contraindication to fibrinolysis, the cases of facial or head trauma in our study were most likely minor injuries.

In the multivariable model, recent facial or head trauma conferred a 12-fold increased risk of intracranial hemorrhage after fibrinolysis. Even if the excess risk was half that number, the risk of intracranial hemorrhage after facial or head trauma would still be approximately 3%. Few patients would have a reduction in mortality greater than this with fibrinolysis; thus, minor facial or head trauma should be considered a contraindication to fibrinolysis. The risk associated with facial or head trauma should be considered for models designed to estimate the potential risks and benefits of fibrinolytic therapy.[3,4]

Risk factors for intracranial hemorrhage and nonhemorrhagic stroke are overlapping and divergent. Atrial fibrillation and warfarin therapy are risk factors unique to nonhemorrhagic stroke; facial or head trauma is unique to hemorrhagic stroke. Prior cerebrovascular disease and hypertension are often associated with both forms of stroke. Neither β-blocker nor nonsteroidal anti-inflammatory drug use is associated with either type of stroke. In the unadjusted model for nonhemorrhagic stroke, warfarin use was associated with greater risk than either previous cerebrovascular disease or diabetes mellitus. Warfarin therapy posed an even greater risk for nonhemorrhagic stroke than for intracranial hemorrhage, which suggests that warfarin use may be a marker rather than a causal agent for other comorbidities that predispose patients to cerebral infarction. Prior data[3] suggest that warfarin therapy not be considered a major contraindication to fibrinolysis without the presence of other risk factors for intracranial hemorrhage or a greatly prolonged international normalized ratio.

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Two-Year Outcomes After Enhanced External Counterpulsation for Stable Angina Pectoris (from the International EECP Patient Registry [IEPR])

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We assessed the long-term outcomes of enhanced external counterpulsation in relieving angina and improving the quality of life in a large cohort of patients with chronic angina pectoris. Seventy-three percent had a reduction by ≥1 angina class at the end of treatment, and 50% reported an improvement in the quality-of-life assessment after enhanced external counterpulsation; these results were sustained at 2-year follow-up. ©2004 by Excerpta Medica, Inc. (Am J Cardiol 2004;93:461–464)

Enhanced external counterpulsation (EECP) was approved by the Food and Drug Administration in 1995 to treat patients with coronary artery disease. EECP is a noninvasive counterpulsation technique that has been shown to reduce angina pectoris and to extend time to exercise-induced ischemia in patients with symptoms of stable angina.[1] In addition to relieving myocardial ischemia, EECP is associated with improved quality of life.[2,3] This technique uses sequential inflation of 3 sets of pneumatic cuffs wrapped around the lower extremities. The cuffs are inflated sequentially at the onset of diastole, producing aortic counterpulsation, diastolic augmentation, and increased venous return. At the onset of systole, the external pressure in the cuffs is released, producing a decrease in systolic pressure. A typical course of EECP involves 1 to 2 hours/day for a total of 35 hours of therapy. This report assesses the long-term outcomes of EECP in patients with angina 2 years after the procedure.

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The International EECP Patient Registry (IEPR) enrolls consecutive patients undergoing EECP for chronic angina. The IEPR began in January 1998, and 5,000 patients have been enrolled from >100 centers in the United States and other countries. Because the Registry aims to collect data on as broad a range of consecutive patients as possible, the criteria for

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TABLE 1 Demographic Factors at Baseline (n = 1,097)

Age (yrs) ± SD	65.8 ± 10.9
Men	74.0%
Systolic hypertension	68.4%
Hyperlipidemia	78.5%
Diabetes mellitus	42.9%
Noncardiac vascular disease	27.8%
Prior smoker	66.0%
Current smoker	7.2%

TABLE 2 Baseline Coronary Disease Factors and Revascularization Status (n = 1,097)

Interval since CAD diagnosis (yrs)	10.7 ± 8.1
Prior myocardial infarction	67.9%
Multivessel coronary artery disease	78.1%
Heart failure	32.4%
Left ventricular ejection fraction	46.2% ± 14.1
Prior percutaneous coronary intervention or bypass	87.5%
Anginal episodes/wk	10.7 ± 13.2
Angina class	
I	2.0%
II	11.0%
III	61.3%
IV	25.6%
Anginal episodes/wk	10.7 ± 13.2

Values are expressed as mean ± SD or percentage.

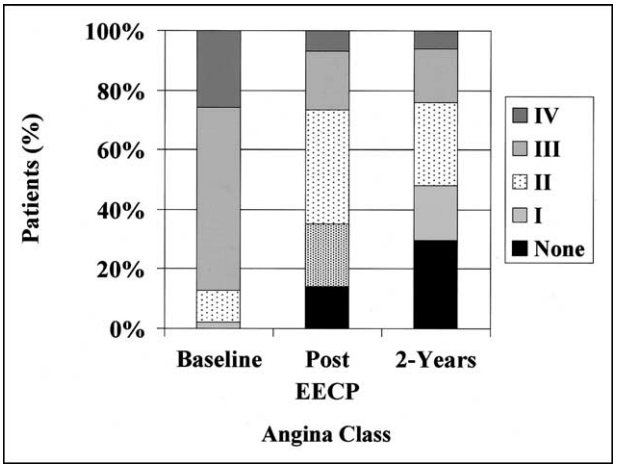

FIGURE 1. Angina class at baseline, immediately after EECP, and at 2-year follow-up.

entry are only that the patient give informed consent and have ≥1 hour of EECP treatment for chronic angina.

The Registry methods have been previously described.[4] All patients signed informed written consent before entry into the Registry. Briefly, the Registry methods involve collecting patient demographics, medical history, coronary disease status, and quality-of-life assessments before EECP treatment. After 35 hours of standard EECP treatment (Vasomedical, Westbury, New York), data are collected on Canadian Cardiovascular Society Classification (CCSC) of anginal status, antianginal medication use, and adverse

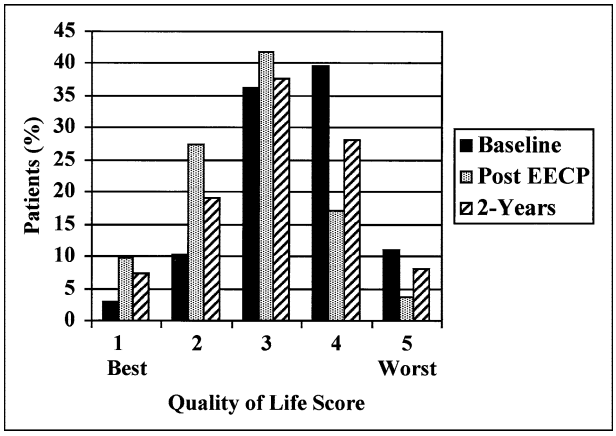

FIGURE 2. Quality-of-life assessment at baseline, immediately after EECP, and at 2-year follow-up.

clinical events. Each patient underwent a quality-of-life assessment using 5-point scales for health status, quality of life, and satisfaction with quality of life. Patients were interviewed by telephone 6 months after their last EECP treatment session, and yearly thereafter for 3 years to record anginal status, quality of life, and cardiac events. We analyzed baseline, immediate post-EECP, and 2-year data from 1,097 patients who started EECP before January 2001 from 24 sites contributing >85% of follow-up results.

In the statistical analyses, data are presented as percentages for categorical variables or as mean values ± SDs for continuous variables. Event rates were estimated using Kaplan-Meier survival analysis. The Cochran Armitage test for trend was performed to assess changes in medication use over time. Two-tailed p values <0.05 were considered significant.

This study examined 1,097 patients (mean age 65.8 ± 10.9 years; range 33 to 101) who underwent EECP for stable angina pectoris and who were enrolled in the IEPR. Ninety-five percent were Caucasian, and 74% were men (Table 1). Risk factors for coronary disease occurred often, including a high prevalence of hypertension (68%), hyperlipidemia (79%), diabetes mellitus (43%), noncardiac vascular disease (28%), and current or prior smoking (73%).

Patients had a long history of coronary artery disease, 10.7 ± 8.1 years before EECP treatment (Table 2). The cohort had a high prevalence of previous myocardial infarction (68%), multivessel coronary disease (78%), heart failure (32%), and previous coronary revascularization with either percutaneous coronary intervention (PCI; 64%) or coronary artery bypass graft surgery (CABG; 70%). Eighty-six percent of patients were not candidates for further revascularization with PCI or CABG. Most patients had CCSC III to IV (Figure 1 and Table 2). Quality of life before EECP was poor (Figure 2). Only 36% of patients rated their health as good or excellent (1 to 3 on a 5-point scale).

Of the 1,097 patients beginning EECP, 82% completed the 35-hour course of therapy, and 10% and 8% discontinued therapy because of clinical events and

TABLE 3 Clinical Outcomes After Enhanced External Counterpulsation (EECP) (n = 1,097)

Clinical Events	During EECP	Cumulative 2-yr Events
Death	0.3%	8.5%
Myocardial infarction	0.9%	8.9%
Unstable angina	3.4%	21.8%
Heart failure exacerbation	2.4%	11.7%
Cardiac hospitalization	NA	39.3%
Noncardiac hospitalization	NA	40.9%
Percutaneous coronary intervention	0.9%	11.0%
Coronary bypass	0.2%	5.2%
Repeat EECP	-	16.1%
Event-free survival	92.8%*	40.8%†
Angina Class	**Immediately After EECP**	**2 Yrs**
0	14.0%	29.7%
I	21.3%	18.4%
II	38.1%	27.8%
III	20.1%	17.9%
IV	6.7%	6.2%
Angina class <pre-EECP	73.0%	74.9%
Anginal episodes/wk (± SD)	2.8 ± 6.6	6.1 ± 10.4
Quality of Life	**Immediately After EECP**	**2 Yrs**
Health improved	54.5%	50.3%
Quality of life improved	53.2%	46.8%
Satisfaction improved	57.8%	51.1%

*Post-EECP event-free survival is defined as freedom from death, myocardial infarction, unstable angina, heart failure exacerbation, and coronary revascularization.

†Two-year event-free survival is defined as freedom from death, myocardial infarction, unstable angina, heart failure exacerbation, coronary revascularization, cardiac hospitalization, and repeat EECP.

TABLE 4 Medication Use (n = 1,097)

	Baseline	Post-EECP	2-yrs
β blockers	71.1%	71.1%	70.5%
Calcium channel blockers	48.4%	47.0%	46.4%
Nitrates (long-acting)	82.0%	79.8%	79.5%
Nitrates (as needed)*	72.9%	36.1%	47.9%
Angiotensin-converting enzyme inhibitors	37.8%	37.7%	37.8%
Angiotensin receptor blockers	8.9%	9.2%	7.3%
Lipid-lowering agents	70.2%	70.7%	69.2%
Aspirin†	75.1%	76.3%	72.1%

*$p < 0.001$; †$p < 0.01$, testing baseline versus 2 years.

patient preference, respectively. Reasons for stopping included problems with transportation, scheduling, or inability to tolerate the treatment. The total cohort completed 32.9 ± 10.0 hours of EECP. The adverse clinical event rate during the course of EECP was low (Table 3). There was a significant and dramatic reduction in CCSC immediately after the 35-hour session of treatment ($p < 0.001$; Figure 1 and Table 3). Of the total cohort, 73% of patients had a decrease in angina class of ≥1, 26% had no change in angina class, and 1% had an increase in angina class. The mean number of weekly anginal episodes decreased by 7.8 ± 12.3 ($p < 0.001$).

Immediately after EECP, quality of life was ranked good to excellent by 79% of patients, satisfaction with quality of life was ranked good to excellent by 74%, and overall health ranked good to excellent by 70% ($p < 0.05$ for all 3 measures). There was an improvement in health status for 55% of patients, in quality of life for 53% of patients, and in satisfaction with life for 58% of patients (all changes were statistically significant; $p < 0.001$) (Table 3).

Cumulative 2-year clinical outcomes for the study cohort showed that 9% of patients died, 22% had unstable angina, 9% had myocardial infarction, 12% had heart failure exacerbation, 41% had cardiac hospitalization, and 15% underwent revascularization with either PCI or CABG (Table 3). There was a sustained reduction in CCSC in survivors ($p < 0.001$) compared with that at baseline (Figure 1 and Table 3). At 2-year follow-up, quality of life was ranked good to excellent by 64% of patients, health was ranked good to excellent by 55% of patients, and satisfaction with quality of life was ranked good to excellent by 61% ($p < 0.05$ for all 3 measures compared with status before EECP). There was an improvement in health status in 50% of patients, in quality of life in 47% of patients, and in satisfaction with life in 51% of patients (Table 3).

Beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and hypolipidemic medications were similar at baseline, immediately after EECP, and at 2-year follow-up (Table 4). Nitroglycerin therapy decreased from a mean of 10.3 ± 13.5 times/week at baseline to 5.8 ± 7.9 after EECP and 8.1 ± 13.0 at 2-year follow-up ($p < 0.01$). There was a significant reduction in the use of aspirin or antiplatelet agents at 2-year follow-up ($p < 0.01$).

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These results represent the largest reported long-term follow-up series of consecutive patients treated with EECP for chronic stable angina pectoris. These patients showed a profile of long-standing multivessel coronary artery disease, a high prevalence of coronary disease risk factors, poor quality of life, and severe angina refractory to medical therapy or conventional revascularization. Most were not candidates for further coronary revascularization.

Most patients experienced a significant reduction in angina and improvement in quality of life after EECP therapy, and this reduction was sustained in

most patients at 2-year follow-up. Patients reported a significant decrease in the frequency of anginal episodes and nitroglycerin use. The sustained 2-year benefits of EECP seen in this registry are consistent with reports from previous clinical trials[1,2] and observational studies.[3,4]

The mechanism linking the acute coronary and ventricular hemodynamic effects during EECP[5] to sustained clinical improvement in angina pectoris remains under active investigation. Recent data support the hypothesis that improvement in endothelial function represents an important mechanism by which EECP exerts its clinical benefit.[6] Increases in shear stress may upregulate eNOS protein expression, resulting in a prolonged improvement in endothelial function.[7,8] Moreover, EECP may (1) increase coronary collateral perfusion by opening preformed collateral channels, (2) induce arteriogenesis and angiogenesis, and (3) provide stimuli similar to those of physical exercise, resulting in a peripheral "training effect."[6]

The extent to which the benefits of EECP persist over longer time periods is a crucial issue. One single-center, nonrandomized study demonstrated a 3-year sustained benefit in patients evaluated with stress thallium testing and angina status.[9] Another single-center, nonrandomized study reported 5-year morbidity and mortality rates comparable to that seen with CABG.[10]

A primary limitation of this analysis is the lack of a control group to assess the extent of the reported improvement due to other interventions (i.e., medical therapy, lifestyle modifications, coronary revascularization) or to a "placebo effect" that may be expected in a population of highly symptomatic patients enthusiastic for an emerging novel treatment. One study compared the clinical demographics and clinical outcomes from patients enrolled in the IEPR with those in the National Heart, Lung, and Blood Institute Dynamic Registry who underwent elective PCI.[11] However, there are significant challenges in identifying a proper comparison group and interpreting differences in outcomes from different registries. This observational registry study cannot directly evaluate whether the anti-ischemic effects observed in the randomized Multicenter Study of Enhanced External Counterpulsation trial[1] extends to a broader population of patients treated with EECP. Self-reported severity of angina based on mail or telephone interview is subject to potential bias, although coordinators in the IEPR were trained in assessing and defining follow-up symptoms. Selection and survival bias may account for differences among patients who were or were not available for 2-year follow-up, but to minimize this we only report on patients from sites with ≥85% follow-up retention.

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