Clinical Investigations

# Enhanced External Counterpulsation in the Treatment of Chronic Refractory Angina: A Long-term Follow-up Outcome from the International Enhanced External Counterpulsation Patient Registry

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ABSTRACT

*Background:* The management of patients who suffer from medically refractory angina and are unsuitable for conventional revascularization therapy is often unsatisfactory. Enhanced external counterpulsation (EECP) is a noninvasive treatment that is safe and effective immediately after a course of treatment. However, the duration of benefit is less certain.

*Hypothesis:* To evaluate the 3-year outcome of EECP treatment.

*Methods:* One thousand four hundred and twenty seven patients from 36 centers registered in the International EECP Patient Registry (IEPR) — Phase 1 was prospectively followed for a median of 37 months. Two hundred and twenty patients (15.4%) died, while 1,061 patients (74.4%) completed their follow-up.

*Results:* The mean age was $66 \pm 11$ years and 72% were men. Seventy-six percent had multivessel coronary disease for $11 \pm 8$ years. Eighty-eight percent had a prior percutaneous or surgical revascularization and 82% were unsuitable for further coronary intervention.

Immediately post-EECP, the proportion of patients with severe angina (Canadian Cardiovascular Angina Classification [CCS] III/IV) were reduced from 89% to 25%, $p<0.001$. The CCS class was improved by at least 1 class in 78% of the patients and by at least 2 classes in 38%. This was sustained in 74% of the patients during follow-up.

Thirty-six percent of the patients had CCS II or less angina, which was better than pre-EECP state without a major adverse cardiovascular event during follow-up. More severe baseline angina and a history of heart failure or diabetes were independent predictors of unfavorable outcome.

*Conclusion:* An EECP improves angina and quality of life immediately after a course of treatment. For most of the patients, these beneficial effects are sustained for 3 years.

Key words: external counterpulsation, angina pectoris, refractory pain, coronary artery disease, ischemic heart disease

## Introduction

The treatment of chronic angina pectoris is difficult when standard medical therapy and conventional revascularization fail to provide satisfactory symptomatic control.[1] Enhanced external counterpulsation (EECP) is a potential treatment that is safe, noninvasive, and technically simple. It involves application of pneumatic cuffs to the lower extremities, which are sequentially inflated during diastole and simultaneously deflated prior to the onset of systole. This augments systemic and coronary perfusion pressure while reducing left ventricular afterload.[2] The action also increases venous return and cardiac output.[3] The EECP can improve angina, quality of life (QOL), exercise tolerance, time to ST-segment depression during exercise stress

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testing, myocardial perfusion at rest and during stress, and dobutamine stress-induced regional wall motion abnormality in patients with refractory angina.[4–8]

The beneficial effects of EECP can be achieved immediately after a course of treatment with long-term sustained improvement in anginal control and QOL.[5] However, the duration of these long-term benefits is less certain.

Phase 1 of International EECP Patient Registry (IEPR-1) enrolled consecutive patients treated with EECP in more than 100 centers with a follow-up duration of 3 years.[9] One of the objectives was to monitor the long-term benefits of EECP in a broad range of patients in a clinical setting. This study aimed to assess the 3-year outcomes of EECP in these patients and the factors associated with a favorable outcome.

## Methods

### International Enhanced External Counterpulsation Patient Registry — Phase 1

The setup of IEPR-1 has been described previously.[9] All participating centers received approval from their Institutional Review Boards and/or Local Ethics Committees, and all patients gave their written informed consent. Consecutive patients from each center who had at least 1 h of EECP treatment were enrolled. Patients were treated using EECP equipment (Vasomedical Inc., Westbury, NY, USA). A standard course of 35 one-hour treatment sessions was recommended.[4,9] The data collected included demographics, medical history, disease characteristics, symptoms, and QOL at baseline. Treatment information, clinical events, and symptoms were documented during and at the end of treatment. The follow-up was conducted by telephone interview or clinic visits at 6 months and 1, 2, and 3 years to collect data on anginal status, QOL, clinical events, and hospitalizations.

### Patients

Five thousands patients from 99 American and 9 international centers were enrolled between January 1998 and July 2001. The 3-year follow-up was completed in October 2004. To avoid selection bias and potential bias introduced by poorly compliant centers, only patients from centers with at least 80% compliance in follow-up data submission were included.

### Outcome Measures

The primary outcome is anginal status measured by Canadian Cardiovascular Angina Classification (CCS). Other measures include weekly angina episodes and nitroglycerin (GTN) use. The patients graded their QOL using a simplified 5-point scale where 1 represents the worst and 5 represents the best QOL. The data at baseline, immediately post-EECP (last treatment hour), and 3-year follow-up were compared.

### Clinical Events

The clinical events included skin breakdown (e.g., abrasions, blisters, and ecchymoses), musculoskeletal problem (e.g., severe back, leg, or muscle pain), unstable angina (UA), new onset or exacerbation of heart failure (HF), percutaneous coronary intervention (PCI), coronary bypass operation (CABG), myocardial infarction (MI), death and major adverse cardiovascular event (MACE) and composite of death/MI/CABG/PCI. Clinical events occurring during the treatment period and within 1 week after the last treatment were considered as treatment events.

### Statistical Analysis

Continuous data are presented as mean ± SD if normally distributed, and as median (interquartile range) otherwise. Categorical data are presented as percentages. Barker's test was used to compare the changes in CCS class. The differences in weekly angina episodes and GTN use were compared using Wilcoxon's t-test approximation. The Cochrane Armitage test for trend was performed to assess the changes in medication use. The event rates were estimated using Kaplan-Meier survival analysis. Logistic regression analysis was performed to identify baseline factor(s) that were associated with unfavorable immediate and long-term outcome and data are presented as (odd ratio [OR], 95% confidence interval [CI]). A 2-tailed test with $p<0.05$ was considered significant.

## Results

One thousand four hundred and twenty seven patients from 36 centers were included. The overall data compliance rate was 89.8%. These patients were followed for a median of 37.4 (33.7–38.5) months. One thousand and sixty one (74.4%) patients completed their 3-year follow-up, while 220 (15.4%) died. However, 146 (10.2%) patients did not complete their 3-year follow-up. They were followed for a median of 15.8 (8.1–26.1) months and were included in analyses for post-treatment outcome and follow-up clinical events.

The patients received a mean of 33.3 ± 9.6 h of treatment over a mean period of 48 days. Eight-two point seven percent of the patients completed their prescribed course of treatment. Seven point one percent of the patients discontinued their treatment, while 8.8% were terminated because of clinical events. The mean diastolic augmentation increased from 0.8 ± 0.5 at the first treatment hour to 1.0 ± 0.6 at the last hour.


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### Baseline Patient Characteristics

The mean age was 66.3 ± 10.8 years. Most of the patients were men and had preserved left ventricular ejection fraction (LVEF). They had a long history of significant coronary artery disease (CAD) and most suffered from frequent and severe angina (CCS III/IV). The majority had had at least one previous revascularization and were not candidates for further conventional intervention (Table 1).

Compared with other patients, the 146 patients who did not complete their 3-year follow-up were younger (64.3 ± 11.7 versus 66.4 ± 10.7 years, $p<0.05$), their angina was more severe (CCSIII/IV 91.7% versus 88.8%, $p<0.01$) and frequent (10 [4–20] versus 6 [3–14] episodes/week, $p<0.01$), and history of HF was more prevalent (44.8% versus 33.8%, $p<0.01$). However, the workload they achieved on exercise stress test at baseline; their LVEF, the duration, distribution, and extent of their CAD; history of prior MI, previous revascularization, other cardiovascular risk factors, and medication use were similar to other patients.

### Angina, Quality of Life, and Medication Use

Immediately post-EECP, the proportion of patients who suffered from CCS III/IV angina reduced from 89.2% to 24.9%, $p<0.001$. The CCS class improved by at least 1 class in 77.9% of the patients and by 2 classes in 38.0%. Sixteen point three percent of patients had no angina. These were sustained in those 1,033 patients whose anginal status was documented at 3-year follow-up (Figure 1A). Of the patients who responded to the QOL questionnaires there was sustained improvement in their QOL after 3 years, $p<0.001$ (Figure 1B).

The frequency of angina reduced by 4 (2–11) episodes/week immediately post-EECP. Seventy-six percent of the patients experienced at least 50% reduction in the frequency of angina. This was sustained at 3-year follow-up (Table I).

The frequency of GTN use and the proportion of patients who required GTN for symptom control reduced immediately post-EECP and at 3 years. There was a small but significant reduction in calcium channel blocker and long-acting nitrate use at follow-up (Table 2).

As any MACE may affect anginal status, subgroup analysis was performed on 743 patients who did not suffer from any MACE. Similar pattern of sustained improvement was observed in these patients and 67% of them reported the same or decreased angina at 3 years (Figure 1A).

### Clinical Events

Clinical events that occurred during the treatment period were mainly due to musculoskeletal discomfort (1.5%), skin breakdown (2.5%), HF (2.2%), and UA (4.5%). A MACE was rare and included MI (0.8%), PCI (0.8%), CABG (0.6%), and death (0.5%).

TABLE 1: Baseline patient characteristics (n = 1427)

| | |
|---|---|
| Age (years) | 66.3 ± 10.8 |
| Age > 65 years | 57.3 |
| Men | 72.2 |
| LVEF (%) | 46.6 ± 14.8 |
| LVEF < 35% | 19.8 |
| Cardiovascular history | |
| Duration of CAD (years) | 10.8 ± 8.2 |
| Prior myocardial infarction | 70.0 |
| Prior PCI | 67.1 |
| Prior CABG | 69.0 |
| Prior PCI or CABG | 87.1 |
| Multivessel CAD | 78.0 |
| Unsuitable for revascularization | 88.0 |
| Heart failure | 34.8 |
| Noncardiac vascular disease | 30.2 |
| Prior EECP | 3.8 |
| Cardiovascular risk factors | |
| Diabetes mellitus | 44.0 |
| Hypertension | 70.5 |
| Hypercholesterolemia | 81.3 |
| Smoker | |
| Previous | 64.4 |
| Current | 8.5 |
| Anginal status | |
| CCS Class | |
| I | 2.2 |
| II | 8.6 |
| III | 62.8 |
| IV | 26.4 |
| Angina frequency (episodes/week) | 6 (3–14) |
| Nitroglycerin use (times/week) | 3 (0–8) |

All data are percentages unless otherwise stated as means ± SD or median (interquartile range). *Abbreviations:* CAD = coronary artery disease; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society anginal classification; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.


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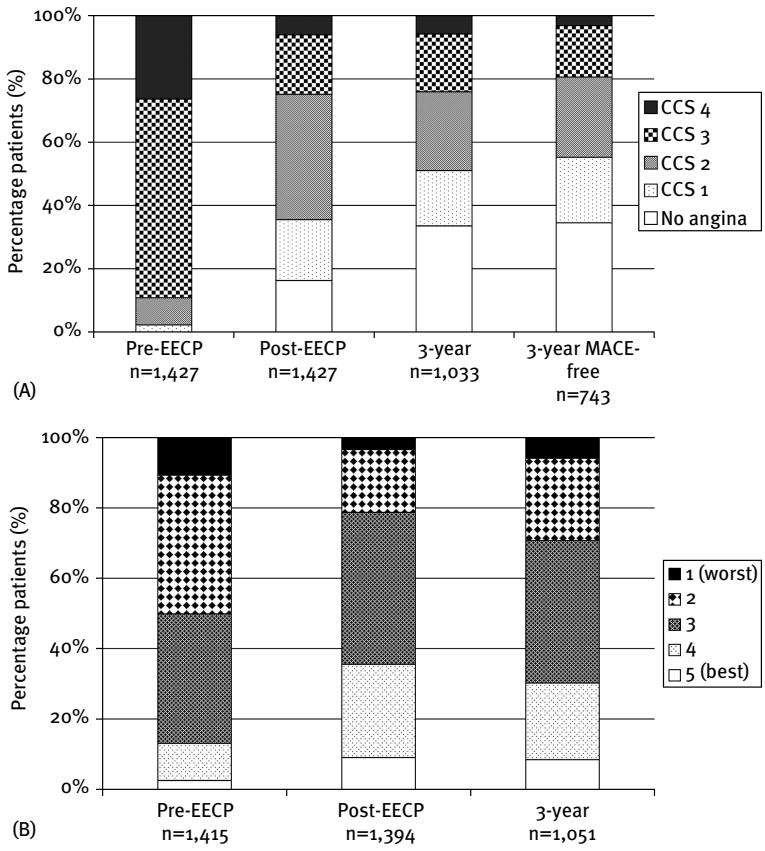


Figure 1: (A) CCS and (B) Simplified 5-point QOL scores.

Table 3 shows the cumulative repeat EECP and clinical event rates during follow-up. Other events included UA (25.4%) and new onset or exacerbation of HF (12.9%).

### Predictors of Outcome

Seventy-six percent of the patients had immediate improvement in CCS class without any cardiovascular events. Univariate logistic regression analysis showed that men, severe pre-treatment angina (CCS III/IV), and absence of a history of HF, diabetes, or hypertension were associated with such an outcome. A CCS III/IV class (OR 1.80 [1.25–2.59]) and freedom from HF (OR 1.82 [1.41–2.32]) were independent predictors of favorable immediate response on multivariate analysis.

We defined favorable long-term outcome as being in CCS II or milder angina that was better than in the pretreatment state and without requiring repeat EECP or suffering from any MACE at 3 years. This was achieved in 36.4% of the patients and was associated with duration of CAD, LVEF, prior revascularization, a history of HF, diabetes or noncardiac vascular disease, angina severity, and suitability for CABG. On multivariate analysis, severe pre-treatment angina (OR 1.54 [1.09–2.17]) and a history of HF (OR 1.43 [1.01–1.82]) and diabetes (OR 1.35 [1.07–1.69]) were independent predictors of unfavorable long-term outcome.

## Discussion

This is the longest follow-up report from the IEPR-1 and confirms the safety and immediate benefits of EECP. It shows that sustained symptomatic and QOL benefit can be achieved in most patients for up to 3 years. This is associated with a reduction in anti-anginal medication use.

The immediate benefit of EECP in improving angina control and QOL has been shown in randomized controlled trials and supported by objective evidence using makers of myocardial ischemia.[4–8] The improvement in exercise tolerance and myocardial perfusion can be sustained for up to 3 years.[10] The proposed mechanisms of sustained long-term benefit are multifactorial and include improvement in endothelial function, collateral recruitment and angiogenesis, exercise training effect, and neurohormonal modulation.[11–14] These may improve myocardial perfusion and metabolism, reduce myocardial oxygen consumption while increasing peripheral oxygen uptake, and improve left ventricular systolic and diastolic function.[13] However, immediate reduction in angina and increase in exercise tolerance can occur without any improvement in myocardial perfusion, suggesting that early benefits of EECP may be attributed to peripheral effects similar to that of exercise training.[15] The improvement in exercise capacity may then lead to long-term improvement in myocardial perfusion and sustained symptomatic control.

Consistent with previous studies, patients with more severe angina and without a history of HF were more likely to gain immediate symptomatic benefit.[16] Patients with more severe angina, diabetes, and a history of HF are more likely to suffer from unfavorable long-term outcome. Nevertheless, EECP can improve symptom, QOL, and exercise tolerance in patients with left ventricular systolic dysfunction and angina, and/or HF.[17,18]

The natural history of chronic refractory angina has not been well described, and whether or not EECP can alter its clinical course is unclear. In a preliminary

TABLE 2: Weekly angina frequency, nitroglycerin use, and medications at pre-EECP, post-EECP, and 3-year follow-up

| | pre-EECP | post-EECP | 3-year |
|---|---|---|---|
| Number of patients | 1427 | 1427 | 1033 |
| Weekly angina (episodes/week) | 6 (3–14) | 1 (0–3)* | 1 (0–3)* |
| Weekly nitroglycerin use (times/week) | 3 (0–8) | 0 (0–2)* | 0 (0–2)* |
| Patients required nitroglycerin | 73.7 | 38.3* | 41.4* |
| Other medications | | | |
| Antiplatelets/coumadin | 80.4 | 80.3 | 78.4 |
| Beta-blockers | 73.9 | 75.2 | 72.2 |
| Long-acting nitrates | 79.0 | 78.2 | 73.1* |
| Calcium channel blockers | 45.2 | 44.0 | 40.3** |
| Lipid lowering agents | 74.3 | 75.5 | 76.0 |
| Angiotensin converting enzyme inhibitors/ angiotensin receptor blockers | 47.6 | 47.2 | 46.4 |

All data are percentages unless otherwise stated as median (interquartile range). * $p<0.001$ and **$p<0.05$ when compared to pre-EECP. *Abbreviations:* EECP = enhanced external counterpulsation.

TABLE 3: Cumulative 3-year repeat EECP and major cardiovascular event rates

| Clinical events | Cumulative event rates |
|---|---|
| Repeat EECP | 22.5 (20.1–24.9) |
| Percutaneous coronary intervention | 16.4 (14.3–18.5) |
| Coronary artery bypass grafting | 7.5 (6.0–9.0) |
| Myocardial infarction | 11.8 (10.0–13.7) |
| Death | 17.0 (14.9–19.1) |
| Major adverse cardiovascular events | 40.8 (38.8–43.5) |

Data are presented as percentage (95% CI). *Abbreviations:* CI = confidence interval; EECP = enhanced external counterpulsation.

report from a randomized controlled trial, the addition of EECP to optimal medical therapy reduces the mortality and MI rates in patients with CAD.[19] The 3-year mortality rate observed in our study is similar to that of a group of patients suffering from CCS IV angina and treated medically, or high-risk CABG candidates who had nonprognostic coronary lesions and received CABG or spinal cord stimulation.[20,21] Consistent with previous studies, the rate of revascularization in our study is high.[20] This reflects the dynamic nature of atherosclerosis that existing lesions may progress and new lesions may develop over time. Therefore, careful re-evaluation is required when there is a change in the symptom status.

The differences between patients who were and were not available for 3-year follow-up may be attributed to selection or survival bias. However, this has been minimized by only including patients from centers with at least 80% compliance in the follow-up data submission. Further, there are similarities between these 2 groups of patients. Although this is an observational study without a control group, it represents the experience of a diverse group of patients in an actual clinical setting. An EECP can benefit patients without the associated risk of other more invasive alternatives. Randomized controlled studies comparing different treatment modalities will help in identifying the most appropriate treatment option.

## Conclusion

An EECP can improve symptom control and QOL in a diverse group of patients suffering from chronic refractory angina. The immediate benefits can be sustained in the majority of patients for up to 3 years, especially in those with better baseline functional class and without diabetes or HF. This study highlights that patients with refractory angina can have significant long-term MACEs. Further effort is needed to address their unmet needs.


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## Conflict of Interest

Dr. Michaels received consulting fees and Speakers Bureau honoraria from Vasomedical Inc., Westbury, New York, USA.

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## References

1. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, et al.: The problem of chronic refractory angina: report from the ESC joint study group on the treatment of refractory angina. *Eur Heart J* 2002;23:355–370
2. Michaels AD, Accad M, Ports TA, Grossman W: Left ventricular systolic unloading and augmentation of intracoronary pressure and doppler flow during enhanced external counterpulsation. *Circulation* 2002;106:1237–1242
3. Taguchi I, Ogawa K, Oida A, Abe S, Kaneko N, et al.: Comparison of hemodynamic effects of enhanced external counterpulsation and intra-aortic balloon pumping in patients with acute myocardial infarction. *Am J Cardiol* 2000;86:1139–1141
4. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, et al.: The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol* 1999;33:1833–1840
5. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, et al.: Effects of enhanced external counterpulsation on health-related quality of life continue 12 months after treatment: a substudy of the multicenter study of enhanced external counterpulsation. *J Invest Med* 2002;50:25–32
6. Bagger JP, Hall RJ, Koutroulis G, Nihoyannopoulos P: Effect of enhanced external counterpulsation on dobutamine-induced left ventricular wall motion abnormalities in severe chronic angina pectoris. *Am J Cardiol* 2004;93:465–467
7. Urano H, Ikeda H, Ueno T, Matsumoto T, Murohara T, et al.: Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. *J Am Coll Cardiol* 2001;37:93–99
8. Loh PH, Louis AA, Windram J, Rigby AS, Cook J, et al.: The immediate and long-term outcome of enhanced external counterpulsation in treatment of chronic stable refractory angina. *J Intern Med* 2006;259:276–284
9. Barsness G, Feldman AM, Holmes DR, Holubkov R, Kelsey SF, et al.: The International EECP Patient Registry (IEPR): design, methods, baseline characteristic, and acute results. *Clin Cardiol* 2001;24:435–442
10. Lawson WE, Hui JC, Zheng ZS, Oster Z, Katz JP, et al.: Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. *Am J Cardiol* 1995;75:840–841
11. Bonetti PO, Barsness GW, Keelan PC, Schnell TI, Pumper GM, et al.: Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. *J Am Coll Cardiol* 2003;41:1761–1768
12. Masuda D, Nohara R, Hirai T, Kataoka K, Chen LG, et al.: Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina; evaluation by(13)N-ammonia positron emission tomography. *Eur Heart J* 2001;22:1451–1458
13. Masuda D, Fujita M, Nohara R, Matsumori A, Sasayama S: Improvement of oxygen metabolism in ischemic myocardium as a result of enhanced external counterpulsation with heparin pretreatment for patients with stable angina. *Heart Vessels* 2004;19:59–62
14. Bonetti PO, Holmes DR, Lerman A, Barsness GW Jr: Enhanced external counterpulsation for ischemic heart disease: what's behind the curtain? *J Am Coll Cardiol* 2003;41:1918–1925
15. Michaels AD, Raisinghani A, Soran O, de Lame PA, Lemaire ML, et al.: The effects of enhanced external counterpulsation on myocardial perfusion in patients with stable angina: a multicenter radionuclide study. *Am Heart J* 2005;150:1066–1073
16. Lawson WE, Hui JC, Kennard ED, Barsness G, Kelsey SF: Predictors of benefit in angina patients one year after completing enhanced external counterpulsation: initial responders to treatment versus nonresponders. *Cardiology* 2005;103:201–206
17. Soran O, Kennard ED, Kfoury AG, Kelsey SF: Two-year clinical outcomes after Enhanced External Counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from The International EECP Patient Registry). *Am J Cardiol* 2006;97:17–20
18. Feldman AM, Silver MA, Francis GS, Abbottsmith CW, Fleishman BL, et al.: Enhanced external counterpulsation improves exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 2006;48:1198–1205
19. Ma H, Zheng ZS, Zhang MQ, Du HJ, Cai NS, et al.: The multicenter research of enhanced external counterpulsation (EECP): One-year follow-up in patients with coronary heart disease. Presented at the first international external counterpulsation symposium. Guangzhou, China. May 2006
20. Allen KB, Dowling RD, Angell WW, Gangahar DM, Fudge TL, et al.: Transmyocardial revascularization: 5-year follow-up of a prospective, randomized multicenter trial. *Ann Thorac Surg* 2004;77:1228–1234
21 Andrell P, Ekre O, Eliasson T, Blomstrand C, Borjesson M, et al.: Cost-effectiveness of spinal cord stimulation versus coronary artery bypass grafting in patients with severe angina pectoris–long-term results from the ESBY study. *Cardiology* 2003;99:20–24