COMMENTS AND RESPONSES

Cardiac Resynchronization Therapy in Heart Failure

TO THE EDITOR: McAlister and colleagues (1), in their systematic review, concluded that cardiac resynchronization therapy (CRT) reduces all-cause mortality and heart failure hospitalizations when added to medical therapy in selected patients with heart failure. Among some U.S. cardiologists, there appears to be a perception that patients with heart failure should receive a device with defibrillator ability and biventricular pacing function. It is likely that the report by McAlister and colleagues will further contribute to this perception and possibly influence practice trends.

McAlister and colleagues used a comprehensive search strategy and intensive extraction and evaluation of data from pertinent studies. However, their analysis could not overcome certain methodologic deficiencies (for example, concealed randomization, lack of blinding or partial blinding, and intention-to-treat analyses) that affected several of the studies. Such deficiencies can lead to preferential management or treatment, resulting in better or improved outcomes that favor the intervention of interest (in this case, CRT). In addition, the crossover design of several studies further restricted the already limited data available for evaluation of mortality rates and hospitalizations.

Among the parallel studies noted in McAlister and colleagues' Figures 2 and 3—the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) (2), the Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter defibrillator] (MIRACLE-ICD) (3), and the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial (4)—only MIRACLE (2) and MIRACLE-ICD (3) had high-quality methods. These 2 trials revealed small, statistically insignificant differences in mortality rates between patients randomly assigned to CRT and those assigned to inactive-device (no cardiac resynchronization) therapy. Of interest, subgroup analyses in the COMPANION trial (4) suggested a beneficial effect of CRT–defibrillator therapy on death rates in patients taking an angiotensin-converting enzyme inhibitor, a β-blocker, or spironolactone. This beneficial effect was not seen in patients who were not taking these drugs.

In summary, McAlister and colleagues' superb effort might be undermined by the weak quality of several studies used in the various analyses. McAlister and colleagues' conclusions regarding the use of CRT in patients with symptomatic heart failure should be assessed and confirmed in large trials without methodologic deficiencies.

Enrique V. Carbajal, MD
Grace W. Huang, DO
Billy Hu, MD
VA Central California Health Care System
Fresno, CA 93703

References

1. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med. 2004;141:381-90. [PMID: 15353430]

2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845-53. [PMID: 12063368]

3. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289:2685-94. [PMID: 12771115]

4. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140-50. [PMID: 15152059]

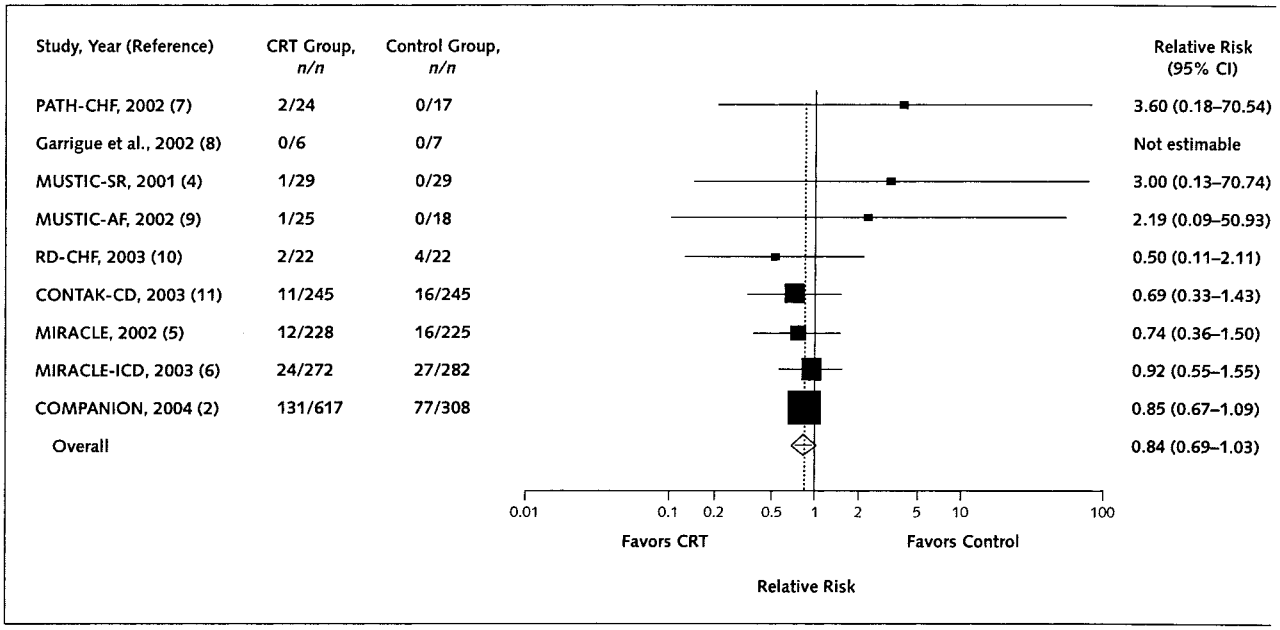
TO THE EDITOR: McAlister and colleagues (1) concluded that in selected patients with heart failure, CRT improves functional and hemodynamic status, reduces heart failure hospitalizations, and reduces all-cause mortality. Such conclusions, however, are unsafe and are based on incorrect presentation of the existing scientific data.

A major problem with McAlister and colleagues' analysis is that it does not deal appropriately with potential differences in the efficacy of CRT delivered with or without an ICD. Of particular concern is the presentation of the all-cause mortality data from the COMPANION trial, which fails to preserve randomization. This ignores a basic tenet of meta-analysis (2, 3). The authors incorrectly split the control arm results in 2 and compared half with the results from CRT alone and the remaining half with results from the CRT-ICD arm. In doing so, they created decreases in all-cause mortality for both active treatment groups. However, in an appropriate and unconfounded analysis that compared only the CRT-alone group ($n = 617$) with the control group ($n = 308$) and preserved randomization, we found a nonsignificant reduction in mortality attributable to CRT (relative risk, 0.85 [95% CI, 0.67 to 1.09]) (**Figure 1**). Indeed, it is the inappropriate inclusion of the data for the CRT-ICD group that led to the appearance of an overall statistically significant pooled reduction in all-cause mortality. Removal of these confounded data leads to a nonsignificant pooled decrease in the relative risk for all-cause mortality (relative risk, 0.84 [CI, 0.69 to 1.03]). Clearly, there are still important unanswered questions about the impact of CRT and the additional impact of CRT-ICD on mortality.

Second, McAlister and colleagues' analysis of heart failure hospitalizations was inconclusive. Their pooled data provided an estimate of 0.68 (CI, 0.41 to 1.12) for the relative risk for hospitalization. This result was based on only 316 events from proof-of-concept studies designed to assess whether CRT could improve symptoms, ventricular function, and exercise capacity. Although this result was nonsignificant, the authors then performed a subgroup analysis, on which they based their conclusion that CRT reduces heart failure hospitalizations in selected patients. The authors failed to include results from the large COMPANION trial, presumably because heart failure hospitalization was reported as part of a composite outcome combined with death from heart failure (2). It is unfortunate that the authors were unable to include results from this large study.

Finally, the authors acknowledged that the trials in their analysis probably overestimate the potential benefits of CRT. In all but 1 trial, only patients who underwent successful device implantation and survived a run-in period were eligible for randomization. Moreover, 2 patients died within hours of crossing over to CRT in the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial (4). For all of these reasons, the encouraging trends observed in meta-analyses presented so far are not secure evidence of benefit in morbidity or mortality. The double-blind MIRACLE and MIRACLE-ICD trials do suggest that CRT improves symptoms in about 35% and 15% of

Figure. **Unconfounded all-cause mortality with cardiac resynchronization therapy (*CRT*) versus randomly assigned controls.**



CHF = congestive heart failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; CONTAK-CD = Guidant CONTAK CD CRT-D System Trial; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter defibrillator]; MUSTIC-AF = Multisite Stimulation in Cardiomyopathies Atrial Fibrillation; MUSTIC-SR = Multisite Stimulation in Cardiomyopathies Sinus Rhythm; PATH-CHF = Pacing Therapies for Congestive Heart Failure.

patients, respectively, compared with controls (5, 6). However, further manipulation of pharmacologic therapy might have achieved similar results. At least 2 other large controlled trials, involving more than 1200 patients, have yet to be reported (7, 8). Although McAlister and colleagues' meta-analysis aimed to address an important question, the efficacy and safety of CRT, it failed to provide substantive evidence of this therapy's effect on mortality and hospitalization due to heart failure.

Melanie Calvert, PhD
Nick Freemantle, PhD
University of Birmingham Medical School
Edgbaston B15 2TT, England, United Kingdom

John G.F. Cleland, MD
University of Hull
Kingston upon Hull HU16 5JQ, England, United Kingdom

Note: Drs. Freemantle and Cleland are steering committee members for the CArdiac REsynchronisation in Heart Failure (CARE-HF) trial. Drs. Freemantle and Calvert are responsible for the analysis of the CARE-HF trial.

References

1. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med. 2004;141:381-90. [PMID: 15353430]

2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140-50. [PMID: 15152059]

3. Egger M, Davey Smith G, Altman D. Systematic Reviews in Health Care: Meta-Analysis in Context. London: BMJ Publishing Group; 2001.

4. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344:873-80. [PMID: 11259720]

5. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845-53. [PMID: 12063368]

6. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289:2685-94. [PMID: 12771115]

7. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol. 2002; 39:2026-33. [PMID: 12084604]

8. Garrigue S, Bordachar P, Reuter S, Jais P, Kobeissi A, Gaggini G, et al. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: prospective haemodynamic study. Heart. 2002;87:529-34. [PMID: 12010933]

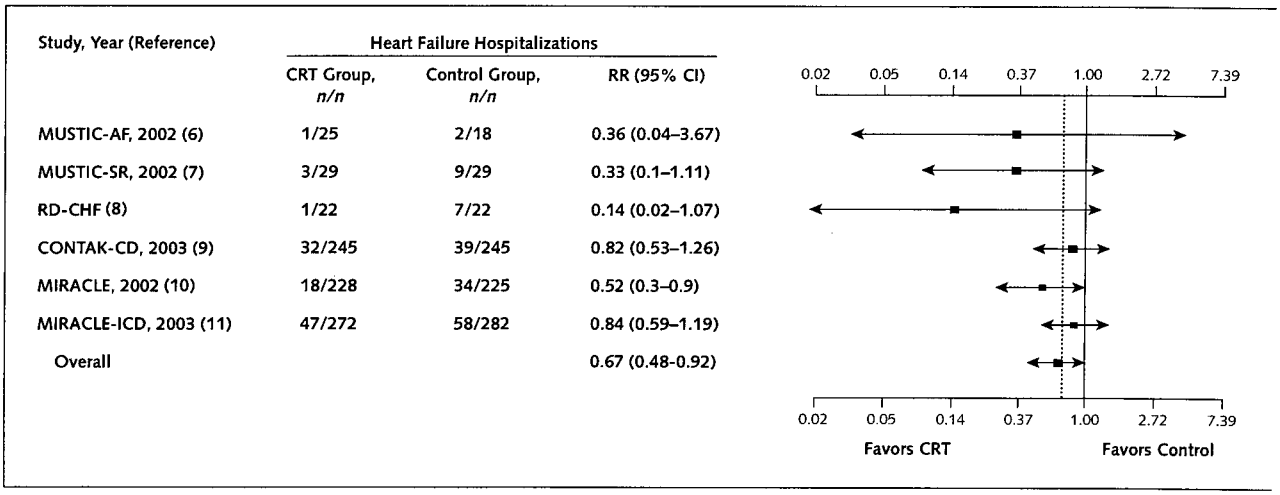
9. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002;23:1780-7. [PMID: 12419298]

10. Leclerq C, Cazeau S, Lellouche D, et al. Upgrading from right ventricular pacing to biventricular pacing in previously paced patients with advanced heart failure: a randomized controlled study (the RD-CHF Trial) [Abstract]. Presented at the European Society of Cardiology Congress, Vienna, Austria, 30 August–3 September 2003.

11. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol. 2003;42:1454-9. [PMID: 14563591]

12. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et

Figure. **Heart failure hospitalizations with cardiac resynchronization therapy (*CRT*) versus controls.**



CHF = congestive heart failure; CONTAK-CD = Guidant CONTAK CD CRT-D System Trial; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter defibrillator]; MUSTIC-AF = Multisite Stimulation in Cardiomyopathies Atrial Fibrillation; MUSTIC-SR = Multisite Stimulation in Cardiomyopathies Sinus Rhythm; RR = relative risk.

al. The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end-points. Eur J Heart Fail. 2001;3:481-9. [PMID: 11511435]

13. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol. 2002;39:194-201. [PMID: 11788207]

IN RESPONSE: We agree with Drs. Carbajal, Huang, and Hu that several trials included in our systematic review had potential methodologic deficiencies. Although we had space to highlight only 1 of these deficiencies in our published manuscript (randomization after implantation of the CRT device in all but 1 trial), we refer interested readers to our full Agency for Healthcare Research and Quality report, available at www.ahrq.gov/clinic/tp/resyntp.htm, for a full description of the methods and the quality assessment tables for all of the studies included in both our efficacy and safety analyses.

We refute the allegation of Drs. Calvert, Freemantle, and Cleland that our analysis of the COMPANION trial data (1) "ignores a basic tenet of meta-analysis." As outlined in our manuscript, we did conduct intention-to-treat analyses for all end points, and halving the control group data when incorporating a 3-arm trial into a meta-analysis is one of the techniques endorsed by the Cochrane Collaboration, as outlined at www.cochrane-net.org/openlearning/HTML/modA2-5.htm. Indeed, we would like to point out that, despite Calvert and colleagues' assertion that we created incorrect decreases for the CRT-alone arm of the COMPANION trial, careful perusal of our Figure 2 reveals that the relative risk we reported for mortality in that arm (0.84 [CI, 0.61 to 1.14]) is not statistically significant and is in fact very similar to the relative risk of 0.85 (CI, 0.67 to 1.09) that they found in their analysis.

On the other hand, Dr. Calvert and colleagues are correct in pointing out (as did Drs. Hlatky and Massie in the editorial accompanying our paper [2]) that exclusion of the CRT-ICD arm of the COMPANION trial would change the pooled relative risk for mortality with CRT to 0.84 (CI, 0.69 to 1.03). We do not disagree that this is one way to approach the data, but we wonder to what extent this argument is moot in light of the current ICD evidence base, particularly given the data from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (3, 4). Shouldn't ICDs be considered in patients who have substantial heart failure symptoms despite medical therapy, prolonged QRS duration, and a left ventricular ejection fraction less than 0.35 (the base case in our systematic review and the subsequent decision analysis), unless there are contraindications or competing comorbid conditions? Indeed, we believe that the vast majority of patients with New York Heart Association class III symptoms who are being evaluated for CRT will also be eligible for an ICD. Given this, aren't the data from the CRT-ICD arm of the COMPANION trial relevant to the discussion? Furthermore, it should be emphasized that the beneficial effects of CRT on functional status, left ventricular ejection fraction, and quality of life reported in our study are present even without inclusion of the COMPANION CRT-ICD data.

Dr. Calvert and colleagues state that the heart failure hospitalization data are inconclusive. Certainly, this is true of the pooled estimate that we reported and that they reiterate in their letter. However, in reexamining our data, we discovered an error in Figure 3 in our published manuscript. We mistyped the number of "no deaths" in the CRT group for the Guidant CONTAK CD CRT-D System Trial (5) when entering the data into our models. A corrected Figure is included here (**Figure**). The corrected pooled relative risk for heart failure hospitalizations is thus 0.67 (CI, 0.48 to 0.92), a result that is statistically and clinically significant and does not include the COMPANION trial results (the data for this end point were not available at the time of our request to the COMPANION investigators).

While we disagree with the specific points that Dr. Calvert and colleagues raise in the first half of their letter, we do not disagree that the trials in our analysis may have overestimated the benefits of CRT. Indeed, we made this very point in our manuscript. We also agree with these CARE-HF investigators that our meta-analysis (which is based on only 429 deaths and 251 heart failure hospital-

izations) should not be used as a reason to prematurely terminate ongoing large trials in this area (such as CARE-HF and RAFT [Resynchronization/Defibrillation for Advanced Heart Failure Trial]).

In closing, we would like to reiterate 3 key points from our original study that we fear some readers may have missed: 1) CRT is not a panacea; 2) CRT is efficacious in selected patients with advanced systolic heart failure and evidence of electromechanical dyssynchrony; and 3) attempts to define which patients are most likely to benefit from CRT should remain a research priority.

Finlay A. McAlister, MD, MSc
University of Alberta Hospital
Edmonton, Alberta T6G 2R7, Canada

Natasha Wiebe, Mmath
University of Alberta Campus
Edmonton, Alberta T6G 2J3, Canada

William Abraham, MD
Ohio State University
Columbus, OH 43210

References

1. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140-50. [PMID: 15152059]
2. Hlatky MA, Massie BM. Cardiac resynchronization for heart failure [Editorial]. Ann Intern Med. 2004;141:399-400. [PMID: 15313731]
3. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Ann Intern Med. 2003;138:445-52. [PMID: 12639076]
4. Cleland JG, Ghosh J, Freemantle N, Kaye GC, Nasir M, Clark AL, et al. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-Lipids and cardiac resynchronisation therapy in heart failure. Eur J Heart Fail. 2004;6:501-8. [PMID: 15182777]
5. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol. 2003;42:1454-9. [PMID: 14563591]
6. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002;23:1780-7. [PMID: 12419298]
7. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344:873-80. [PMID: 11259720]
8. Leclerq C, Cazeau S, Lellouche D, et al. Upgrading from right ventricular pacing to biventricular pacing in previously paced patients with advanced heart failure: a randomized controlled study [the RD-CHF Trial] [Abstract]. Presented at the European Society of Cardiology Congress, Vienna, Austria, 30 August–30 September 2003.
9. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol. 2003;42:1454-9. [PMID: 14563591]
10. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845-53. [PMID: 12063368]
11. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289:2685-94. [PMID: 12771115]

Relative Cost-Effectiveness of Different Tests for *Chlamydia trachomatis*

TO THE EDITOR: I read Hu and colleagues' cost-effectiveness analysis for *Chlamydia trachomatis* screening (1) with great interest. One topic that was not explicitly covered but could easily be addressed by the same decision model is the relative cost-effectiveness of different laboratory tests for *C. trachomatis* detection. Nucleic acid amplification methods, which Hu and colleagues used in their analysis, are substantially more sensitive than nonamplified DNA methods, which in turn are much more sensitive than the older enzyme immunoassay methods (2, 3). From the individual patient perspective, then, the amplified tests are clearly optimal. However, many laboratories continue to offer these other less sensitive tests (4), a phenomenon that appears to be driven by cost. If it could be demonstrated that amplified DNA tests were cost-effective (or, even better, cost-saving) versus nonamplified tests from a health system perspective, then perhaps payers could be convinced to cover the modestly increased cost of amplified testing for *C. trachomatis*. This would benefit both individual patients and the public health.

Brian Jackson, MD
University of Utah and ARUP Laboratories
Salt Lake City, UT 84108

Potential Financial Conflicts of Interest: Dr. Jackson is employed by ARUP Laboratories, which performs testing for *Chlamydia trachomatis*.

References

1. Hu D, Hook EW 3rd, Goldie SJ. Screening for *Chlamydia trachomatis* in women 15 to 29 years of age: a cost-effectiveness analysis. Ann Intern Med. 2004;141:501-13. [PMID: 15466767]
2. Black CM, Marrazzo J, Johnson RE, Hook EW 3rd, Jones RB, Green TA, et al. Head-to-head multicenter comparison of DNA probe and nucleic acid amplification tests for *Chlamydia trachomatis* infection in women performed with an improved reference standard. J Clin Microbiol. 2002;40:3757-63. [PMID: 12354877]
3. Watson EJ, Templeton A, Russell I, Paavonen J, Mardh PA, Stary A, et al. The accuracy and efficacy of screening tests for *Chlamydia trachomatis*: a systematic review. J Med Microbiol. 2002;51:1021-31. [PMID: 12466399]
4. College of American Pathologists. Surveys 2003. Northfield, IL: Coll of American Pathologists; 2003.

IN RESPONSE: We appreciate Dr. Jackson's interest and comment. We believe that our model has the potential to help inform many questions relating to chlamydia screening and chose to start by exploring the impact of different approaches to routine screening for young women from a long-term, societal perspective. Our analysis was intended to inform broad recommendations for national screening guidelines, with particular emphasis on optimal target age range and frequency. At the same time, a wide variety of diagnostic tests are available for *C. trachomatis* detection, including cell culture, antigen-detection tests, nucleic acid hybridization tests, and, most recently, nucleic acid amplification tests. Compared with nonamplified tests, nucleic acid amplification tests have been demonstrated to have superior sensitivity and greater acceptability among adolescents and young adults (1–3), although at a higher cost. As pointed out in

Stamm's commentary (4), many public health–based screening programs have limited resources and consequently are able to offer screening to less than half of the target population. This fact illustrates an important distinction between the cost-effectiveness (that is, "value for money") of an available technology from a societal perspective and the affordability of that technology from the perspective of one particular payer (for example, a public health clinic). An analysis that comparatively evaluates a wide array of available screening tests and considers a shorter time horizon, while explicitly taking into account the available budget, would be useful for regional and local decision making. Such analyses are complex: To accurately reflect the tradeoffs associated with different tests, data on the likelihood of adherence to different tests and the correlation between adherence and preferences would be required. We agree that this type of analysis is of high priority.

Sue J. Goldie, MD, MPH
Delphine Hu, MD, MPH
Harvard School of Public Health
Boston, MA 02115

Edward W. Hook III, MD
University of Alabama at Birmingham
Birmingham, AL 35294

Potential Financial Conflicts of Interest: Dr. Hook has received research support from Abbott Laboratories; Roche Molecular Systems, Inc.; Gen-Probe; and Becton, Dickinson, & Co. and honoraria from Abbott Laboratories and Gen-Probe.

References

1. Watson EJ, Templeton A, Russell I, Paavonen J, Mardh PA, Stary A, et al. The accuracy and efficacy of screening tests for *Chlamydia trachomatis*: a systematic review. J Med Microbiol. 2002;51:1021-31. [PMID: 12466399]
2. Nsuami M, Cohen DA. Participation in a school-based sexually transmitted disease screening program. Sex Transm Dis. 2000;27:473-9. [PMID: 10987455]
3. Wiesenfeld HC, Lowry DL, Heine RP, Krohn MA, Bittner H, Kellinger K, et al. Self-collection of vaginal swabs for the detection of *Chlamydia*, gonorrhea, and trichomoniasis: opportunity to encourage sexually transmitted disease testing among adolescents. Sex Transm Dis. 2001;28:321-5. [PMID: 11403188]
4. Stamm WE. Chlamydia screening: expanding the scope [Editorial]. Ann Intern Med. 2004;141:570-2. [PMID: 15466776]

Treating Controls in Unblinded Trials

TO THE EDITOR: In the study by Yardley and colleagues (1) on vestibular rehabilitation for patients with chronic dizziness, it is not clear what scientific information was gained by crossing controls over to vestibular training at 3 months. Efficacy could not be measured, since the intervention group was not crossed over to the control condition (nor could it be, given an inability to wash out the initial vestibular training). Maintenance of effect at 3 months was already measurable in the intervention group, so a similar 3-month period for controls would not add new information. And since vestibular training was not the standard of care, a "staggered-start" trial to measure adverse effects during a 3-month control window was not ethically mandated.

One nonscientific reason for offering controls vestibular training may have been to reduce the likelihood that they would drop out of the trial because of disappointment at not receiving the training. Because the trial was unblinded, controls would have been aware of their control status. These patients, who suffered from chronic dizziness, may have entered the trial in hopes of receiving the vestibular training. Offering them such training after 3 months may have served as an inducement to them to remain in the trial as controls.

There are, however, 2 concerns about offering controls delayed intervention in an unblinded trial without valid scientific reasons for doing so. First, such an offer might be considered potentially coercive. But more important, it portrays the study intervention as "treatment" rather than as something being investigated under equipoise concerning its efficacy (2, 3). An honest null hypothesis at this trial's inception must have allowed for the possibility that vestibular training would have proven ineffective at 3 months compared with the control condition. Given this possibility, what is the justification for providing this "treatment" to controls at 3 months as part of the trial?

Paul S. Heckerling, MD
University of Illinois at Chicago
Chicago, IL 60612

References

1. Yardley L, Donovan-Hall M, Smith HE, Walsh BM, Mullee M, Bronstein AM. Effectiveness of primary care-based vestibular rehabilitation for chronic dizziness. Ann Intern Med. 2004;141:598-605. [PMID: 15492339]
2. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med. 1987;317:141-5. [PMID: 3600702]
3. Miller FG, Rosenstein DL. The therapeutic orientation to clinical trials. N Engl J Med. 2003;348:1383-6. [PMID: 12672867]

IN RESPONSE: Dr. Heckerling argues that by offering vestibular rehabilitation to patients in the control group after 3 months, we implied that vestibular rehabilitation is an effective treatment, thereby violating the important principle of equipoise. However, in a pragmatic (1) or phase III trial such as ours, it is assumed that the treatment has already been shown to be beneficial under ideal conditions (normally, this will have been established in efficacy or phase II trials). Consequently, equipoise is maintained instead with regard to the research question: Is the treatment more effective than usual care in typical clinical practice? Moreover, it is accepted that clinician and patient attitudes toward the treatment will affect outcomes. It was important for this reason (as well as to permit fully informed consent) that we explained to potential participants that there was some existing evidence of efficacy but no previous demonstration of effectiveness, particularly when vestibular rehabilitation was delivered by practice nurses in a primary care setting. We therefore also drew attention in our paper to the likelihood that positive motivation and placebo effects may have contributed to outcomes, although the pattern of findings was indicative of specific effects on the balance system rather than simply a generalized improvement in subjective well-being. However, if controls had stayed in the study simply because they were "coerced" by our offer of a treatment of unknown effectiveness after 3 months, then substantial dropout might have been expected at follow-up in both control and intervention groups. On the contrary, dropout at 3 months was as low in the treatment group as in the control group and remained similarly low in both groups at 6 months.

Regarding Dr. Heckerling's subsidiary point, we concur that

there was no compelling scientific rationale for presenting outcomes in the control group after controls had received therapy. However, we had collected follow-up data in both groups to analyze predictors of adherence to treatment in the whole sample (manuscript in preparation), and we felt that if we failed to report these outcomes alongside the longitudinal follow-up of the intervention group, readers might reasonably wonder whether this was because the intervention had inexplicably proved to be less successful in controls.

Lucy Yardley, PhD
University of Southampton
Southampton SO17 1BK, United Kingdom

Reference

1. Roland M, Torgerson DJ. What are pragmatic trials? BMJ. 1998;316:285. [PMID: 9472515]

CLINICAL OBSERVATIONS

Debilitating Muscle Cramps after Teriparatide Therapy

TO THE EDITOR: *Background:* Teriparatide, a recombinant human 1–34 amino acid sequence of parathyroid hormone, was recently approved in the United States for the treatment of men and postmenopausal women at high risk for osteoporotic fracture and in Europe for the treatment of postmenopausal women with osteoporosis. When given by once-daily injection, teriparatide increases bone mass by stimulating formation of new bone, resulting in the restoration of bone architecture (1). The adverse reactions that have been described are relatively mild. However, we observed a previously unreported reaction to teriparatide.

Case Report: Teriparatide therapy was started in a 75-year-old woman with progressive osteoporosis (compression fracture at T8 and T-scores ranging from −3.0 to −4.2) who had been previously treated with antiresorptive therapy. The patient received careful instruction on proper use of the medication and on its adverse effects. At initial use, within 5 minutes of self-administration, the patient developed a severe, debilitating lower back spasm and discomfort. Lower back pain lasted approximately 60 minutes, during which time the patient was seen in a local emergency department and required narcotics for pain relief. The patient was subsequently seen in our endocrinology outpatient clinic, where medical personnel administered teriparatide. Findings on physical examination were unremarkable. Under observation and monitoring, the patient developed recurrent lower back pain 6 minutes after administration of 20 μg of teriparatide. Back examination revealed tense and tender paraspinal muscles in the lumbar region. Findings on the remainder of the musculoskeletal examination were unremarkable. Cramping and lower back discomfort lasted approximately 30 minutes, and intravenous narcotics were again required for pain relief. With rest and analgesic therapy, the patient was able to walk 1 hour after the incident.

Conclusion: Although leg cramps have been reported with the use of teriparatide, to our knowledge this is the first description of severe muscle spasm occurring within minutes of the injection of this hormone. No precipitating factors were seen in our patient. However, one of the inactive ingredients of teriparatide is metacresol, a preservative that has been linked to local and systemic reactions to insulin injections (2). Whether metacresol played a role in our patient's adverse reaction requires further investigation.

Parul J. Kakaria, MD
George Washington University Hospital
Washington, DC 20037

David J. Nashel, MD
Eric S. Nylen, MD
Veterans Affairs Medical Center
Washington, DC 20472

References

1. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-41. [PMID: 11346808]
2. Clerx V, Van Den Keybus C, Kochuyt A, Goossens A. Drug intolerance reaction to insulin therapy caused by metacresol. Contact Dermatitis. 2003;48:162-3. [PMID: 12755733]

Statins and Nasal Polyps

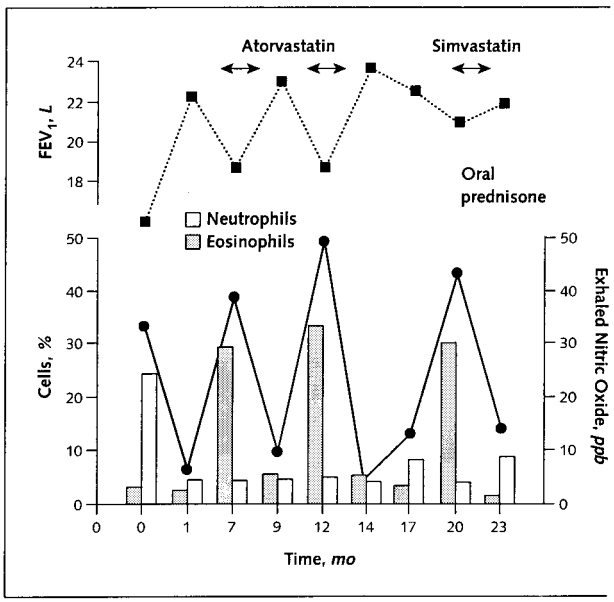
TO THE EDITOR: *Background:* Chemotaxis of eosinophils is the crucial event in the development of nasal polyposis related to chronic hyperplastic eosinophilic sinusitis (1, 2). Several statins, including atorvastatin, inhibit T-helper 1 differentiation and induce T-helper 2 polarization and production of T-helper 2 cytokines, such as interleukin (IL)-5, that promote the activation and chemotaxis of eosinophils.

Methods and Findings: A 57-year-old woman with nonallergic rhinosinusitis (low serum levels of total and specific IgE, negative results on skin prick tests, and neutrophils and *Staphylococcus aureus* in nasal lavage), asthma, and no aspirin sensitivity presented in May 2002 for recent onset of rhinosinusitis associated with asthma attacks. She had no systemic disease. After a 2-week course of amoxicillin–clavulanate and long-term treatment with intranasal and inhaled corticosteroids plus inhaled long-acting β_2-agonist, the patient's condition nearly normalized.

Six months later, the patient returned because of severe persistent nasal obstruction with extensive bilateral polyposis, mild airway obstruction, and increased levels of exhaled nitric oxide despite long-term treatment with intranasal and inhaled corticosteroids. Eosinophilia was noted in nasal scrapings and in peripheral blood (969 eosinophils/mL). The **Figure** shows FEV_1, exhaled nitric oxide, and nasal cytologic characteristics throughout follow-up. Computed tomography showed extensive opacification of all paranasal sinuses; right maxillary and frontal sinuses were completely stuffed by polypoid tissue.

An otolaryngologist surgically removed the polyps, and histologic examination showed relevant edema and inflammatory infiltrate, with predominant eosinophils. Nasal polyps returned within 1 month after surgery and were associated with persistent eosinophilia. The patient reported taking atorvastatin, which her practitioner had prescribed in October 2002 for hyperlipemia. Three weeks after atorvastatin withdrawal, nasal symptoms had dramatically improved, nasal polyps had disappeared, and only a few neutrophils and eosino-

Figure. **FEV_1, exhaled nitric oxide, and nasal cytologic characteristics during treatment with statins and after statin withdrawal.**



phils were found in nasal scrapings. Suspecting that atorvastatin was responsible for the development of eosinophilic polyposis, we asked the patient to resume atorvastatin therapy. Nasal symptoms and polyps recurred shortly thereafter, together with nasal eosinophilia. The patient improved again soon after drug withdrawal. Of note, the patient returned 6 months later for recurrence of polyps: Her general practitioner had prescribed simvastatin. We have seen 2 other patients, one 68 years of age and one 74 years of age, who had nonatopic chronic obstructive pulmonary disease and reported having severe nasal obstruction since the start of statin therapy (6 months and 6 years, respectively). Both patients were former smokers. In both cases, nasal lavage showed eosinophilia and nasal biopsies confirmed the presence of eosinophilic nasal polyposis. Polyps resolved in both patients after statin withdrawal.

Discussion: To our knowledge, this is the first report of nasal polyposis associated with statin treatment. Growing evidence suggests that statins, besides their lipid-lowering effect, also have anti-inflammatory and immunomodulatory properties (3–5). These properties involve inhibition of T-helper 1 differentiation and T-helper 2 polarization, with increased production of T-helper 2 cytokines (IL-4, IL-5, and IL-10) that promote activation and chemotaxis of eosinophils. The latter mechanism is the crucial event in the development of chronic hyperplastic eosinophilic sinusitis (1, 2).

Conclusion: Statins may lead to development of eosinophilic polypoid rhinosinusitis by switching inflammation from the T-helper 1 phenotype to the T-helper 2 phenotype.

Caterina Bucca, MD
Andrea Marsico, MD
Erika Panaro, MD
University of Turin
10128 Turin, Italy

Patrizia Bigo, MD
Luisa Brussino, MD
St. Giovanni Battista Hospital
10126 Turin, Italy

References

1. Bachert C, Van Cawenberge P. Nasal polyps and sinusitis. In: Adkinson NF, Yunginger JW, Busse WB, Bochner BS, Holgate ST, Simons FE, eds. Middleton's Allergy. Principles & Practice, 6th Edition. St. Louis: Mosby; 2003:1421-36.

2. Steinke JW, Bradley D, Arango P, Crouse CD, Frierson H, Kountakis SE, et al. Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis: importance to eosinophilia and asthma. J Allergy Clin Immunol. 2003;111:342-9. [PMID: 12589355]

3. Hakamada-Taguchi R, Uehara Y, Kuribayashi K, Numabe A, Saito K, Negoro H, et al. Inhibition of hydroxymethylglutaryl-coenzyme a reductase reduces Th1 development and promotes Th2 development. Circ Res. 2003;93:948-56. [PMID: 14563711]

4. Nath N, Giri S, Prasad R, Singh AK, Singh I. Potential targets of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor for multiple sclerosis therapy. J Immunol. 2004;172:1273-86. [PMID: 14707106]

5. Youssef S, Stuve O, Patarroyo JC, Ruiz PJ, Radosevich JL, Hur EM, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature. 2002;420:78-84. [PMID: 12422218]

CORRECTION

Correction: Cardiac Resynchronization in Patients with Symptomatic Heart Failure

In a review on cardiac resynchronization in patients with symptomatic heart failure (1), Figure 3 contained errors. The relative risk for heart failure hospitalizations in the Guidant CONTAK CD CRT-D System Trial should have been reported as 0.82 (95% CI, 0.53 to 1.26), and the pooled relative risk should have been reported as 0.67 (CI, 0.48 to 0.92).

Reference

1. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med. 2004;141:381-90. [PMID: 15353430]