.0% or 69.3%, $P<.0001$) than those receiving weekly or daily formulations. Last, nearly all users of monthly bisphosphonates belonged to comprehensive or point-of-service health plans (85.5% vs 81.4% or 44.0%, $P<.001$) compared with weekly users or daily users.

Figure 2 shows the adherence levels of newly started oral bisphosphonate users by dosing frequency. Approximately, 49% of once-monthly bisphosphonate users achieved an MPR of 80% or greater compared with 49% of once-weekly users (not significant) or 23% of daily users ($P<.002$). Moving the MPR threshold to 60% or greater showed adherence was highest for weekly users (63%) compared with monthly users (60%, $P<.002$) or daily users (31%, $P<.0001$).

Figure 3A and B show the mean MPR adherence levels from the stratified analyses. In general, the adherence of monthly users varied little by the subgroups, and the MPRs of monthly users were nearly identical to those of weekly users although markedly different from those of daily users. For instance, among monthly users, men had an average MPR of 69.8% (95% CI, 65.4-74.2) compared with an average MPR of 68.6% (CI, 67.7-69.5) for weekly users, and 41.0% (CI, 34.1-48.0) for daily users. Average adherence of monthly users exhibited a slight decline in adherence after age 80 years (63.2% MPR, 95% CI, 59.7-66.8) relative to those aged 50 to 59 years (66.3% MPR, 95% CI, 64.3-68.3), a similar pattern to that of weekly users. Monthly users in health maintenance organizations (61.2% MPR, 95% CI, 56.8-65.6) or preferred provider organizations (61.8% MPR, 95% CI, 59.8-63.9) also had slightly lower MPRs than those in comprehensive plans (68.5% MPR, 95% CI, 66.9-70.1).

Testing for bone mineral density before initiating therapy was associated with a modest adherence improvement among monthly users (67.2% MPR, 95% CI, 65.9-68.6 vs 61.2% MPR, 95% CI, 58.9 vs 63.5) and weekly users but not by daily users. No adherence improvement was found in monthly users with increased risk of serious gastrointestinal disorders, a prior fracture, or previous hospitalization. Last, adherence decreased slightly among monthly users with higher comorbidity burden (67.5% MPR for low burden, 95% CI, 65.2-69.8 vs 62.5% MPR for high burden, 95% CI, 59.7 vs 65.2). Again, this relationship also occurred with weekly users but not with daily users.

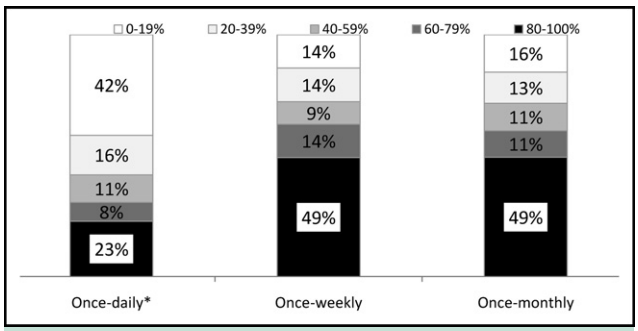

Figure 2 Overall year 1 adherence of bisphosphonate initiators by dosing frequency. The frequency distribution of the MPR for new users of daily, weekly, and monthly bisphosphonates.

DISCUSSION

In this large study of older adults with osteoporosis and newly initiated on bisphosphonates, we found once-monthly dosing conferred no additional benefit in adherence compared with once-weekly dosing, although adherence with either weekly or monthly dosing was significantly better than with daily dosing. During the first year of therapy, 49% of monthly users had an MPR $\geq$ 80% compared with 49% weekly users (not significant) or 23% daily users ($P<.0001$). Furthermore, we found modest evidence of preferential prescribing of monthly bisphosphonates to certain types of patients. There were no detectable differences among the dosing groups in the history of serious gastrointestinal disorders, comorbidity burden, or prior osteoporotic fractures. Despite the unclear advantages of the novel formulation, the once-monthly bisphosphonates were prescribed to 10% of all newly initiated patients on this class of drugs within the first year of availability.

Prior research on adherence with once-monthly bisphosphonates is not entirely consistent with these findings. Cooper et al[17] found higher rates of persistence with the once-monthly users compared with once-weekly users in an open-label study of 1103 postmenopausal women in the United Kingdom (56.6% vs 36.6%, $P<.0001$). However, the simultaneous intervention of a patient support program for only the once-monthly users makes the independent influence of dosing on adherence impossible to evaluate. In contrast, 2 studies using only pharmacy dispensing records found no difference in the adherence or persistence of newly initiated weekly versus monthly bisphosphonate users after the first refill.[10,18] Although, in the one case the study lasted only 6 months, covered the period of initial market availability, and used nonconcurrent cohorts. Furthermore, in both prior studies, adherence may have been underestimated because of limited data capture on prescriptions filled outside the study pharmacy network.[10]

Research also is mixed on patient preference for a once-monthly bisphosphonate and how much this preference influences adherence. Two studies have reported conflicting findings on patient preference, but both asked women who had experience in taking only the weekly or monthly formulations but not both.[10,19] A third study used a crossover design of 298 women who initiated either weekly or monthly bisphosphonates for 3 months and then switched to the alternative treatment. That study found the majority (71% vs 29%, $P<.0001$) preferred the monthly bisphosphonate; however, no findings were reported on adherence.[11]

LIMITATIONS

Our study has several important limitations. First, we cannot assess the reasons for discontinued therapy, so some of our classification of noncompliance may have been in accor-

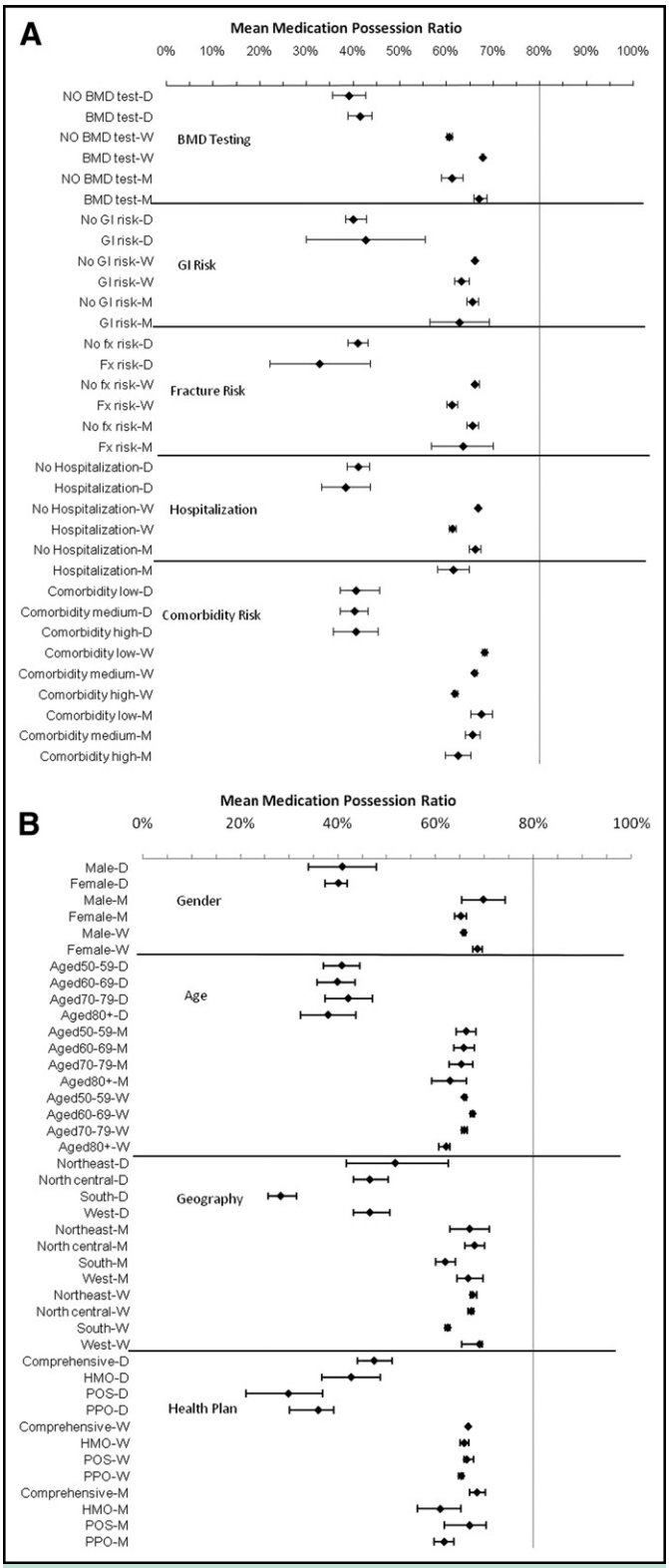

Figure 3 **A, B.** Stratified year 1 adherence of bisphosphonate initiators by dosing frequency and key baseline characteristics. The mean MPR for new users of daily, weekly, and monthly bisphosphonates stratified by gender, sex, health plan, geographic residence, bone mineral density testing, gastrointestinal disorder risk, hospitalization, and comorbidity risk. D = daily dosing users; W = weekly dosing users; M = monthly dosing users; BMD = bone mineral density; GI = gastrointestinal.

dance with the advice of physicians. We also did not evaluate the use of estrogen therapy, etidronate, or nasal calcitonin, so patients who switched to these therapies would have been considered noncompliant. Second, we do not know whether patients actually took the medication, only that they acquired the medication. Third, we did not evaluate the effects of noncompliance on treatment outcomes, although the relationships between adherence and bone mineral density, as well as fracture risk, has been demonstrated in other studies.[20,21] Also, there may have been unmeasured confounders. For instance, we found few differences in the characteristics of patients by dosing formulation, but there may have been unmeasured differences, such as previous experiences with adverse drug events. Physicians may preferentially prescribe the monthly bisphosphonates to individuals believed to be at increased risk for nonadherence. Fourth, the patterns of monthly use come from the first year of market availability, and these patterns may change over time. Last, the generalizability of our study is limited to insured patients who face fewer cost barriers to medications available in only branded versions.

Despite these limitations, this study offers one of the first assessments of the adoption of once-monthly bisphosphonates into general clinical practice. The similarity in patient characteristics between early adopters of the monthly formulations and the users of the established weekly formulation was notable; we found few differences and even those observed (eg, slightly older age for monthly users) were statistically significant because of the large sample size but not clinically meaningful. Instead, regional practice patterns and types of health plans seemed to be the stronger predictors of receipt of the monthly formulation, particularly in comparison with patients receiving daily bisphosphonates. Also, our dataset as drawn from comprehensive health insurance records provides a more complete assessment of prescription use than can be made using only the dispensing records of one pharmacy network.

CONCLUSIONS

The low adherence observed among all dosing groups suggests that merely reducing the dosing frequency of oral bisphosphonates is not enough to improve adherence. Instead, multimodal interventions may be needed, especially with a technology innovation in dosing schedule that may require a paradigm shift in adherence management. In the one study reporting an adherence advantage with monthly bisphosphonates, patients received a phone call reminder from a trained nurse a few days before the next dose was due.[17] However, even with this support, the proportion of patients persisting with the once-monthly bisphosphonate was still only 57% after 6 months of therapy.[17] From research conducted on the older bisphosphonates, we know that compliance improves with regular bone mineral density testing and patient–physician discussions about how the results relate to the progression of osteoporosis.[22] All patients initiated on bisphosphonates, regardless of dosing schedule, require reinforcement in the importance of adherence.

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REVIEW

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Postprandial Hypotension

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ABSTRACT

Postprandial hypotension is both common in geriatric patients and an important but under-recognized cause of syncope. Other populations at risk include those with Parkinson disease and autonomic failure. The mechanism is not clearly understood, but appears to be secondary to a blunted sympathetic response to a meal. This review discusses the epidemiology, risk factors, and pathophysiology of postprandial hypotension in the elderly, as well as diagnosis and treatment strategies. Diagnosis can be made based on ambulatory blood pressure monitoring and patient symptoms. Lifestyle modifications such as increased water intake before eating or substituting 6 smaller meals daily for 3 larger meals may be effective treatment options. However, data from randomized, controlled trials are limited. Increased awareness of this disease may lead to improved quality of life, decreased falls and injuries, and the avoidance of unnecessary testing.
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KEYWORDS: Geriatric; Postprandial hypotension

Postprandial hypotension is a common but under-recognized condition among older adults. It was first described in 1977 in a patient with severe Parkinson disease,[1] but a later prospective trial showed that postprandial hypotension is common among institutionalized geriatric patients.[2] Subsequent studies have shown that the prevalence in institutionalized elders is approximately 25%-38%, although one study conducted in a Dutch hospital reported a prevalence as high as 67%.[3-6]

EPIDEMIOLOGY

Classically, postprandial hypotension has been defined as a decrease in systolic blood pressure of ≥20 mm Hg or a decrease below 90 mm Hg from a pressure of ≥100 mm Hg within 2 hours after a meal.[7] This precipitous decrease in blood pressure is associated with a number of hypotensive phenomena, including syncope,[8] falls,[4,5] and even coronary events and stroke.[9] One study found that 23% of hospitalized elderly patients with either syncope or falls experienced postprandial hypotension.[4] A prospective study of patients with essential hypertension demonstrated that large decreases in postprandial blood pressure correlated with magnetic resonance imaging findings indicative of cerebrovascular damage; 83% of elderly hospitalized patients with postprandial decreases in blood pressure of 10 mm Hg or more had evidence of lacunae on magnetic resonance imaging, as compared with 44% of patients without such decreases.[10] There also have been case reports of transient ischemic attacks occurring in patients with significant postprandial hypotension.[11,12] Coronary events and overall mortality also are associated with postprandial hypotension.[9,13] In a study of 179 low-level-care residents in a long-term health care facility, patients with postprandial hypotension had a mortality rate of 145 per 1000 person-years, compared with 98.5 per 1000 for unaffected individuals.[13]

Risk factors for postprandial hypotension include certain medications, type and time of meal, premeal blood pressure, and specific comorbid conditions (Table 1). Polypharmacy appears to be a risk factor for postprandial hypotension, as the degree of postprandial hypotension is positively correlated with the number of cardiovascular and psychotropic medications taken.[3,4] Diuretics, in particular, are likely to cause postprandial hypotension.[3,14] One clinical trial did not find that the chronic use of cardiovascular medications induced more postprandial hypotension; however, the study was relatively small.[15]

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Composition, temperature, and timing of the meal are all important. Carbohydrate-rich meals predispose patients to more immediate decreases in blood pressure compared with meals containing mostly protein or fat,[16] and cause greater decreases in blood pressure and symptoms when compared with meals of lower carbohydrate content.[17] Carbohydrate-rich meals also cause more postprandial hypotension than meals comprised mostly of fat, possibly secondary to increased amounts of insulin and its corresponding vasodepressor effect.[18] Warm meals (50°C) appear to cause a greater decrease in postprandial blood pressure than meals served cold (5°C).[19] Postprandial hypotension can occur after any meal, but breakfast and lunch appear to be associated with the most pronounced decrease in blood pressure, resulting in more severe symptoms.[4,20] It is not clear why these meals are associated with the greatest degree of postprandial hypotension, but it is not likely due to meal composition or drugs. One clinical trial examined postprandial hypotension at different times of the day in patients not taking their usual medication. The same test meal was used for breakfast, lunch, and dinner, but breakfast and lunch elicited the most pronounced blood pressure decrease, possibly secondary to baroreflex dysfunction associated with increased premeal systolic blood pressure.[20] Higher early morning blood pressure is associated with larger decreases in postprandial blood pressure, but these changes have not been correlated with symptoms.[4,21,22] Orthostatic hypotension, at one time thought to be a risk factor for postprandial hypotension, appears instead to be additive rather than synergistic with postprandial hypotension.[23,24]

Postprandial blood pressure decreases occur even in the healthy elderly. In a study of 21 community-dwelling elderly adults, the mean postprandial decrease in systolic blood pressure was 11 mm Hg, and 2 patients (~5%) had a decrease in systolic blood pressure of 20 mm Hg or more.[25] The degree of meal-related blood pressure decrease is positively correlated with age,[21] and the institutionalized elderly are at greater risk than the community-dwelling elderly. Postprandial hypotension is common among patients with diabetes mellitus[26,27] and in patients with essential hypertension.[14] Patients with Parkinson disease are at particular risk,[28] with older patients and those with more severe disease experiencing the greatest decreases in blood pressure.[29] Anti-Parkinson medications such as levodopa/benserazide, however, do not appear to worsen postprandial hypotension.[29] Patients with end-stage renal disease undergoing hemodialysis also are at increased risk for postprandial hypotension.[30,31] In addition, there are case reports of postprandial hypotension occurring in patients with Fragile X mutation and Shy-Drager syndrome.[32,33]

CLINICAL SIGNIFICANCE

- Postprandial hypotension is common and under-recognized among the elderly.
- Postprandial hypotension is a common cause of falls, syncope, and stroke.
- Diagnosis should be made based on ambulatory blood pressure monitoring and symptoms.
- Treatment options include lifestyle modifications and pharmacotherapy.

Table 1 Risk Factors for Postprandial Hypotension

Medications	Polypharmacy (>3 medications)
	Diuretics
Meals	Carbohydrate-rich meals
	Breakfast
	Hot meals
Comorbid conditions	Diabetes mellitus
	Autonomic dysfunction
	Parkinson disease
	Hypertension
	End-stage renal disease on hemodialysis
	Fragile X mutation

PATHOPHYSIOLOGY

There are numerous theories as to why postprandial hypotension occurs in older adults, but the mechanism has yet to be fully delineated. It was previously thought that abnormal splanchnic pooling played a role, but studies in patients with autonomic failure and in the elderly do not support this.[34,35] Instead, postprandial hypotension appears to result from inadequate compensation for the normal physiologic postmeal decrease in blood pressure rather than to an exaggerated amount of splanchnic pooling. Healthy geriatric patients with stable blood pressures also experience splanchnic pooling after a meal, but are able to maintain systemic blood pressure by increasing peripheral vascular resistance, heart rate, and cardiac output.[36,37]

A blunted sympathetic response to hypotension appears to be responsible for the compensatory failure that underlies postprandial hypotension. A microneurographic study of muscle sympathetic activity demonstrated that compared with younger subjects, elders respond to an oral glucose load with a smaller increase in sympathetic activity.[38] Stretch receptors in the stomach also might modulate sympathetic activity, as gastric distention normally has a pressor effect; in the elderly, this "gastrovascular reflex" is blunted. This hypothesis is supported by the observation that there is no difference in muscle sympathetic nerve activity between the healthy elderly and young patients in response to an *intraduodenal* glucose load.[39] Heart rate spectral analysis studies also corroborate that elderly patients with postprandial hypotension do not have as great an increase in sympathetic activity as younger patients or geriatric patients

without postprandial hypotension.[37,40] An additional heart rate spectral analysis trial determined that a 200% increase in sympathetic nervous activity would be necessary to prevent postprandial hypotension in elderly patients.[41] Similarly, although patients with postprandial hypotension do increase sympathetic hormone levels after a meal, the increase is significantly less than that seen in normal subjects.[8,37,42] Elderly patients also might compensate poorly for postprandial decreases in blood pressure and fail to appropriately increase heart rate.[2,8]

Besides a lack of appropriate sympathetic response, there are likely other mechanisms responsible for postprandial hypotension. Intraduodenal glucose appears to cause a greater decrease in postmeal blood pressure in the elderly than in younger patients, but does not correspond with a difference in muscle sympathetic nerve activity or the magnitude of heart rate response.[39] This suggests that gut vasoactive hormones also might play a role.

It is not clear why postprandial hypotension is so common and profound in Parkinson disease. One proposed mechanism is impaired dopamine secretion; however, 2 small clinical trials that measured mealtime blood pressure shifts and dopamine levels offer conflicting results. One found that decreased systolic blood pressure correlated with lower urinary dopamine excretion, but a second, measuring plasma dopamine, found no clear relationship.[43,44]

DIAGNOSIS

Postprandial hypotension should be suspected in any elderly patient presenting with syncope or falls. In this setting, clinicians should inquire about hypotensive symptoms following meals, especially in patients with Parkinson disease, diabetes mellitus, or end-stage renal disease. Symptomatic patients should undergo ambulatory blood pressure monitoring with careful documentation of each meal, and close analysis of breakfast and lunch hemodynamics, because postprandial hypotension is most prevalent after the first 2 meals of the day.[4,20] Ambulatory blood pressure monitoring should be timed to at least include the meal that the patient considers most symptomatic, but 24-hour monitoring may be needed in order to determine the severity and frequency of postprandial hypotension. The maximum decrease in blood pressure typically occurs within the first 35 minutes to 1 hour after a meal;[2,3,45] however, monitoring of blood pressure and symptoms should continue for 2 hours after a meal, as the nadir in blood pressure can occur up to 2 hours postprandially.[46] Because blood pressure responses to a meal are similar after an equally timed meal on different days, it is, in fact, possible to make the diagnosis of postprandial hypotension after only one abnormal test.[15,22] In contrast, a negative test cannot rule out the diagnosis,[22] and further blood pressure monitoring may be needed. Currently, postprandial hypotension is defined analogously to orthostatic hypotension as a decrease in blood pressure of $\geq$20 mm Hg;[7] however, there have not been sufficient trials to correlate blood pressure decreases with symptoms. Therefore, diagnosis should be individualized. At a minimum, the patient should have symptoms accompanied by some blood pressure decrease to suggest the diagnosis.

TREATMENT

There is no definitive treatment for postprandial hypotension, but both nonpharmacologic modifications and medications can be beneficial (Table 2). Clinical trials of both types of postprandial hypotension treatments are mostly limited to patients with autonomic failure and the asymptomatic healthy elderly. While it is unclear whether the conclusions drawn from these studies can be applied to geriatric patients with symptomatic postprandial hypotension, many of the nonpharmacologic therapies are relatively benign and therefore worth trying. Larger randomized trials of pharmacological treatment of postprandial hypotension in older adults are needed to better determine risks and benefits.

Nonpharmacologic Modifications

Drinking water before a meal has been shown to attenuate the decrease in blood pressure in patients with autonomic failure and in elderly patients, and offers a simple and relatively risk-free intervention. Drinking 350-480 mL (12-16 ounces) can attenuate the decrease in blood pressure by as much as 20 mm Hg in patients with autonomic failure.[47,48] In healthy older adults, postprandial blood pressure declines are less severe when glucose is given in a

Table 2 Treatment Options for Postprandial Hypotension

Nonpharmacologic Modifications	Pharmacotherapy		
	Drug	Dose	Common Side Effects
Drink water before meals	Caffeine	60-200 mgs	Restlessness, palpitations, insomnia
Decrease carbohydrate intake	Alpha-glucosidase inhibitors		Diarrhea, flatulence
Eat frequent, smaller meals	Acarbose	100 mg	
Assume a recumbent or sitting position after a meal	Voglibose	200 μg	
	Guar gum	4 gm	Diarrhea, flatulence, abdominal pain
	Octreotide	50 μg	Arrhythmia, abdominal and injection site pain

larger volume (600 mL vs 200 mL).[49] Similar volumes of water will prevent a 14 mm Hg decrease in blood pressure precipitated by an intraduodenal glucose infusion in healthy elders.[50]

Advising patients to decrease their carbohydrate consumption or to eat smaller, more frequent meals also can attenuate postmeal hypotension and related symptoms.[17,51] Autonomic failure patients who were assigned to eat 6 small meals rather than 3 large meals of equal caloric content had less postprandial hypotension and fewer symptoms.[51]

Patients suffering from postprandial hypotension are often advised to lie in a recumbent position. Despite this, one clinical trial found that when patients walk 20 minutes after a meal, the pressor effect of exercise completely compensates for the expected postmeal decrease in blood pressure.[52] This protective effect on blood pressure lasts only while the patient is walking, and blood pressure again decreases once the patient stops ambulating.[52] Patients should therefore maintain a sitting or recumbent position after a meal, unless they are walking, in which case they should once again resume a recumbent position immediately upon stopping. Individual patients should remain recumbent for the period during which symptoms usually occur and through the nadir in ambulatory blood pressure recorded.

Medications or therapies that can cause hypovolemia should be avoided. Diuretics, particularly furosemide, have been shown to exacerbate postprandial hypotension,[14,53,54] and meals may worsen blood pressure decreases during hemodialysis.[30]

Pharmacotherapy

Caffeine, acarbose, guar, and octreotide are the most common medications used for postprandial hypotension, but efficacy studies offer conflicting results, and side effects limit their use. Many pharmacologic trials have included only autonomic failure patients or the asymptomatic healthy elderly; both efficacy and side effects for symptomatic elders are unknown.

Caffeine. Caffeine, an adenosine receptor antagonist, may ameliorate postmeal blood pressure decreases when coffee or tea is given before a meal.[55-58] However, it is unclear how caffeine exerts its effects on blood pressure, and data about its impact on postprandial hypotension are inconsistent. One study of patients over 50 years of age without postprandial hypotension showed that a dose of 60 mg of caffeine in coffee or tea 5 times daily attenuated the decrease in postmeal blood pressure by about 4 mm Hg in some groups of patients but not others.[56] Interestingly, caffeine does not seem to affect baseline systolic blood pressure in elders.[56] A randomized, controlled cross-over trial of 7 healthy elderly subjects with postmeal blood pressure decreases of approximately 14 mm Hg showed that 200 mg of caffeine (approximately 2 cups) completely prevented the decrease in postmeal blood pressure.[58] Unfortunately, 2 studies that included elderly patients with postprandial hypotension were conflicting. First, a study of 20 frail elderly patients, 4 of whom had postprandial hypotension, showed that a dose as small as 100 mg of caffeine prevented seated postmeal blood pressure decreases and associated symptoms.[57] In contrast, a randomized placebo-controlled trial of 9 elderly patients with symptomatic postprandial hypotension failed to show any attenuation of postprandial hypotension with 250 mg of caffeine.[59] Until more definitive evidence is available, caffeine may be worth trying for symptomatic patients, titrating from 60 to 200 mg before meals.

Alpha-glucosidase Inhibitors. Alpha-glucosidase inhibitors such as acarbose or voglibose have been shown to diminish the decrease in postprandial blood pressure. These medications are typically used in the treatment of type 2 diabetes mellitus and act by inhibiting carbohydrate digestion at the level of the brush border in the small intestine. Their effects on postprandial hypotension might reflect alterations in circulating vasodilators and in the amounts of gut peptides secreted.[60-62] In a double-blind, cross-over study of 8 healthy elderly patients, 100 mg of acarbose ameliorated a 6 mm Hg decrease in systolic blood pressure following a sucrose drink.[62] In another analysis, voglibose at a dose of 200 μg attenuated the decrease in postmeal blood pressure by 20 mm Hg.[61] Although these drugs appear promising, their use is limited by gastrointestinal side effects; 31% of patients experience diarrhea and most develop flatulence.

Guar. Guar gum is derived from the guar bean and acts as a bulking agent. It has been used for weight reduction and to promote regularity. It may prevent postprandial hypotension by slowing glucose absorption. In healthy elders, a dose of 4 grams attenuated a decrease of 10 mm Hg in systolic blood pressure following a 50 gram glucose load.[63] Unfortunately, guar gum also causes diarrhea, flatulence, and abdominal pain.

Octreotide. Octreotide, a somatostatin analog used in the treatment of acromegaly, carcinoid tumors, and diarrhea, has been shown to alleviate symptomatic blood pressure decreases in elderly patients, hypertensives, and in those with autonomic failure,[64-67] perhaps by increasing splanchnic and peripheral vascular resistance.[65] A single premeal 50-μg subcutaneous injection completely prevented a 15 mm Hg postmeal decrease in systolic blood pressure in hypertensive elderly patients.[64] Octreotide also has been shown to have a pressor effect on elderly patients with autonomic failure.[65] While promising, octreotide's use is hindered by its high cost, QT prolongation, and abdominal and injection site pain.

Inotropes/Pressors. While pressor medications can be used for orthostatic hypotension, their use in elderly patients with postprandial hypotension has not been studied. Agents such as midodrine, denopamine, and vasopressin have been investigated in patients with multiple system atrophy. In a

study of 8 patients, the combination of denopamine (a β1 agonist) and midodrine (4 mg) attenuated an approximate 25 mm Hg decrease in postprandial hypotension.[68] Another study of 5 patients with multiple system atrophy showed that an infusion of vasopressin of 0.3 U/minute before a 75-gram glucose load prevented postprandial hypotension.[69] More studies are needed before these agents can be recommended in the treatment of older patients with postprandial hypotension.

CONCLUSION

Postprandial hypotension is common in older adults, especially the institutionalized elderly, and is associated with significant morbidity and mortality. Falls, syncope, strokes, transient ischemic attacks, angina, and myocardial infarctions can result, and postprandial hypotension is an independent predictor of mortality. Prompt diagnosis and treatment with lifestyle adjustments such as drinking water before meals, avoiding diuretics, and eating smaller, more frequent meals might prevent recurrent syncope, further ischemic insults, unnecessary testing, and anxiety. Future research is required to fully elucidate the mechanism of postprandial hypotension in the elderly and to identify effective therapies with tolerable side effects.

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CLINICAL RESEARCH STUDY

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Physical Activity and the Risk of Community-acquired Pneumonia in US Women

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ABSTRACT

BACKGROUND: Exercise bolsters the immune system and can prevent various infections in certain populations. However, limited data exist regarding the role of physical activity and the risk of community-acquired pneumonia.

METHODS: During a 12-year period, we prospectively examined the association between physical activity and the risk of community-acquired pneumonia among 83,165 women in the Nurses' Health Study II who were between the ages of 27 and 44 years in 1991. We excluded women who had pneumonia before 1991 and those with a history of cancer, cardiovascular disease, or asthma. Biennial self-administered mailed questionnaires were used to determine activity level. Cases of pneumonia required a diagnosis by a physician and confirmation with a chest radiograph.

RESULTS: We identified 1265 new cases of community-acquired pneumonia during 965,168 person-years of follow up. After adjusting for age, women in the highest quintile of physical activity were less likely to develop pneumonia than women in the lowest quintile (relative risk [RR] = 0.72; 95% confidence interval [CI], 0.60-0.86; P for trend $< .001$). However, the association was attenuated and only marginally significant after further adjusting for body mass index, smoking, and alcohol use (RR = 0.84; 95% CI, 0.70-1.01; P for trend = .06). Women in the highest quintile of walking were less likely to develop pneumonia compared with women who walked the least (multivariate adjusted RR = 0.82; 95% CI, 0.69-0.98); however, the trend across quintiles was not significant (P for trend = .25).

CONCLUSION: Higher physical activity does not substantially reduce pneumonia risk in well-nourished women.

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Pneumonia and influenza combined rank as the seventh leading cause of death in the United States, accounting for more than 65,000 deaths annually.[1] In addition, pneumonia is a significant cause of outpatient visits and hospitalizations, particularly among individuals aged 65 years or older.[2,3] Despite advances in pharmacologic therapy for individuals with community-acquired pneumonia, hospitalization rates have increased over the past 15 years, and mortality rates have been increasing.[1,2]

Physical inactivity along with poor diet account for more than 15% of all deaths in the United States, and the rapid increase in the prevalence of overweight suggests that this figure is likely to increase over the next few years.[1] Exercise can bolster many components of the immune system, including antibody titers, T-cell function, and macrophage response, all of which are integral to lung defenses in providing protection against pneumonia.[4]

Despite evidence that exercise improves immune function, few studies have investigated the role of physical activity in the development of infection in general, and

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pneumonia specifically. A cohort study conducted in 3 geographically distinct communities found an increased risk of pneumonia mortality among individuals with limitations in activities of daily living and cognitive impairment in both men and women.[5] Inability to walk a half mile, climb stairs, or perform heavy housework was associated with increased risk of pneumonia mortality for women but not for men.[5] Physical activity was inversely associated with pneumonia risk in a large prospective cohort of women; however, this risk was attenuated after further adjusting for body mass index.[6] The study had only 300 cases of pneumonia, and individuals were followed for only 4 years.

CLINICAL SIGNIFICANCE

- Higher overall physical activity does not substantially reduce pneumonia risk in well-nourished women.
- Women who walk the most are less likely to develop pneumonia than women who walk the least.

There are limited data regarding the role of physical activity and the risk of community-acquired pneumonia. We extend and expand on prior studies by prospectively investigating the role of physical activity in the development of community-acquired pneumonia among a large cohort of well-nourished US women.

MATERIALS AND METHODS

Study Population

The Nurses' Health Study II began in 1989 when 116,671 US female registered nurses aged 25 to 42 years returned a mailed questionnaire. Details of the study design and data collection used in the Nurses' Health Study II have been published.[7] At the time of enrollment, participants provided a detailed medical history of diagnosed diseases, medications, and information on lifestyle factors, including smoking, physical activity, and alcohol use. Information on dietary and supplemental vitamin intake was first ascertained in 1991and updated every 4 years using a semiquantitative food frequency questionnaire. Women were excluded from the analysis if they had incomplete questionnaires (12,360), had pneumonia before the baseline in 1991 (14,156), died before 1991 (37), or had a history of conditions known to affect pneumonia risk (6953), including cancer, cardiovascular disease (myocardial infarction, stroke, or arterial surgery), or asthma diagnosed before or during the study period.

Identification of Cases of Pneumonia

We considered a case to be self-reported, physician-diagnosed pneumonia confirmed by chest radiography and included only the first documented event of community-acquired pneumonia occurring between June 1, 1991, and May 31, 2003. Women who reported pneumonia were sent a supplementary questionnaire asking whether the pneumonia diagnosis had been confirmed by x-ray. To examine the validity of self-reported pneumonia during the first 2 years of follow-up, a study physician blinded to exposure status examined the medical records of 76 women who had reported pneumonia. A radiology report of a pulmonary infiltrate confirmed the presence of pneumonia in 82% of the cases.[6] After the first 2 years of follow-up, medical records were obtained from all women who reported physician-diagnosed pneumonia that was confirmed with a chest radiograph. We reviewed medical records from a sample of 99 confirmed cases and found only one that was potentially hospital-acquired. Therefore, we considered all the cases to have community-acquired pneumonia.

Ascertainment of Physical Activity

Women were first asked about physical activity in 1989, and information was updated every 2 years. Women indicated the average time spent per week at various types of physical activity, such as walking, jogging, bicycling, and swimming, and time spent performing leisure activity, such as watching TV, driving, and sitting at home. We calculated a metabolic equivalents per hour score for recreational or leisure-time physical activity. One metabolic equivalent, the energy expended by sitting quietly, is equivalent to 3.5 mL of oxygen uptake per kilogram of body weight per minute, or to 1 kcal/kg of body weight per hour. For example, running (12 metabolic equivalents) requires 12 times the energy as sitting quietly. The metabolic equivalents per hour score was calculated for each participant by multiplying the reported average time spent at each activity per week by the typical energy expenditure requirements for the activity, expressed in metabolic equivalents per hour.[6,8] The validity of self-reported physical activity in this cohort has been described in detail.[9] Recall of physical activity within the previous year performed well when compared with previous week activity recalls ($r = 0.79$) in this cohort.[9,10]

Assessment of Other Covariates

Covariates considered in the multivariate model included age, body mass index, cigarette smoking, and alcohol intake. Body mas index was calculated as weight in kilograms divided by height in meters squared using the reported height of the women at the start of the study and updated weight. Participants reported on the biennial questionnaire if they currently smoked and the number of cigarettes per day. Alcohol intake was assessed by the food frequency questionnaire.

Data Analysis

Person-time of follow-up was calculated as the time between the return of the 1991 questionnaire until the first report of community-acquired pneumonia, death, or the end of the study period (May 31, 2003). We first examined age-adjusted models for the association between physical

Table 1 Baseline Characteristics of Women According to Quintile of Physical Activity

	Quintile of Physical Activity (MET-h/wk)[b]				
Characteristic[a]	1	2	3	4	5
Median MET-h/wk	1.9	6.3	12.5	22.7	47.9
Range of MET-h/wk	0.2-3.8	3.9-9.0	9.1-16.9	17.0-31.8	31.9-591
Walking MET-h/wk (median)	0.6	2.7	3.8	5.0	10.0
Age (y)	37.0	36.0	36.0	36.0	35.0
Body mass index (kg/m^2)	25.8	25.0	24.4	24.0	23.3
Alcohol intake (g/d)	2.6	2.8	3.0	3.4	3.8
Current smoker (%)	13.9	12.9	11.2	10.2	11.1

MET = metabolic equivalent.
[a]All values (except age) were standardized to the age distribution of the cohort. Values for age, body mass index, and alcohol intake are means.
[b]The MET-hours represent the average amount of time per week spent in each of 8 activities multiplied by the MET value of each activity. One MET is defined as the energy expended in sitting quietly, which is equivalent to an oxygen uptake of 3.5 mL/kg of body weight per minute for an average adult.

activity and the risk of pneumonia. Cox proportional hazards multivariate models with updating of exposure variables were used to estimate multivariate relative risks (RR). The multivariate models adjusted for age, body mass index (<21, 21-22.9, 23-24.9, 25-29.9, 30+ kg/m^2), alcohol intake (0, 0.1-5, 5-9.9, 10-14.9, 15-29.9, 30+ g/d), and cigarette smoking (never, past, current smoker of 1-14 cigarettes per day, 15-24 cigarettes per day, or 25+ cigarettes per day). The adjusted relative risk of pneumonia was calculated per quintile of physical activity, with the referent group being the lowest quintile.

In additional analyses, we assessed the association between walking and pneumonia risk. We also assessed the relation between physical activity and pneumonia risk, stratifying by age (<40 and >40 years).

We also assessed the relation between vigorous physical activity (running, jogging, biking, swimming, tennis, racquetball, squash, calisthenics, heavy outdoor work, and weight training) and pneumonia risk. Vigorous physical activity was categorized into 5 groups, including a category of none, followed by quartiles.[11] Last, we assessed the relation between running and jogging (none, <1 hour per week, 1.0-1.9 hours per week, >2.0 hours per week) and pneumonia risk.[12]

We used the Mantel extension test to calculate tests for trends across quintiles of intake using the respective median values.[13] SAS statistical software (version 9.1; SAS Institute; Cary, NC) was used for all analyses. Two-sided *P* values less than .05 were considered significant. This study was approved by the Human Subjects Committee of the Harvard School of Public Health.

RESULTS

During 12 years of follow up (965,168 person-years), there were 1265 new cases of nonfatal community-acquired pneumonia. At baseline in 1991, women who were more active were leaner, were less likely to be current smokers, and consumed slightly more alcohol than women who were less active (Table 1).

After adjusting for age, women in the highest quintile of physical activity were 28% less likely to develop pneumonia than women in the lowest quintile (Table 2). This association was attenuated but remained significant after adjusting for body mass index (RR = 0.83; 95% confidence interval [CI], 0.69-1.00; *P* for trend = .049); however, the association was no longer significant after further adjusting for smoking and alcohol use (RR = 0.84; 95% CI, 0.70-1.01; *P* for trend = .06).

Women in the highest quintile of metabolic equivalents per hour from walking were 18% less likely to develop community-acquired pneumonia compared with women

Table 2 Relative Risk of Community-Acquired Pneumonia by Quintile of Physical Activity

	Quintile of Physical Activity (MET-h/wk)					*P* Value
	1	2	3	4	5	for Trend
No. of cases	294	276	237	239	219	
Person-y	186,701	188,367	196,616	195,765	197,719	
Age-adjusted RR (95% CI)	1.00 Referent	0.94 (0.80-1.11)	0.77 (0.65-0.92)	0.79 (0.66-0.94)	0.72 (0.60-0.86)	<.001
Multivariate RR[a] (95% CI)	1.00 Referent	0.97 (0.84-1.17)	0.85 (0.71-1.00)	0.89 (0.75-1.06)	0.84 (0.70-1.01)	.06

CI = confidence interval; MET = metabolic equivalent; RR = relative risk.
[a]Adjusted for age, body mass index, smoking, and alcohol use.

Table 3 Relative Risk of Community-Acquired Pneumonia by Quintile of Walking

	Quintile of Physical Activity Spent Walking (MET-h/wk)					*P* Value for Trend
	1	2	3	4	5	
Median walking MET-h/wk (range)	0.1 (0-0.6)	2.0 (0.7-2.5)	3.0 (2.7-3.8)	5.6 (4.0-7.5)	11.2 (10.0-56.2)	
No. of cases	281	274	268	191	251	
Person-y	190,540	183,491	207,053	154,079	228,005	
Age-adjusted RR (95% CI)	1.00 Referent	1.00 (0.85-1.18)	0.86 (0.73-1.02)	0.85 (0.71-1.02)	0.75 (0.63-0.89)	.04
Multivariate RR[b] (95% CI)	1.00 Referent	1.00 (0.85-1.18)	0.90 (0.76-1.07)	0.90 (0.75-1.09)	0.82 (0.69-0.98)	.25

CI = confidence interval; MET = metabolic equivalent; RR = relative risk.
[b]Adjusted for age, body mass index, smoking, and alcohol use.

who walked the least; however, the trend across quintiles was not significant (*P* for trend = .25) (Table 3).

Among women aged less than 40 years, we observed an inverse relation between physical activity and pneumonia risk. After adjusting for age, women in the highest quintile of physical activity had a 32% lower risk of developing pneumonia (RR = 0.68; 95% CI, 0.52-0.90; *P* for trend = .004). This association was attenuated after multivariate adjustment (RR = 0.78; 95% CI, 0.59-1.03; *P* for trend = .06). Among women aged more than 40 years, we again observed an inverse relation between physical activity and pneumonia risk (age-adjusted RR = 0.74; 95% CI, 0.59-0.93; *P* for trend = .02), which was no longer significant after adjusting for body mass index (RR = 0.88; 95% CI, 0.70-1.11; *P* for trend = .34).

Women in the upper quartile of vigorous physical activity did not have a significantly lower risk of pneumonia than women who reported no vigorous physical activity (adjusted RR = 0.86; 95% CI, 0.71-1.04; *P* for trend = .09). Last, women who reported running or jogging more than 2.0 hours per week had a lower risk of pneumonia than women who spent no time running or jogging (adjusted RR = 0.46; 95% CI, 0.29-0.72; *P* for trend = .006). However, only 20 cases of pneumonia were reported in this group of women.

DISCUSSION

We found that physical activity was not consistently associated with community-acquired pneumonia in well-nourished, young, and middle-aged adult US women. Women who exercised more frequently, as well as those who walked more, were less likely to develop pneumonia; however, these results were not significant after adjusting for body mass index, smoking, and alcohol use. We observed that women who walked the most had an 18% lower risk of pneumonia compared with women who walked the least.

Prior studies have shown that immune function improves with exercise[14-16] and that exercise may slow an age-related decline in immune function.[4] An improvement in natural killer cell activity was observed in older women who participated in chronic resistance training compared with controls.[17] Natural killer cell activity declines with age; however, this decline might be attenuated in individuals who exercise on a regular basis.[18] Physical fitness improves the immune response to antigens in vivo. Another study demonstrated that adults who regularly performed aerobic exercise had greater amounts of anti-influenza immunoglobulin-G and immunoglobulin-M 2 weeks post-immunization when compared with less-active individuals.[4,19]

A population-based study in China found pneumonia and influenza combined to be the fourth leading cause of mortality, accounting for 3.7% of all deaths in women.[20] In the same cohort, physical inactivity was associated with an increased risk of mortality (RR = 1.20, 95% CI, 1.16-1.24) with a population attributable risk of death of 6.8%. An early prospective study among longshoremen in San Francisco found that lower physical activity was associated with an increase in all-cause mortality (RR = 1.46) and an increased, but nonsignificant, risk of death due to pneumonia specifically (RR = 3.86).[21] In a study of male smokers 50 to 69 years of age, compared with those with light leisure physical activity, moderate and heavy activity were not associated with pneumonia risk.[22] This study examined the first occurrence of hospital-treated pneumonia during a 3-year follow-up period as part of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.

Another prospective study investigating the relation between lifestyle factors and pneumonia risk found that physical activity was associated with a decreased risk of community-acquired pneumonia among women (RR comparing extreme quintiles = 0.66, 95% CI, 0.46-0.95) but not in men (RR comparing extreme quintiles = 0.96, 95% CI, 0.67-1.38).[6] Physical activity was calculated for each participant by multiplying the reported average time spent for recreational or leisure-time physical activity per week by the typical energy expenditure requirements for the activity. This study included 300 cases of pneumonia in the Nurses' Health Study II during 4 years of follow-up.[6] In the current study, we extended the follow-up and included approximately 1000 more cases, and the results were attenuated.

We observed that women who reported running or jogging more than 2 hours per week had a significantly lower risk of pneumonia compared with women who spent no time running or jogging. Although these results are interesting, there were only 20 cases of pneumonia in this active group of women.

STUDY LIMITATIONS

Limitations of the study should be noted. Physical activity was self-reported but has been demonstrated to be valid, and the information was collected prospectively. Misclassification of the diagnosis of community-acquired pneumonia is certainly possible; however, we included only participants with physician-diagnosed and radiographically confirmed pneumonia. We were unable to distinguish between bacterial and viral pneumonia, but even in the best of circumstances the microbiological cause of pneumonia is difficult to establish.[23-25] Also, because some of the nurses were working in a hospital setting, it is possible that more than 1% of the cases may have been "hospital-acquired pneumonia." We could not account for the impact of influenza or pneumococcal immunization, because we did not collect that information for a majority of the study period. Last, our results may not be generalizable to older women or men.

CONCLUSIONS

Physical activity does not substantially alter community-acquired pneumonia risk in healthy young and middle-aged women.

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Severe H1N1-Associated Acute Respiratory Distress Syndrome: A Case Series

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ABSTRACT

BACKGROUND: Acute respiratory distress syndrome resulting from novel influenza A virus (H1N1) infection remains uncommon.

METHODS: We describe the clinical profiles of adult patients with acute respiratory distress syndrome due to microbiologically confirmed H1N1 admitted to a medical intensive care unit in San Francisco, California over a 2-month period.

RESULTS: Between June 1 and July 31, 2009, 7 patients (age range: 25-66 years; 4 patients under the age of 40 years; 6 male; 1 pregnant) were diagnosed with H1N1, with 5 of 6 (83%) having initial false-negative rapid testing. All developed respiratory failure complicated by acute respiratory distress syndrome, with 4 additionally developing multiorgan dysfunction. All were managed with a lung protective ventilator strategy (average number of days on the ventilator: 16), and 4 patients also required additional rescue therapies for refractory hypoxemia, including very high positive end-expiratory pressure, inhaled epoprostenol, recruitment maneuvers, and prone positioning. Despite these measures, 3 patients (43%) ultimately died.

CONCLUSIONS: Clinicians should be vigilant for the potential of H1N1 infection to progress to severe acute respiratory distress syndrome in a variety of patient demographics, including younger patients without baseline cardiopulmonary disease. A high degree of suspicion is critical, especially with the relative insensitivity of rapid testing, and should prompt empiric antiviral therapy.

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KEYWORDS: Acute respiratory distress syndrome; ARDS; H1N1 influenza

The pandemic novel influenza A virus (H1N1) was first documented in April 2009 and has since been associated with significant morbidity and mortality. Early investigations described an epidemiology and clinical course similar to previous influenza trends,[1] including an initial skew toward younger and sicker patients,[2] but the full extent of its impact is not yet known.

There have been few published studies of severe pulmonary disease, particularly acute respiratory distress syndrome, in adults, although more data are emerging.[3-10]

This report describes the clinical profiles of adult patients with documented H1N1 and consequent development of acute respiratory distress syndrome who were admitted to our medical Intensive Care Unit (ICU) over a 2-month period.

METHODS

San Francisco General Hospital is a 300-bed county hospital with 14 medical intensive care beds, affiliated with the University of California, San Francisco. Through chart review, adult patients aged 18 years or older admitted to the medical ICU with the diagnosis of acute respiratory distress syndrome from June 1 through July 30, 2009. Polymerase

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chain reaction (PCR)-confirmed H1N1 were included in this series. Acute respiratory distress syndrome[11] and multiorgan dysfunction syndrome[12] were defined as per standard accepted definitions. This study was approved by the Institutional Review Board at the University of California, San Francisco.

RESULTS

Between June 1 and July 30, 2009, 66 inpatients were tested for influenza; 8 were positive for influenza A, and 1 was positive for influenza B. Of these, 7 adult patients with PCR-confirmed H1N1 infection developed acute respiratory distress syndrome (**Table**). The age range was 25-66 years, with 4 patients under the age of 40 years. Six were male, and the 1 female patient was pregnant. Most presented with fever, cough, dyspnea, or hemoptysis. The number of days from symptom onset to hospitalization ranged from 1-10. Five of 6 patients (83%) initially evaluated with rapid antigen testing for influenza on nasal wash samples tested negative. Three (43%) were bacteremic on presentation with *Staphylococcus* or *Streptococcus*.

CLINICAL SIGNIFICANCE

- The sensitivity of rapid antigen testing for influenza remains suboptimal, so a high degree of suspicion is critical and should prompt empiric antiviral therapy.
- H1N1 can rapidly progress to acute respiratory distress syndrome, including in younger patients and those without comorbidities.
- Severe acute respiratory distress syndrome can complicate management, carries a high mortality rate, and thus should be promptly identified and treated.

All 7 patients required intubation and mechanical ventilation and were managed with a conventional low volume, low pressure lung protective ventilation strategy,[13] with an average of 16 days on the ventilator. Four of 7 patients (57%) rapidly developed severe hypoxemia refractory to the conventional approach and were managed with rescue therapies. These included the administration of very high levels of positive end-expiratory pressure, recruitment maneuvers, inhaled epoprostenol, or prone positioning. One of these patients, without underlying lung disease, developed marked pneumomediastinum and diffuse subcutaneous emphysema (**Figure 1**) that resolved with tube thoracostomy drainage.

Four patients were evaluated for pulmonary embolism, 1 with echocardiographic findings highly suggestive of pulmonary embolism, resulting in empiric lysis, and 1 confirmed by computed tomography angiogram. Four required vasopressors for septic shock and also developed multiorgan dysfunction. All had been immediately treated upon admission to the medical ICU with oseltamivir at standard doses for at least a 5-day course.

Three of the 4 patients (ages 38, 52, and 66 years) managed with rescue therapies ultimately died. One of these was the pregnant woman, and her 32-week-old fetus ultimately survived. The other 2 were patients with chronic medical conditions. The 1 survivor was an obese 25-year-old man who spent 24 days on the mechanical ventilator. Autopsy of 1 patient revealed histopathology characteristic of the fibroproliferative, later phase of acute respiratory distress syndrome (**Figure 2**).

Of the other 3 patients not requiring additional rescue therapies, 1 was discharged home in good condition; 1 was transferred to another medical facility for further management; and 1 was transferred to the Neurology service with a poor neurologic prognosis.

Detailed profiles of 3 of our patients are provided in the Appendix (available online), highlighting the severity of H1N1 infection in the young and healthy, pregnant, and those with underlying co-morbidities.

DISCUSSION

Over a 2-month period, our medical ICU managed 7 patients with severe H1N1 infection complicated by acute respiratory distress syndrome, with 3 deaths. These cases are notable for their relatively young age and lack of significant underlying co-morbidities, as has been reported in prior reports.[3,6-9]

The majority of our patients had initial falsely negative rapid antigen tests, highlighting the limitations of this technique. At our institution, the rapid test has a sensitivity of 51%-80% and a specificity of 93%-100%,[14] which are comparable with reported test characteristics from other institutions.[15] Thus, a high index of clinical suspicion remains paramount, and the use of PCR testing may assist in confirming the diagnosis but should not delay empiric treatment.

In 4 of the 7 patients, the rapid development of severe hypoxemia refractory to a conventional lung-protective ventilation strategy led to the implementation of rescue therapies. Of these 4, 3 died. One of the deaths was a pregnant woman, supporting prior data that pregnant individuals represent a population that is more vulnerable to severe H1N1-associated complications than the general population.[8,16] The severity of hypoxemia may reflect a novel virologic effect,[17] as well as a possible lack of pre-existing immunity in this patient population. Clinicians should be prepared to manage severe hypoxemia that may be refractory to a conventional lung-protective ventilation strategy with the use of rescue therapies.

The expected high rate of incident infection for this influenza season, and its potentially critical morbidity, may portend a significant resource burden on health care institutions.[10] Clinicians should be vigilant for the potential severity of H1N1-associated complications in all affected patients admitted to the hospital setting, implement prompt isolation, and administer immediate antiviral therapy.

Table Selected Clinical Characteristics of Patients with H1N1-associated Acute Respiratory Distress Syndrome

Patient	Age (Years)	Sex	Comorbid Conditions	Symptoms	BMI (kg/m^2)	Rapid Influenza Antigen Test	Blood Cultures on Admission	MODS and Vasopressor Use	Rescue Therapies	Days of MV	Days in ICU	Outcome
1	66	M	ESRD, CHF, DM, HTN	Fever, chills, dyspnea, cough, hemoptysis, orthopnea, myalgias	21.9	Negative	Negative	Yes	NMBA day 9; prone day 9; epoprostenol day 9	15	16	Death
2	59	M	HIV (CD4 = 673), DM, HTN , epilepsy, dementia, polyneuropathy	Confusion, dyspnea, diarrhea	27.9	Initially negative, then repeat positive	MSSA	Yes	None	28	30	Discharged with poor neurologic prognosis
3	25	M	Smoker, obesity, remote methamphetamine	Fever, chills, dyspnea, cough	37.1	Negative	Negative	No	NMBA day 1; RM day 1; PEEP >20 day 1; prone day 8	24	30	Improved, discharged
4	39	4	32 weeks pregnant, smoker	Fever, dyspnea, cough, hemoptysis, myalgias	41.7	Negative	Negative	Yes	NMBA day 2; epoprostenol day 2; prone day 3; PEEP >20 day 3; RM day 4	19	19	Death, fetus survived
5	62	M	COPD, chronic pleural effusion, HCV, PSA, bipolar	Dyspnea, hemoptysis	23.9	Not done	S. pneumoniae	No	None	7	9	Improved, transferred
6	35	M	Smoker, LVH/HTN diagnosed on admission	Fever, chills, dyspnea, hemoptysis, diarrhea	30.0	Negative	Negative	No	None	10	12	Improved, discharged
7	52	M	DM, HTN	Fever, dyspnea, cough	23.6	Positive	MRSA	Yes	NMBA day 2; prone day 2; PEEP >20 day 2; epoprostenol day 2	6	6	Death

BMI = body mass index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ESRD = end-stage renal disease; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTN = hypertension; ICU = intensive care unit; LVH = left ventricular hypertrophy; MODS = multi-organ dysfunction syndrome; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; MV = mechanical ventilation; NMBA = neuromuscular blocking agent; PEEP = positive end-expiratory pressure; PSA = polysubstance abuse; RM = recruitment maneuver.

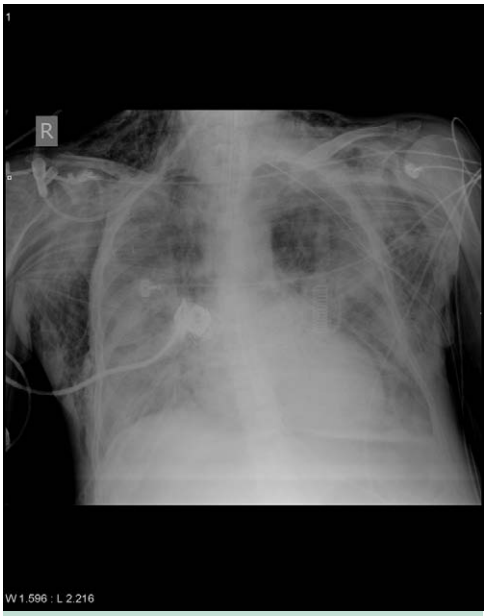

Figure 1 Chest radiograph of a mechanically ventilated patient with H1N1-associated acute respiratory distress syndrome complicated by pneumomediastinum.

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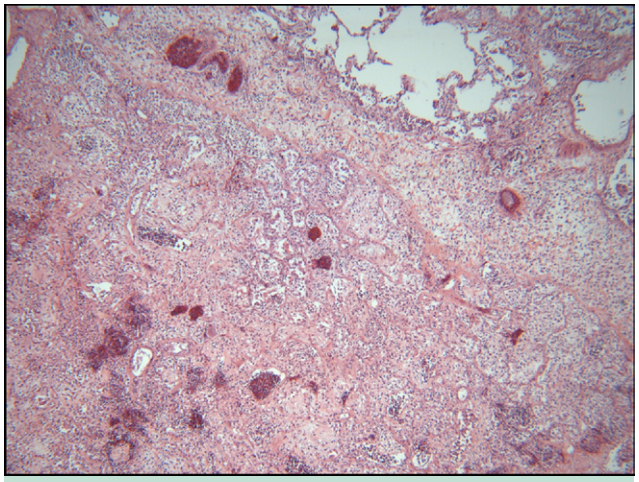

Figure 2 Histopathology of H1N1-associated acute respiratory distress syndrome (4× magnification).

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APPENDIX

Clinical Profiles

Below we describe 3 of the 7 unique cases of novel influenza A virus (H1N1) admitted to our medical intensive care unit (ICU), highlighting the severe presentation of H1N1 and acute respiratory distress syndrome in patients who were: young, pregnant, and with multiple co-morbidities.

Case 1: A 25-year-old Obese Male Smoker Who Survived

A 25-year-old Filipino man with a history of smoking, methamphetamine use, obesity, sleep apnea, and treated latent tuberculosis infection was admitted with a 3-day history of fevers, chills, dry cough, dyspnea, and weakness.

On admission, he was febrile to 40°C, tachycardic to 120 beats per minute and had an initial room air oxygen saturation of 75%, which improved with 4 L of oxygen therapy by nasal cannula. Examination was remarkable for tachypnea with accessory muscle use, poor air movement, and scattered wheezes. Rapid antigen test for influenza was negative. Initial chest radiograph revealed a left lower lobe pneumonia and a pleural effusion. In the Emergency Department he received vancomycin, ceftriaxone, and doxycycline, and was admitted to the stepdown unit.

Within 24 hours, he quickly developed severe hypoxemia, and a trial of noninvasive ventilation was attempted but failed. He was transferred to the medical ICU for invasive mechanical ventilation and was diagnosed with acute respiratory distress syndrome. He then developed shock and was treated with aggressive intravenous fluid resuscitation (12 L) and vasopressors. His antimicrobial coverage was expanded to include oseltamivir.

Within hours, his hypoxemia became refractory to 100% FiO_2, and a positive end-expiratory pressure of 18 cm H_2O, so he was paralyzed to reduce ventilator dysynchrony and underwent a recruitment maneuver. The recruitment maneuver consisted of the delivery of sustained continuous positive airway pressure of 35 cm H_2O for 40 seconds and the subsequent delivery of very high positive end-expiratory pressure set at 24 cm H_2O. After 8 days, prone positioning was initiated due to refractory hypoxemia. The patient was treated with a fluid conservative management approach after the resolution of his shock. The H1N1 diagnosis was confirmed by polymerase chain reaction. He was extubated after 24 days of mechanical ventilation and was 1 of 2 patients to be discharged home at his baseline health status.

Case 2: A 39-year-old Pregnant Woman with Presumed Pulmonary Embolus

A 39-year-old Caucasian G4P1 woman with a history of polysubstance abuse presented at 32 weeks' gestation to Obstetrics triage with a 3-day history of fevers, dyspnea, productive cough with hemoptysis, nausea, vomiting, and myalgias. She had an initial oxygen saturation of 74% on room air, respiratory rate of 40 breaths per minute, and a PaO_2 of 50 mm Hg while receiving 10 L of oxygen therapy via a nonrebreathing mask. She was immediately intubated, diagnosed with acute respiratory distress syndrome, and underwent an emergent caesarean section in the medical ICU. She was empirically treated with vancomycin, ceftriaxone, azithromycin, and oseltamivir. Immediately after the delivery, she developed severe hypoxemia, refractory to 100% FiO_2, and high levels of positive end-expiratory pressure, which prompted paralysis. Shock was treated with aggressive fluid resuscitation (14 L) and vasopressors. Initial rapid antigen testing for influenza was negative.

Over the following days, her hypoxia worsened, and she was treated with inhaled epoprostenol (day #2), prone positioning (day #3), and a recruitment maneuver (day #4). This recruitment maneuver consisted of a brief period of ventilation in a pressure-controlled mode with the inspiratory plateau pressure set at 55 cm H_2O and positive end-expiratory pressure of 36 cm H_2O. She also was treated with packed red blood cell transfusions, stress dose steroids, and a fluid conservative management strategy after shock was resolved.

On hospital day #13, she developed a new fever and worsened hypoxia. On examination, new diastolic and systolic murmurs and gallop were noted. Duplex Doppler ultrasonography of her lower extremities revealed a deep vein thrombosis in the right common femoral vein, and transthoracic echocardiogram demonstrated new right ventricular enlargement, tricuspid regurgitation, and pulmonary hypertension. Because she was too tenuous to transport to the computed tomography scanner to confirm pulmonary embolus, empiric thrombolytic therapy was initiated. Subsequently, she developed acute renal failure due to acute tubular necrosis and was treated with a continuous infusion of bumetanide. Continuous renal replacement therapy was not possible because of her inability to lie supine to obtain vascular access. On hospital day #19, she suffered an asystolic cardiac arrest. Cardiopulmonary resuscitation was not performed given her do-not-resuscitate status. The H1N1 diagnosis was confirmed by polymerase chain reaction. Notably, her 32-weeks infant survived.

Case 3: A 66-year-old Salvadoran Man with Multiple Comorbidities

A 66-year-old Salvadoran man with a history of end-stage renal disease, congestive heart failure, hypertension, diabetes mellitus, and remote tobacco and alcohol use presented with a 1-day history of left-sided pleuritic chest pain and dyspnea. He also reported a 1-month history of a productive cough and 1 week of fevers, chills, night sweats, worsening cough, and hemoptysis. Initial temperature was 38.5°C, blood pressure was 219/108 mm Hg, and room air oxygen saturation was 92%. Examination was significant for left basilar crackles and an elevated jugular venous pressure. Laboratory values were significant for a B-type natriuretic peptide >5000 pg/nL and a creatinine of 4.9 mg/dL. Chest

radiograph revealed mild pulmonary edema and bilateral lower lobe opacifications. Rapid viral antigen testing was negative. The patient was diagnosed with community-acquired pneumonia and acute heart failure. He was treated with ceftriaxone, doxycycline, diuretic therapy, and subsequent hemodialysis for worsening renal failure.

By hospital day #5, he continued to spike high fevers and developed worsened hypoxemia, thrombocytopenia, and sepsis. The patient was transferred to the medical ICU and treated with high-flow oxygen therapy (40 L, 100% FiO_2). Antibiotics were broadened to vancomycin, meropenem, fluconazole, and oseltamavir. The patient was intubated on ICU day #6 to undergo bronchoscopy and was subsequently diagnosed with acute respiratory distress syndrome and treated with a lung-protective ventilation strategy. The culture of the bronchoalveolar lavage fluid grew H1N1 after 1 week.

On day #4 of mechanical ventilation (hospital day #8), he developed dysynchrony with the ventilator and acute worsening of his hypoxia. Chest radiograph revealed pneumomediastinum, extensive subcutaneous emphysema, and a small pneumothorax, which was treated with tube thoracostomy drainage. On day #9 of mechanical ventilation, his hypoxemia became refractory to 100% FiO_2 and moderate levels of positive end-expiratory pressure, so he was paralyzed and treated with inhaled epoprostenol, with temporary PaO_2 improvement. However, by day #15 of mechanical ventilation, the patient required the prone position for refractory hypoxemia. Subsequently, he developed atrial fibrillation requiring amiodarone and then pulseless ventricular tachycardia treated successfully with defibrillation. Because continuous renal replacement therapy could not be carried out in the prone position due to malfunction of the central venous catheter, the patient was made supine. On day #16 of mechanical ventilation (hospital day #20), the patient developed shock refractory to high dose vasopressors and died.

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Measuring Resident Hours by Tracking Interactions with the Computerized Record

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The impact of resident duty hours on clinical and educational outcomes continues to concern professional and government oversight groups. Duty hours regulations have both stimulated and responded to a growing literature; but even after considerable study, the relationships remain uncertain among sleep, fatigue, effective education, hospital working conditions, hand-offs, patient safety, and resident burnout. To be persuasive, reports investigating these relationships must accurately and completely measure the independent variable: resident duty hours. The almost universal practice of deriving duty hours from retrospectively completed time-cards, whether actual or computerized, has been criticized as potentially biased and poorly reproducible.

Regulation of resident duty hours began as a legislative initiative in New York 25 years ago.[1] This local issue appeared nationally in 2002 when the Occupational Safety and Health Administration, under petition by 3 concerned groups, first considered limiting hours for the sake of both resident and patient safety.[2-4] Anticipating federal regulation, the Accreditation Council for Graduate Medical Education, a professional certification body, issued requirements the following year and subsequently to all training programs, regardless of specialty.[5-8] Most recently, the Institute of Medicine, an influential watchdog organization, has recommended that resident hours be further reduced to approach requirements in Europe. The European Working Time Directive requires that medical training be limited to 48 hours per week with 11 hours of rest in each 24-hour period.[7,8]

Lack of sleep impairs vigilance and task-oriented performance.[9-11] Less clear is the effect of fatigue on cognitive and team-based activities, such as rounding. Other workplace variables may bear as much on impairment and fatigue as do hours of sleep.[12,13]

At least a dozen investigators have systematically examined changes in patient outcomes before and after Accreditation Council for Graduate Medical Education duty hours regulation implementation.[14-18] Review of 7 such studies in 2004 found insufficient data to demonstrate effectiveness.[14] Since then, one large study in pediatric patients detected significantly less resident "burn-out," but found no effect of the new regulations on hours of sleep or total hours of work. The authors reported a small increase in medication errors after the new hours.[15] On the other hand, 3 recent studies demonstrated medical (but not surgical) mortality improvement among Medicare beneficiaries and in teaching hospitals (but not in non-teaching hospitals) comparing the years before and after reduction of resident hours.[16-18]

Such disparity among studies examining the outcomes of regulation suggests that the extent (and perhaps therefore the effect) of decreasing resident hours may be local and variable. Only a credible method for measuring hours will confirm or refute this suggestion or provide a direct link between hours and outcomes.

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Several authors have suspected, and one has measured, substantial unreliability of time-card data.[19]

MATERIALS AND METHODS

We aimed to validate self-report of duty hours (and of their distribution within the week) during a busy rotation in the medical intensive care unit using a more objective method: surveillance of all resident interactions with the electronic medical record.

The Internal Medicine Residency Training Program at New York University Langone Medical Center rotates 164 residents through thirteen 28-day blocks per year at the University Hospital and two affiliated institutions. Typically, 2 blocks are spent in the medical intensive care unit. During 5 successive blocks between December 2008 and March 2009 (as previously for several years), we distributed index cards to all residents every 2 weeks during geriatrics, general medicine, intensive care, cardiology, hematology/oncology, and intensive care rotations at the University Hospital. In accordance with previous practice, residents were asked to be both truthful and precise in recalling the numbers of hours worked each day during the previous 2 weeks. Cards were distributed and collected on the same day.

Residents were unaware that data also were collected from the electronic medical record system (Sunrise Clinical Manager, Eclypsis Corporation, Atlanta, Ga), capturing the times of all their interactions with the system. Interactions included entering orders, viewing results, writing notes, and opening notes to read them. We hypothesized that the data-rich and quickly changing clinical environment in our medical intensive care unit demanded frequent interaction with the electronic medical record; we proposed that residents could not therefore be engaged in patient care in this milieu without regular recourse to the computer.

Residents were considered working if no 6-hour period passed without their contacting the institution's electronic medical record. We recorded a resident as having left work at the time of last computer interaction before a 6-hour hiatus. An Excel (Microsoft Corp, Redmond, WA) spreadsheet with preprogrammed calculated columns permitted rapid determination of the beginning and end of resident work days by the noted criteria. In addition, the spreadsheet automatically summed the number of violations specific to each of the 4 hour-related rules set by the Residency Review Committee in Internal Medicine following Accreditation Council for Graduate Medical Education standards.[20]

The spreadsheet, written by one of our nontechnical authors (D.S.), required approximately 6 hours to construct and test, as well as 15 minutes to apply to each monthly data set. The downloaded electronic medical record data were pasted into the spreadsheet and required 10 minutes for our technical author (B.W.) to enter resident names and run each monthly data set.

PERSPECTIVES VIEWPOINTS

- Regulatory oversight of resident work schedules has obliged training programs to monitor resident hours closely. Work time is usually measured by self-report using resident time-cards, actual or computerized.
- This study compares measurement of hours using paper, resident-completed time-cards to automated reports of resident interactions with the institution's electronic medical record (EMR).
- EMR surveillance yielded information similar to time-cards with greater ease and timeliness.

At the end of the 4-month study period, we compared total resident hours and occurrence of violations between electronic medical record surveillance and resident self-report. Fractional hours on time-cards were rounded to whole numbers. Violations were expressed as a fraction in which the numerator was the measured number of violations and the denominator was the number of opportunities for violation, based on the number of days for which each resident submitted time-cards. Table 1 defines the 4 violation types and the method for applying those definitions to time-cards and to surveillance downloads from the electronic medical record.

For residents submitting time-cards, we calculated potential violations and reported data only for those days on which the cards were submitted. We tested the significance of differences in occurrence of individual violation types between the 2 methods using the Fisher exact test (for < 6 occurrences) and otherwise chi-square testing with continuity correction. For residents not submitting any cards, we calculated potential violations and reported hours data for days that were scheduled and on which electronic medical record reflected any interaction. No data were reported for days left undocumented by residents submitting incomplete time-cards.

Thirty-six residents rotated through the medical intensive care unit during the 4 study months, accounting for 744 scheduled resident days. Twenty-eight residents returned time-cards, accounting for 462 days and ranging from 11% to 100% of scheduled days. Eighteen responding residents reported all their scheduled days, and 4 residents reported less than one half of their scheduled days. Eight residents did not respond at all. Relying only on electronic medical record data, we

Table 1 Explanation and Details of Hours Violations

				Violations among Residents Submitting Cards (n = 28)				Violations Among Residents Not Submitting Cards (n = 8)		
Brief Regulation Name	Summary of Regulation	How Regulation Was Applied to EMR	How Regulation Was Applied to Time-Cards	a Potential Violations	b Observed Violations by Time-Card (%)	c Observed Violations by EMR (% of Potential)	b/a vs c/a *P* Value by Chi-square with Continuity Correction (Fisher Exact Test*)	d Potential Violations on Dates with Computer Contact	e Observed Violations by EMR (% of Potential)	e/d vs c/a *P* Value by Chi-square with Continuity Correction (Fisher Exact Test*)
80-h	Residents must not spend > 80 h per week in a training site. Weekly hours may be averaged over the individual rotation.	Starting with the first scheduled day in MICU on which there was computer activity, working periods were continuously summed until exactly 1 week later, when the process began again. Any week with summed working periods > 80 h was considered in violation.	Hours were tallied for each week, starting with days 1 and 8 on the card. Any week > 80 h was considered in violation.	71	5 (7%)	1 (1.4%)	*P* = .21*	14	0 (0%)	*P* = .4*
27-h	Residents must not spend > 24 h on call. A 3-h period is allowed for signout of patients.	Any continuous period > 27 hours was considered in violation.	Any continuous period > 27 h was considered in violation.	154	9 (5.8%)	9 (5.8%)	*P* = 1.0	32	2 (6.3%)	*P* = .6*
24-h	Residents must have 24 h away from all training sites in each week.	Any week (as defined for 80-h violations above) in which there was not a single ≥ 24-h period with no computer activity was considered in violation.	Any week (days 1-7 or 8-14) on the time-card in which there was not a stated or easily calculable 24-h period off was considered in violation.	71	0 (0%)	2 (2.8%)	*P* = .5*	14	0 (0%)	*P* = .7*
10-h	Residents must have 10 h away from all training sites after each shift.	Time of first EMR interaction after a 6-h hiatus is considered a violation if it is > 10 h from the time of the last interaction.	Time intervals > 10 h between reported end of a shift and reported start of another is considered a violation.	462	1 (0.2%)	3 (0.6%)	*P* = .4*	97	10 (3.1%)	*P* = .06*

EMR = electronic medical record; MICU = medical intensive care unit.

Definitions of hours regulations, electronic medical record, and time-card criteria for violation used in the study, and distribution of violations and percentage occurrence using electronic medical record surveillance and time-card review.

tested for significance differences in occurrence of each violation type between those residents who did and did not hand in any cards.

RESULTS

Responding residents reported a total 4383 hours; the electronic medical record surveillance report returned 4062 for these same days, a 7.3% discrepancy. Considering only scheduled days for which time-cards had been submitted, there were 71 opportunities to violate the 80-hour work week rule and the same number of opportunities to violate the standard of 1 day off weekly. There were 154 opportunities to violate the 27-hour rule and 462 opportunities to violate the requirement for 10 hours off between shifts (Table 1). The 758 possible total violations (1.9% of which actually occurred according to time-cards) yielded 80% power to detect a significant ($P < .05$) difference from the time-cards method it frequency of violation by electronic surveillance was less than 0.5% or more than 4.5%.

On review of time-cards, there were five 80-hour violations (7%), nine 27-hour violations (5.8%), no 24-hour violations (0%), and one 10-hour violation (0.2%). There were therefore a total of 15 time-card violations (1.9%). By electronic medical record surveillance there was one 80-hour violation (1.4%), nine 27-hour violations (5.8%), two 24-hour violations (2.8%), and three 10-hour violations (0.6%). Total violations by electronic medical record were 15 (1.9%). Occurrence of individual violations did not differ significantly between methods.

Among the 8 residents who did not return time-cards, there were no 80-hour violations (0%), two 27-hour violations (6.3%), no 24-hour violations (0%), and three 10-hour violations (3.1%). Total violations were therefore 5 (5.2%). There was no significant difference in occurrence of any violation type between residents who did and did not return any cards, although occurrence of 10-hour violations was 3% among individuals who did not return cards and 0.6% among residents who did return cards ($P = .06$).

Electronic medical record surveillance and time-card completion were approximately equivalent methods for measuring resident duty hours and occurrence of hours violations. Average total hours were 7.3% higher by time-cards, and total violations were identical. Electronic medical record surveillance had the advantages of ready availability and more complete data. The 8 noncompliant residents cannot be assumed to resemble the compliant 28 residents. It is easy to imagine, for example, that compliance in returning cards might have been lower in residents with more frequent hours violations. In fact, we found a trend toward more 10-hour violations among noncompliant residents.

A 7.3% disparity was not unexpected. The Accreditation Council for Graduate Medical Education regulations require not only that residents go off duty at the correct time but also that they physically leave the training site. We reasoned that a resident using the computer is always at work (high positive predictive value), but that a resident not using the computer may be still in the hospital (lower negative predictive value). The electronic medical record surveillance method is thus likely only to underestimate duty hours. Detected violations by electronic medical record provide strong evidence that a problem exists; apparent compliance measured by electronic surveillance, on the other hand, cannot entirely verify compliance.

LIMITATIONS

Limitations of this study include its performance at a single institution with an advanced electronic medical record and among only those residents who were assigned to the medical intensive care unit of the University Hospital. It is likely that residents rotating in areas where the patients are less ill will interact less frequently with the electronic medical record; underestimates of hours might therefore be greater than in a medical intensive care unit. The extent of additional underestimation will determine how much less useful this method is on a ward rotation than it seemed to be in an intensive care setting.

Electronic medical record surveillance is easily employed in hospitals with developed systems. This method is inexpensive, provides information about residents who do not return cards, produces real-time results, and requires little special expertise. However, it is but one of several possible solutions to the alleged uncertainties of time-cards. Electronic monitoring of transmitter-fitted resident badges might yield times of coming and going, and the addition of global positioning technology might even monitor location within the hospital. Expense may be a limiting factor. Malfunction and failure to wear the badge recreates the time-cards problem of interpreting missing data. Signing in and out is a far cheaper alternative, but subject to noncompliance.

CONCLUSIONS

Our finding that residents—compared with an independent and objective data source—accurately recorded their own hours and violations must be confirmed in other institutions and especially in less intensive clinical settings. This study suggests a possible alternative to time-cards but also provides validation for their use and therefore supports a method frequently used in published studies to measure the impact of resident duty hours on patient and resident outcomes.

ACKNOWLEDGMENTS

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Polymyalgia Rheumatica with Bilateral Subclavian Artery Stenosis

To the Editor:

The overlap between polymyalgia rheumatica and giant cell arteritis has prompted physicians' attention since the early 1970s.[1,2] Polymyalgia rheumatica occurs in approximately 50% of patients with giant cell arteritis, and approximately 15% of patients with polymyalgia rheumatica develop giant cell arteritis.[3] Some experts consider polymyalgia rheumatica and giant cell arteritis to be different manifestations of the same pathologic process.[4] Although the association of occlusive vascular disease is well known in giant cell arteritis, it is not considered to be a typical manifestation of polymyalgia rheumatica.

A 66-year-old woman presented to our rheumatology practice in May 2007 with proximal muscle pain and stiffness of 1 year's duration. The patient also reported acute onset of tingling with bluish discoloration in the nailbeds and fingertips of her left hand, exacerbated with overhead activity. She denied any headaches, vision changes, scalp tenderness, or jaw claudication. Physical examination revealed warm hands and good capillary refill in all digits despite a diminished right radial artery pulse and nonpalpable left radial artery pulse. She had good pulsation without tenderness over the temporal arteries. Laboratory test results showed a normal complete blood count, elevated erythrocyte sedimentation rate of 47 mm/H, C-reactive protein of 32.4, negative rheumatoid factor and antinuclear antibody, and normal creatine phosphokinase.

Polymyalgia rheumatica was diagnosed, and the patient was started on prednisone 10 mg twice per day for 1 week, followed by 10 mg daily. There was significant improvement in her proximal arthralgias and myalgias, but left arm claudication persisted. Doppler ultrasound of the upper extremities revealed bilateral moderate (50%-74%) stenosis of the subclavian, axillary, and brachial arteries. Magnetic resonance angiography of the aortic arch with gadolinium disclosed bilateral severe subclavian artery stenosis, distal to the origin of the vertebral arteries, with the axillary and brachial arteries not well demonstrated because of the severe proximal stenosis of the subclavian arteries (Figure).

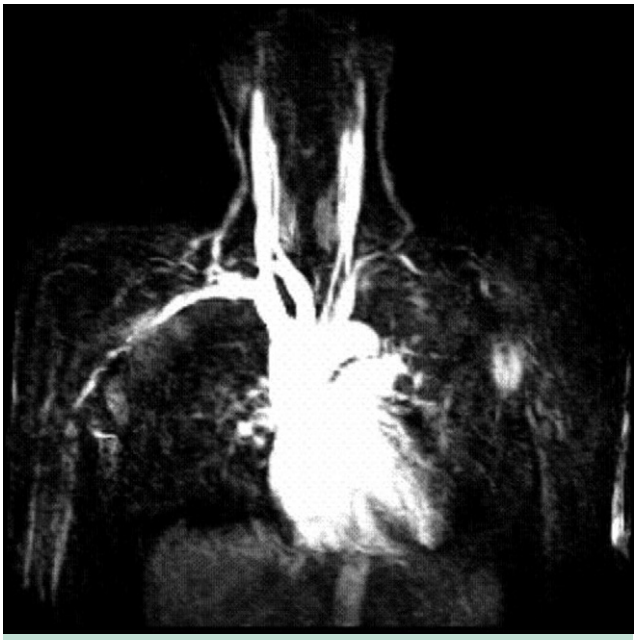

Figure Bilateral severe subclavian artery stenoses. These are approximately 2.5 cm beyond the origin of the subclavian artery from the brachiocephalic artery on the right and 4.5 cm from the origin of the subclavian artery of the aortic arch on the left.

Although the patient had no cranial symptoms, giant cell arteritis was suspected to be the cause of occlusive vasculopathy. Treatment with prednisone 60 mg daily showed dramatic improvement in left arm symptoms. In August 2007, the patient underwent angiography followed by angioplasty and stenting of the left subclavian artery. Postoperatively, the patient was administered aspirin because of clopidogrel bisulfate (Plavix; Bristol-Myers Squibb, New York, NY) and aspirin with extended-release dipyridamole (Aggrenox; Boehringer-Ingelheim, Ingelheim, Germany) intolerance. The upper-extremity arterial Duplex ultrasound revealed a patent left subclavian stent. The patient was doing well, maintained with an average dose of 5 mg of prednisone per day. In February 2008, she presented with

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return of left arm claudication, discoloration, and absent left radial artery pulse. Noninvasive vascular testing demonstrated severe narrowing of the subclavian artery distal to the left subclavian stent. We concluded that the patient had vasculitis, most likely secondary to giant cell arteritis, evidenced by recurrent occlusive disease in the upper extremities. The decision was made to control the disease with steroid treatment and no further surgical interventions unless absolutely necessary.

This case underlines the fact that physicians should be vigilant when assessing patients with polymyalgia rheumatica. Polymyalgia rheumatica and giant cell arteritis share pathogenic principles and are not mutually exclusive but overlapping.[2] The challenge is to recognize atypical cases presenting with occlusive vasculopathy but lacking cranial symptoms suggestive of giant cell arteritis. Patients with occlusive arterial disease caused by giant cell arteritis typically respond well to a high dose of steroids. Surgery should be restricted to cases with severe persistent ischemia after the inflammatory syndrome has receded.[5]

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Bromide Toxicity from Consumption of Dead Sea Salt

To the Editor:

Bromide salt is an effective antiepileptic and sedative in small doses and was once a common ingredient of many medicines and patent tonics such as Dr. Miles' Nervine and Bromo-Seltzer.[1] Unfortunately, the long 10-12 day half-life of bromide results in an intolerably narrow therapeutic window. Bromide toxicity or "bromism" accounted for over 2% of admissions to psychiatric hospitals before the removal of bromide salts from most US medications in 1975.[1] With the advent of Internet commerce, patients now have greater access to relatively unregulated medications and products.[2] We report a case of bromide toxicity after the consumption of Dead Sea salt obtained over the Internet.

A 57-year-old man with Asperger syndrome presented complaining of diffuse pain and generalized malaise. Mentally, he was impaired, with disjointed thoughts, labile mood, and disorganized, slurred speech. He denied taking any over-the-counter or herbal medications, and his history was otherwise uninformative. A screening basic metabolic panel returned with a chloride level of ">175 mEq/L" (normal 95-110), yielding an anion gap of −55 mEq/L. To rule out laboratory error, a repeat basic metabolic panel was performed and confirmed the initial value. Such marked hyperchloremia prompted a measurement of the patient's serum bromide, which was found to be 2540 mg/L (32 mEq/L).

Upon further questioning, the patient reported consuming 3-4 tablespoons of Dead Sea salt daily for several months. He stated that he purchased the Dead Sea salt due to websites' claims of its holistic, calming effects and health benefits. The Dead Sea has the highest bromide concentration of any large body of water in the world, with a bromide concentration of approximately 5 g/L.[3] Bromide intoxication is reported at serum levels as low as 400 mg/L (5 mEq/L), with 1500 mg/L (19 mEq/L) considered toxic.[1] Our patient's bromide level was impressive by these criteria.

The most common manifestations of bromism are psychiatric and dermatologic. Patients present with weakness, slurred speech, emotional instability, agitation, hallucinations, seizures, and coma.[4] Bromoderma occurs in approximately 35% of cases and is characterized by acneiform eruptions or, less commonly, granulomatous plaques, ulcers, or bullae, usually on the face and trunk.[4]

The finding of hyperchloremia was instrumental in establishing the diagnosis. On many laboratory assays, bromide causes a false hyperchloremia sufficient to yield a negative anion gap. Assays register an additional 3-4 mEq of Cl^- per mEq of Br^- due to the greater affinity of bromide for the silver or mercury species used in measuring chloride levels.[1,4] Other etiologies of a negative anion gap include hyperlipidemia and, rarely, iodide intoxication or paraproteinemia in multiple myeloma.[1,5] Bromism should be con-

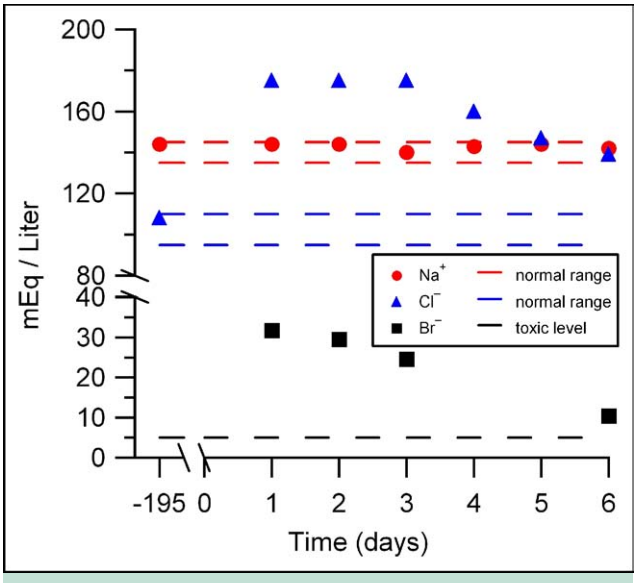

Figure Electrolyte concentrations over time. Patient's admission electrolytes on day 1 were: Na^+ 144, K^+ 3.6, Cl^- 175, HCO_3^- 25, Ca^{2+} 8.3 (reported in mEq/L). The patient was seen several months earlier in outpatient appointment and as reflected in day −195, had normal chloride levels. Saline diuresis was initiated on day 2. Bromide and chloride levels over the next 5 days show a decrease in both values over time. Normal range of chloride and sodium levels are denoted by dashed blue (95-110 mEq) and red (135-145 mEq) lines, respectively. Toxic bromide levels are denoted by dashed black line (5 mEq).

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sidered whenever new-onset psychiatric symptoms accompany an elevated chloride level, especially in the setting of a negative anion gap.[1] A case of bromism can be missed if hyperchloremia is dismissed as laboratory error.

Awareness of this diagnosis is important because the symptoms of bromism are usually completely reversible with cessation of bromide ingestion. Bromide is renally excreted, and its 10-12 day half-life can be shortened to <1 day with saline loading and diuresis.[4] Dialysis should be considered in patients with severe symptoms or renal impairment.[4] Our patient was successfully treated with saline and furosemide over 5 days and discharged with improved mental status and the recommendation to avoid consuming Dead Sea salt. (Figure).

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Emergence of Fluoroquinolone Resistance in Outpatient Urinary *Escherichia Coli* Isolates

To the Editor:

Johnson et al[1] recently reported in a large area a rapid and impressive increase in fluoroquinolone resistance in *Escherichia coli* urine isolates after switching from trimethoprim-sulfamethoxazole to levofloxacin for the initial therapy of urinary tract infection (UTI).

Curiously, they recommend treating all complicated UTIs either with fluoroquinolone (levofloxacin or ciprofloxacin) or with third-generation cephalosporin (ceftriaxone) or aminoglycoside (gentamicin or tobramycin) in case of risk of fluoroquinolone resistance. Complicated UTIs are very diverse, from easy-to-treat infections (eg, cystitis in diabetic patients) to life-threatening conditions (eg, severe sepsis). We consider it inappropriate to mix all these diseases in the same recommendation. Even complicated cystitis is a benign infection, for which current French guidelines[2] recommend the use of fluoroquinolones, cephalosporins, and aminoglycosides; the drugs of choice for pyelonephritis, prostatitis, and urosepsis.

To recommend a parenteral treatment (ceftriaxone, gentamicin, or tobramycin) for nonserious complicated UTIs appears unjustified, because such route of administration is painful and expensive. In addition, aminoglycosides require a renal function evaluation, which here seems unrealistic.

As well, the use of fluoroquinolone or cephalosporin is ecologically incorrect. Besides the increase of fluoroquinolone resistance community-acquired extended-spectrum beta-lactamase-producing *E. coli* have emerged worldwide during the past 5 years.[3]

The only way to disrupt the "vicious circle" of multidrug resistance is to limit the use of antibiotics. The French guidelines now recommend delaying antibiotics for complicated cystitis (excepted for rare situations) until the results of an antibiogram in order to prescribe the narrowest-spectrum drug.[2] When an empirical treatment is required, nitrofurantoin is a first choice.[2] Johnson et al[1] recommend avoiding it because of the broad spectrum of uropathogens causing complicated cystitis. Nitrofurantoin is approved for the treatment of UTI due to susceptible strains of *E. coli*, *Enterococci*, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.[4] Such species are common among inpatients and outpatients,[5] and multidrug-resistant *E. coli* strains remain susceptible to nitrofurantoin.[6]

Thus, we would recommend considering initial abstention or nitrofurantoin instead of fluoroquinolone, third-generation cephalosporin, or aminoglycoside for the management of nonserious complicated UTIs.

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Program Director Satisfaction Revisited: An Alternate View

To the Editor:

Your February 2009 issue included a landmark contribution from Hinchey and colleagues[1] regarding the second administration of the internal medicine program director satisfaction survey. It is important to recognize that among the variables measured, the program director salary, balance of time on service, and number of support staff were important factors in the satisfaction of the cohort. I must confess that I too scanned Table 3 to view the spectrum of salary responses—that is only human nature. But I realized that maybe we missed the point here and that an alternate perspective needed to be shared.

As residency program directors, we are rewarded by more than the length of our residency review committee cycle, our own individual faculty rank, the number of associate program directors who help us meet administrative duties, or the proportion of time we have to perform our educational roles; our satisfaction is much more complex, much more rich, and much less ephemeral.

Rather, program director satisfaction is measured in events, such as

- watching a resident become a master clinician;
- receiving a note from an appreciative patient describing the resident's role in his/her recovery from a life-threatening illness;
- learning that a resident has had his/her first manuscript accepted for publication;
- hearing that a resident will become a new mother or father;
- learning about a resident's first job;
- receiving good news in the fellowship match;
- witnessing high-quality care; and
- allowing a resident to learn from a mistake.

The value of the article by Hinchey et al[1] is that the data allow us to identify key constructs of the program director position that will allow program directors to remain comfortable in their positions. This is critical to developing and sustaining these important educational leaders. The structure of the program, including support staff and associates, is indeed an important factor to allow a program director to succeed and find satisfaction. However, the true satisfaction for the program director lies in the residents' successes.

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Reference

1. Hinchey K, MacDonald F, Beasley B. Sources of satisfaction for Residency Program Directors. *Am J Med.* 2009;122:196-201.

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The Reply:

Kane thoughtfully and correctly recognizes factors that contribute to program director satisfaction. The important landmark events in the lives and training of the young physicians in our programs triggered happy memories and general assent from all of us. In fact, the data we presented are concordant with Kane's statements. To understand the components of the Program Director Satisfaction Survey (PD-Sat) instrument, the reader is referred to Table 2 of our article,[1] where it is clear that the facets of "work with residents" and "work with colleagues" make up the near majority of total satisfaction compared with the other 5 facets combined. Furthermore, the essence of what Kane has identified, "work with residents," was the only facet to demonstrate statistical stability in both the 1996 and 2005 administrations of the instrument, indicating that this is a particularly enduring component of program director satisfaction. Kane focused on the associations in Tables 3 and 4 of our article, which were found by assessing the link between scores on the PD-Sat instrument and the variables that were otherwise measured in the 2005 Association of Program Directors in Internal Medicine Program Director's Survey. We note in the results that the regression model identifying the 4 potentially modifiable, statistically independent, and significant factors associated with program director satisfaction accounted for only 14% of the total variance in PD-Sat scores. Clearly, there are other variables that account for program director satisfaction, and it is likely that many of them relate to the primary facet of "work with residents," as Kane has suggested. We look forward to further studies of program director satisfaction that may test this and other hypotheses to further delineate the components of program director satisfaction so that we may all better mentor the next generation of program directors to provide the stability in leadership our residents deserve for the growth of their careers.

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1. Hinchey K, McDonald FS, Beasley BW. Sources of satisfaction for residency program directors: a second administration of the Program Director Satisfaction Survey. *Am J Med.* 2009;122:196-201.

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Influence of Hispanic Ethnicity and Diabetic End-stage Renal Disease

To The Editor:

I read with interest the large national Veterans Administration cohort study by Choi et al[1] on the white/black racial differences in risk of end-stage renal disease and death. In the results section, it is noted that 325,568 or 13.9% of patients with nonwhite/black or unknown race were excluded. This study of patients receiving care in the Veterans Health Administration is then based on analysis of 2,015,891 (84.5%) patients (1,704,101 white and 311,790 black patients), and it would be important to find out if they have data analysis of the Veterans Administration groups studied according to ethnicity (Hispanic, non-Hispanic, or unknown).

On page 673, the highlighted clinical significance of this study notes: "Public health efforts to reduce racial disparities may benefit from screening and prevention efforts focused on chronic kidney disease in blacks."[1] However, it should be noted that other minorities, including Hispanics and Native Americans, have high prevalence of end-stage renal disease, which is gradually being recognized and also should be a focus of public health effort and additional studies. In fact, in 2003, we reported previous 1998 data on 19,336 patients in 80 counties in Texas, wherein it is noted that for diabetic nephropathy end-stage renal disease in Texas, Hispanics showed the highest prevalence, followed by blacks and then by non-Hispanic non-blacks.[2] The latest US Renal Data System Annual Data Report, which can be accessed on the Internet,[3] shows, in Figure 2.15, the prevalent rate of end-stage renal disease in 2006. Please note that for Hispanic patients, the figure-reported rate was 2326 per million population, which is 1.5 times greater than the rate of 1576 per million seen in the non-Hispanic population! Hispanics are becoming the new minority and deserve public health efforts similar or equal to blacks.

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The Reply:

We thank Pazmiño for his interest in our article[1] and for his important comments on the burden of kidney disease among Hispanics in this country. In our study, we focused on the disparities in risk of mortality and end-stage renal disease between white and black patients. Non-black race/ethnic minorities represent approximately 6% of the patients receiving care in the Veterans Health Administration, therefore, we were underpowered to examine end-stage renal disease and mortality in these groups.[2] However, we are in complete agreement with Pazmiño that disparities in kidney disease are not limited to blacks and that public health efforts to reduce the burden of kidney disease will need to account for Hispanics—who are a rapidly increasing segment of the population—along with other underrepresented groups. We plan further study of kidney disease in these race/ethnic minority groups in the future.

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Authorship: AIC and AMO had access to the data; all authors had a role in writing the manuscript.

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Nocturia: An Uncommon Presentation of Lower-Limb Lymphedema

To the Editor:

We report a case of nocturia as an uncommon presentation of lower-limb lymphedema in a 56-year-old man. To our knowledge, this is the first case reported in the literature.

CASE REPORT

A 56-year-old man was admitted to the Department of Internal Medicine, University of Genova, on May 2008 for progressively worsening edema of the lower limbs. He had a history of nocturia (6-7 voids per night) since February 2007. Laboratory examination showed normal serum creatinine (0.7 mg/dL), urea nitrogen (13 mg/dL), and glucose (68 mg/dL). Urinalysis revealed normal urine pH (5.5), specific gravity (1.020), and osmolarity (750 mOsm/kg), and absence of proteinuria. Microalbuminuria, serum total protein, and albumin levels were in the normal range (20 mg/24 h, 7.2 g/dL, and 4.2 g/dL, respectively). Serum levels of protein C, protein S, and antithrombin III were in the normal range. Methylenetetrahydrofolate reductase C677T gene mutation, factor V Leiden, and prothrombin G20210A gene mutations were absent. Thoracic and abdominal computed tomography scans excluded thoracic duct obstruction and thrombosis of the superior and inferior venae cavae and the renal and iliac veins, and showed normal kidneys without perfusion defects. Lower-limb venous Doppler ultrasonography excluded venous insufficiency and thrombosis. Echocardiography showed only septal myocardial hypertrophy. Lower-limb ^{99m}Tc lymphoscintigraphy suggested dilated superficial lymphatic collectors and deep lymphatic trunks, delayed and asymmetric visualization of regional lymph nodes, and the presence of "dermal back-flow." Clinical and imaging data were suggestive for the diagnosis of lower-limb lymphedema. Treatment with low-dose aspirin (100 mg/d), low-molecular-weight heparin (4.000 IU/d), and chlortalidone (25 mg/d) was started. Edematous enlargement was treated with massage and a compression stocking. This approach was helpful and allowed the complete remission of nocturia and lymphedema within 10 days. The use of an elastic stocking transmitted high-grade compression (60 mm Hg) and prevented fluid accumulation. At present, the patient feels good, always uses an elastic stocking, and is receiving treatment with low-dose aspirin (100 mg/d).

DISCUSSION

Nocturia, defined as "waking at night to void," is now being examined as a clinical entity in its own right, as opposed to being viewed as a symptom of another condition.[1,2] Nocturia can be associated with the administration of drugs (ie, diuretics, β-blockers, xanthines), diabetes mellitus, diabetes insipidus, congestive heart failure, low blood albumin, venous stasis, high salt intake, renal insufficiency, and sleep apnea syndrome.[3,4] Our patient developed nocturia as the first manifestation of an idiopathic form of lymphedema caused by lymphatic vessel insufficiency. A broad spectrum of inherited and acquired diseases are characterized by an impaired ability of the lymphatic vasculature to collect and transport fluid.[5] Primary lymphedema comprises a heterogeneous group of recessive and dominant transmitted disorders.[5] Secondary lymphedema is favored by surgical and radiotherapeutic interventions for cancer,[6] pregnancy, contact dermatitis, and rheumatoid arthritis.[5]Although the diagnosis of lymphedema relies on physical examination (edema, *peau d'orange*, cutaneous fibrosis, and positive "Stemmer sign"), ^{99m}Tc lymphoscintigraphy plays a key role in confirming the suspicion. Our patient responded to treatment with lymphatic-specific massage, exercise, applied compression, and diuretics, in agreement with current literature.[5] To our present knowledge, this is the first reported case of nocturia as the first presentation of lower-limb lymphedema.

CONCLUSIONS

The present case suggests that nocturia may be the first symptom of lower-limb lymphedema and that lymphatic-specific massage, compression stocking, and diuretics might be an adequate therapeutic approach.

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Authorship: All authors meet the criteria for authorship, including acceptance of responsibility for the scientific content of the article. All authors had access to the data and a role in writing the article.

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Eroded Pacemaker in an Elderly Patient

To the Editor:

An 84-year-old man with severe ischemic cardiomyopathy and history of congestive heart failure was transferred to our hospital for biventricular implantable cardioverter defibrillator pocket erosion. He had originally undergone dual-chamber pacemaker implantation for intermittent complete atrioventricular block in 2000. He then developed worsening heart failure symptoms in the setting of declining left ventricular (LV) systolic function, and the device was upgraded to a biventricular system in 2006. There was initial improvement that disappeared due to LV lead dislodgement. Attempted LV lead revision in July 2007 was not successful. Two weeks later he underwent epicardial LV lead placement via mini-thoracotomy. Postoperatively he had ongoing discomfort at the wound, and in December 2007 he developed worsening redness and discomfort over the device.

Unfortunately, he did not seek medical attention until he noticed the pacemaker was eroding through his skin (Figures 1, 2). On presentation he was afebrile without other complaints.

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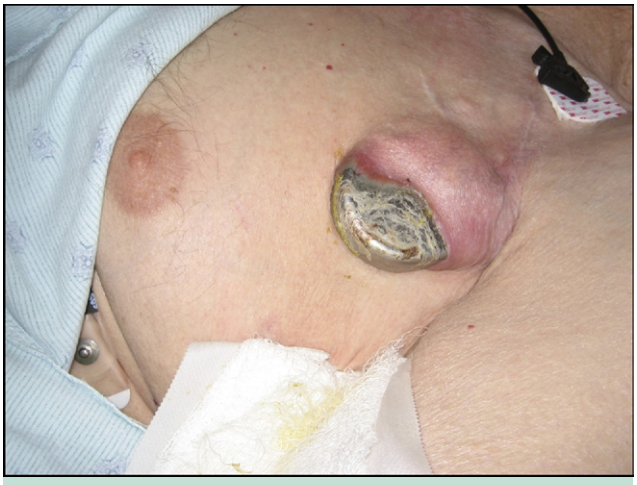

Figure 1 Left lateral view of the site upon presentation. Photo taken prior to extraction and debridement of the eroded pacemaker.

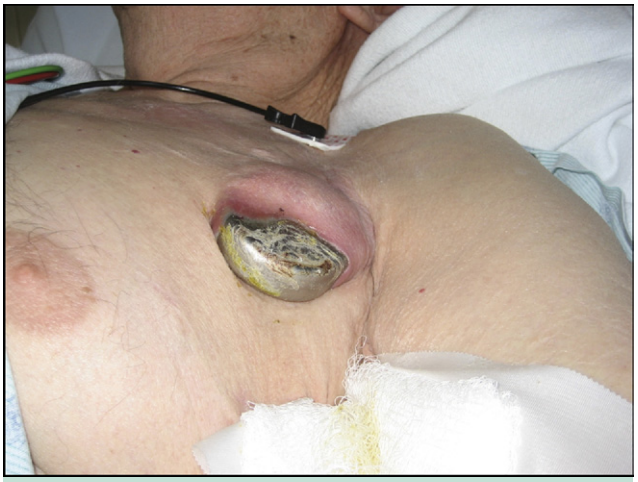

Figure 2 Anterior view of the eroded device.

Wound and blood cultures did not grow an organism, but intravenous vancomycin was initiated at the outside hospital for presumed infection. The patient was transferred to our hospital on his 12th day of antibiotics. He underwent successful total system extraction. Exposure of the pocket revealed purulent drainage beneath the device. The leads were entirely removed using laser lead extraction sheathes.

The pocket was debrided down to normal tissue, and the wound was packed and left open. By holding beta-blockers, temporary pacing was avoided. Wound healing progressed nicely, and a wound vacuum was placed. After 7 days of continued antibiotics and negative cultures, a new biventricular implantable cardioverter defibrillator was implanted successfully on the right side. The patient was discharged home the next day with home intravenous infusion of antibiotics for 3 more weeks. The wound vacuum was removed after 3 weeks.

Risk factors for implanted cardiac device infection include multiple device revisions, early re-interventions, temporary pacing wires at time of implantation, and lack of antibiotic prophylaxis at the time of the procedure. Removal of the device, along with all leads and infected tissue, is necessary for clearance of the infection. Separating the explant procedure from the reimplant procedure is ideal, and when the patient is pacemaker dependent, pacing becomes necessary. Redness and swelling over the device site inar-

guably indicates infection and frequently leads to erosion if not managed appropriately. Erosion of the device can result in loss of pacing or ineffective defibrillation.

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Relief of Chronic Neuropathic Pain through Endothelin Antagonism

To the Editor:

The endothelin system and the potent vasoconstrictor endothelin-1 are fundamentally involved in the development and progression of pulmonary arterial hypertension. The effects of endothelin-1 are predominantly mediated through actions at 2 receptors, endothelin-A and endothelin-B. Nonselective endothelin receptor antagonism and selective endothelin-A antagonism have both proved to be successful treatment strategies for pulmonary arterial hypertension.[1,2]

In addition to actions as a vasoconstrictor, endothelin has effects on cell proliferation, fibrosis, and inflammation. Endothelin-1 also is secreted from cancer cells and may be involved in tumor progression, while animal models have demonstrated a potential role for endothelin-1 in cancer and neuropathic pain.[3]

We recently treated a 47-year-old man with the selective endothelin-A antagonist, sitaxsentan, for pulmonary arterial hypertension. He had been referred with a history of gradually increasing dyspnea. Past medical history was notable for ventricular septal defect closure in childhood and sciatica of 2 years' duration. His sciatica had been managed with a number of medications, including paracetamol, nonsteroidal anti-inflammatory agents, and narcotic analgesia, all with limited success. Physical examination revealed a loud, palpable pulmonary second heart sound and evidence of tricuspid regurgitation on auscultation. A diagnosis of pulmonary arterial hypertension was confirmed at right heart catheterization. He was given sitaxsentan 100 mg daily, with improvements in dyspnea and exercise tolerance reported at review 4 weeks later. He also volunteered that he had experienced a substantial improvement in his sciatica, allowing discontinuation of analgesia. On questioning, pain scores were reduced from 8/10 to 2/10. Unfortunately, 4 months later, despite improvement in his pulmonary arterial, his sitaxsentan was discontinued due to hepatic dysfunction. He reported a prompt return of his sciatica following cessation of endothelin-A antagonist therapy.

Endothelin-1 has been shown to induce pain and hyperalgesia in experimental pain models. Although stimulation of either endothelin-A or endothelin-B has effects on sensation, the predominant effect seems to be mediated via endothelin-A. Endothelin-A receptor antagonists have had reported benefits on pain perception in metastatic prostate cancer, but we believe this to be the first description of clinical benefit of endothelin antagonism in chronic neuropathic pain.[4] The improvement in our patient's sciatica, while entirely unexpected, is consistent with an emerging understanding of the role of endothelin in pain. We believe further mechanistic and clinical studies examining the role of endothelin and endothelin-A antagonism in pain syndromes are now required. The endothelin axis might ultimately prove a useful therapeutic target in the treatment of chronic pain syndromes.

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Authorship: All authors had full access to the data necessary for the preparation of this article and were involved in manuscript preparation.

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Transient Collateral Circulation during Coronary Vasospasm

To the Editor:

A 62-year-old man who was a heavy smoker presented to the hospital with chest pain that occurred while he was sleeping. Coronary angiography was performed, which showed collateral vessels from the left anterior descending artery to the right coronary artery but no significant organic stenosis in the left coronary artery. Right coronary angiography was immediately performed, showing severe stenosis of the proximal right coronary artery (Figure 1), although no electrocardiographic changes were observed. Vasospasm of the right coronary artery was treated immediately by intracoronary administration of isosorbide dinitrate. A left coronary angiography performed immediately after the isosorbide dinitrate administration showed disappearance of the collateral vessels from the left anterior descending artery to the right coronary artery seen in the earlier test (Figure 2).

DISCUSSION

A transient appearance of the collateral vessels was observed, which could serve to salvage otherwise jeopardized ischemic areas during coronary vasospasm. In this patient with coronary spastic angina, coronary vasospasm of a major coronary artery might have been associated with transient collateral augmentation supplied by the nonspastic artery during the anginal period.

The development of coronary collateral vessels has been described in a patient with coronary spastic angina associated with ST-segment depression. The collateral vessels disappeared after the vasospasm was relieved by intracoronary administration of isosorbide dinitrate, suggesting that the collateral vessels were formed during coronary vasospasm and localized to the perfused ischemic area, preventing transmural myocardial ischemia.[1-3] These findings indicate that ST-segment depression during coronary vasospasm could be attributed to subendocardial ischemia caused by incomplete occlusion of a large coronary artery and transient reduction or augmentation of collateral blood flow.[4]

It has been speculated that recruitable collateral vessels can remain patent long after spontaneous attacks of angina have resolved and become visible in the event of a pressure difference between 2 small coronary arteries. This suggests

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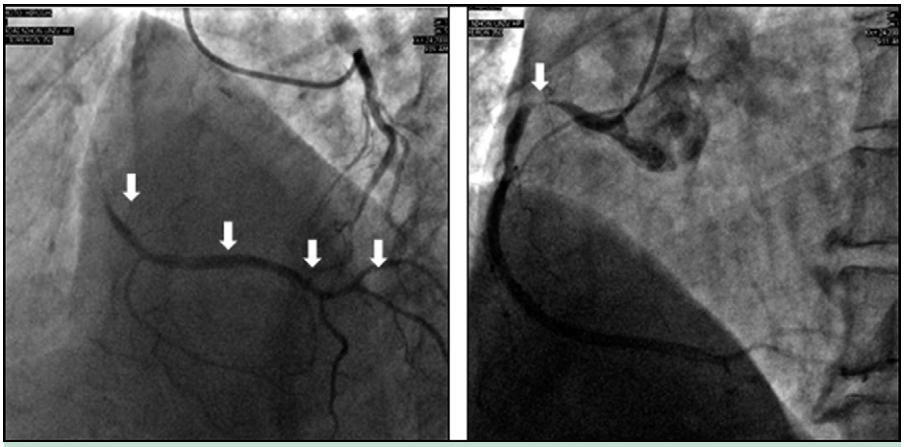

Figure 1 Initial left coronary angiogram (left: left anterior oblique view) shows the collateral vessels from the left anterior descending artery to the right coronary artery (arrows). Right coronary angiogram (right: left anterior oblique view) shows severe stenosis of the proximal right coronary artery (arrow).

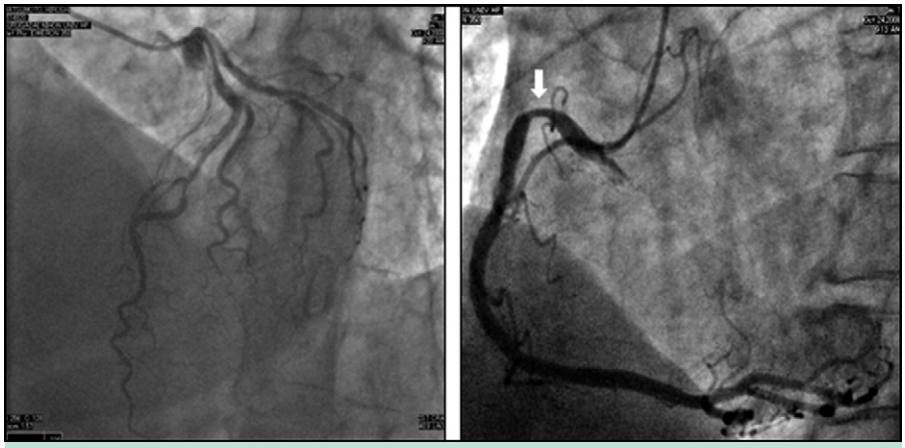

Figure 2 The vasospasm of the right coronary artery was relieved by administration of isosorbide dinitrate to the right coronary artery, and moderate organic stenosis remained (arrow). The collateral vessels to the right coronary artery, which were seen on the initial left coronary angiogram, can no longer be visualized.

that collateral blood supply may occur transiently through preexisting vessels to perfuse the ischemic area during coronary vasospasm and that such collateral flow might play a role in preventing transmural myocardial ischemia, reducing the severity of ischemia.[5]

In this case, the collateral vessels from the left anterior descending artery to the myocardial region perfused by the right coronary artery are speculated to have been formed gradually, by repeated myocardial ischemia caused by coronary vasospasm, even in the absence of severe organic stenosis of the right coronary artery. Such a situation is likely to exist in many patients with rest angina associated with ST-segment depression, in which coronary vasospasm has been implicated. The possible reasons why no ischemic ST changes were seen on the electrocardiogram in this case are as follows: the right coronary artery ischemia was released immediately, and the ischemic period was too short for the electrocardiographic changes to appear; the amount of blood supplied by the collateral vessels was sufficient, and significant myocardial ischemia potentially induced by right coronary vasospasm might have failed to occur.

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