

Chelation Therapy for Ischemic Heart Disease

A Randomized Controlled Trial

Merril L. Knudtson, MD

D. George Wyse, MD, PhD

P. Diane Galbraith, BN

Rollin Brant, PhD

Kathy Hildebrand, BN

Diana Paterson, BScN

Deborah Richardson, RN

Connie Burkart, BN

Ellen Burgess, MD

for the Program to Assess Alternative
Treatment Strategies to Achieve
Cardiac Health (PATCH)
Investigators

ISCHEMIC HEART DISEASE CONTINUES to be the leading cause of death and disability among North American adults. Testimonials of symptomatic improvement frequently lead patients with ischemic heart disease to seek alternative therapies that have not been scrutinized in clinical trials. One such therapy is the repeated intravenous administration of the chelating agent EDTA in combination with oral vitamins and minerals. Two small randomized controlled clinical trials showed no benefit of EDTA in patients with peripheral arterial disease,^{1,2} and the few available trials in ischemic heart disease are uninformative.³⁻⁵ Although the recent review by Ernst⁶ concluded that chelation therapy for coronary heart disease should be considered "obsolete," many patients continue to seek alternative therapy.⁷

There are no current data on the number of patients seeking chelation therapy. In 1993, Grier and Meyers⁸ estimated that more than 500 000 people in the United States are treated with EDTA therapy each year. In a recent Ca-

Context Chelation therapy using EDTA is an unproven but widely used alternative therapy for ischemic heart disease.

Objective To determine if current EDTA protocols have a favorable impact on exercise ischemia threshold and quality of life measures in patients with stable ischemic heart disease.

Design Double-blind, randomized, placebo-controlled trial conducted between January 1996 and January 2000.

Setting Participants were recruited from a cohort of cardiac catheterization patients and the practices of cardiologists in Calgary, Alberta.

Participants We screened 3140 patients, performed a qualifying treadmill test in 171, and enrolled 84. Entry criteria included age at least 21 years with coronary artery disease proven by angiography or a documented myocardial infarction and stable angina while receiving optimal medical therapy. The required treadmill test used a gradual ramping protocol and patients had to demonstrate at least 1-mm ST depression.

Interventions Patients were randomly assigned to receive infusion with either weight-adjusted (40 mg/kg) EDTA chelation therapy (n=41) or placebo (n=43) for 3 hours per treatment, twice weekly for 15 weeks and once per month for an additional 3 months. Patients in both groups took oral multivitamin therapy as well.

Main Outcome Measure Change from baseline to 27-week follow-up in time to ischemia (1-mm ST depression).

Results Thirty-nine patients in each group completed the 27-week protocol. One chelation patient had therapy discontinued for a transient rise in serum creatinine. The mean (SD) baseline exercise time to ischemia was 572 (172) and 589 (176) seconds in the placebo and chelation groups, respectively. The corresponding mean changes in time to ischemia at 27 weeks were 54 seconds (95% confidence interval [CI], 23-84 seconds; $P < .001$) and 63 seconds (95% CI, 29-95 seconds; $P < .001$), for a difference of 9 seconds (95% CI, -36 to 53 seconds; $P = .69$). Exercise capacity and quality of life scores improved by similar degrees in both groups.

Conclusion Based on exercise time to ischemia, exercise capacity, and quality of life measurements, there is no evidence to support a beneficial effect of chelation therapy in patients with ischemic heart disease, stable angina, and a positive treadmill test for ischemia.

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nadian study, 8% of patients who had undergone cardiac catheterization and responded to a survey had used chelation therapy.⁹ Assuming 8% of the 1.25 million US residents who have undergone cardiac catheterization¹⁰ have tried chelation therapy, we project that 100 000 have tried chelation therapy. Estimating a cost of \$4000 for the usual series of treatment sums to an annual expenditure of approximately \$400 mil-

lion. The actual amount is likely higher because these estimates do not include all the cardiac patients who do

Author Affiliations: Division of Cardiology, University of Calgary and Calgary Regional Health Authority, Calgary, Alberta.

A list of the PATCH Investigators appears at the end of this article.

Corresponding Author and Reprints: Merrill L. Knudtson, MD, Foothills Medical Center, 1403 29th St NW, Calgary, Alberta, Canada T2N 2T9 (e-mail: knudtson@shaw.ca).

not undergo catheterization and all other noncardiac patients who seek chelation therapy.

We undertook a randomized, double-blind, placebo-controlled clinical trial of chelation therapy using the American College for Advancement in Medicine (ACAM) protocol¹¹ to determine the efficacy of EDTA with respect to exercise ischemia threshold, symptoms, and quality of life in patients with stable ischemic heart disease.

METHODS

Study Subjects

Patients were recruited from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) cohort of cardiac catheterization patients¹² and the practices of community cardiologists in Calgary. Participants had to be aged 21 years or older and have coronary artery disease proven by coronary angiography or a documented myocardial infarction and stable angina while receiving optimal medical therapy. To qualify for randomization patients were required to have a treadmill test, using a gradual ramping protocol, demonstrating at least 1 mm of horizontal or downsloping ST-segment depression from the isoelectric line 80 milliseconds after the J point. The study protocol required detection of ST-segment depression between 2 and 14 minutes from the onset of exercise.

Exclusion criteria included planned revascularization, previous chelation therapy, evidence of heart failure, inability to walk on the treadmill, resting electrocardiographic (ECG) changes that would interfere with ischemic assessment, abnormal renal or liver function, or untreated lipid abnormality at the time of randomization.

Treadmill Testing

Treadmill testing was done at baseline and at 15 and 27 weeks after randomization. The protocol began with a level of exercise equivalent to 2 metabolic equivalents (METs) and increased slowly every 10 to 15 seconds, reaching an equivalent of 13 METs at 14 min-

utes. A 12-lead ECG was recorded every 20 seconds. Maximum oxygen consumption ($\dot{V}O_2\text{max}$) and anaerobic thresholds were determined by continuous measurement of expired gases using a gas analyzer (MedGraphics model CPX/D; MedGraphics Corporation, St Paul, Minn) calibrated online.

Randomization and Treatment

Patients were randomized in blocks of 10. Investigators were blinded to treatment assignment. The hospital pharmacy assigned the randomized therapy and prepared solutions for blinded administration of infusions. The 500-mL infusion solution of 5% dextrose in water for the active treatment containing disodium EDTA (Endrate; Abbott Laboratories, Abbott Park, Ill) was weight adjusted (40 mg/kg), with a maximum total dose for each treatment of 3 g. Each treatment solution also contained 750 mg of magnesium sulfate, 5 g of ascorbic acid, and 5 g of sodium bicarbonate (titrated to physiologic pH) in the 5% dextrose. Lidocaine, 80 mg, was added to relieve pain at the administration site. In the placebo infusion solution the EDTA was replaced by 20 mL of 0.9% sodium chloride. The infusion solutions were indistinguishable by color and labeling. The infusion solution was administered over 3 hours to minimize the potential unblinding effect of infusion-related adverse effects. All patients received treatments twice weekly for 15 weeks and once monthly for an additional 3 months, for a total of 33 treatments. In accordance with the ACAM protocol, patients in both groups took oral multivitamin therapy, 2 tablets 3 times daily as tolerated, except on treatment days. All patients were seen at the University of Calgary Cardiovascular Risk Reduction Clinic and had treatment of their risk profile optimized according to American Heart Association guidelines (including management of diet, lipid levels, angina, stress, and exercise).

Other Tests and Safety Monitoring

Dipstick urine testing was performed at each visit. Urinalysis and serum cre-

atinine were measured at every fifth visit. Hematology, electrolyte, and cholesterol panels were measured at baseline and at 15 and 27 weeks. The study nurse supervised patients throughout the duration of therapy, and hourly pulse and blood pressure measurements were obtained.

Study End Points

Exercise parameters and quality of life questionnaires were collected at 15 and 27 weeks after randomization. The primary end point was the change in time to reach at least 1 mm of ST-segment depression at the 27-week evaluation. Patients who did not achieve ischemic changes at 27 weeks had the test period truncated at 14 minutes, and 14 minutes was recorded as their "time to ischemia." Functional reserve was also measured by determination of $\dot{V}O_2\text{max}$ and time to reach anaerobic threshold. Quality of life instruments included the Duke Activity Status Index,¹³ Health Status Survey Short Form-36,¹⁴ and Seattle Angina Questionnaire.¹⁵

Follow-up and Clinical Events

All patients were followed up for 1 year from randomization. During this time, all clinical events were tabulated, including death, myocardial infarction, coronary artery bypass graft surgery, and percutaneous coronary intervention.

All patients signed an informed consent form. The Conjoint Ethics Committee of the University of Calgary and the Calgary Regional Health Authority approved this study and its consent form. All clinical events were reported to an independent safety monitoring committee.

Statistical Analysis

A sample size of 40 per group was chosen to provide 90% power to detect a 60-second difference in mean change in exercise time from baseline to the 27-week follow-up, assuming an SD of 80 seconds within each group. The 60-second difference was based on a minimally important difference determined by a consensus of Calgary cardiologists. Statistical analysis was

performed using S-plus, version 6.0 (Mathsoft, Seattle, Wash). Categorical variables were analyzed with the χ^2 or Fisher exact test, as appropriate. Continuous variables were examined with paired and unpaired *t* tests. Graphical examination of the data showed that normal assumption was viable. All reported significance levels are 2-sided, and $P < .05$ was set as the significance level. All analyses of exercise and quality of life data were conducted using last-observation-carried forward.

RESULTS

Patients

A total of 3140 patients (FIGURE) were screened and 171 of these agreed to undergo a qualifying exercise test. Eighty-four patients met the treadmill test criteria, consented, and were randomized between January 1996 and January 2000. Baseline characteristics according to treatment assignment are shown in TABLE 1. There were no important differences between the groups. Of the 84 patients randomized, 78 completed treatment, the final treadmill test, and the final quality of life assessments (39 in each group). Four placebo patients and 2 chelation patients were unable to complete the treatment phase (Figure).

Exercise End Points

At baseline, mean (SD) treadmill test times to ischemic ECG changes were 572 (172) seconds in the placebo and 589 (176) seconds in the chelation groups. Both groups were able to significantly ($P < .001$) increase their exercise time to ischemia at the 27-week treadmill test (TABLE 2). Changes in exercise measurements of functional reserve (time to anaerobic threshold and $\dot{V}O_2\text{max}$) are shown in Table 2. The magnitude of the increases in time to ischemic changes and to anaerobic threshold were not statistically different in the 2 groups. The increase in $\dot{V}O_2\text{max}$ was not significant at the 27-week treadmill test in the placebo group but the increase in the chelation group was significant ($P = .03$). However, the difference between these 2 results was not significant ($P = .46$).

Quality of Life

The changes in quality of life scores between baseline measurement and those obtained at the 27-week evaluation are shown in Table 2. There was a tendency for modest increases in quality of life scores in both groups with significant but similar improvements in the exertional capacity component of the Seattle Angina Questionnaire. Differences between the groups were not significant.

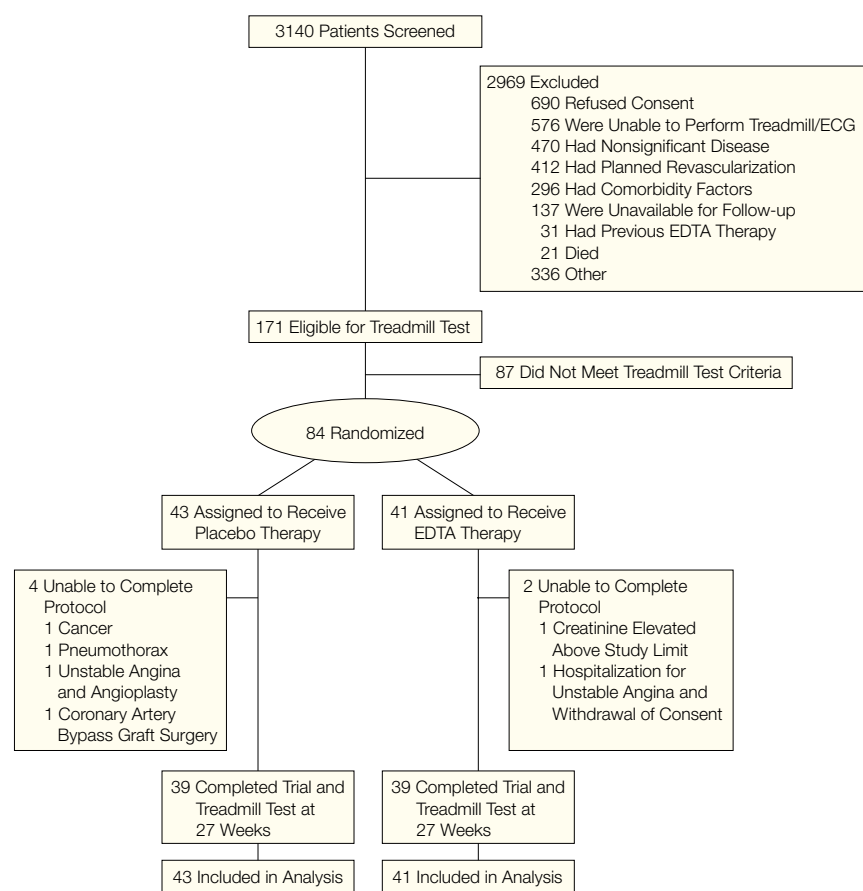
Ischemia and Other Clinical Events

Clinical events are presented on an intention-to-treat basis (all 84 patients included). The duration of follow-up was 1 year from randomization for each patient. There were no deaths during that time. One patient in the placebo group had a documented myocardial infarction and 6 other patients were admit-

ted at least once for worsening angina. Four of these 7 patients had angioplasty and none had coronary artery bypass graft (CABG) surgery for these events, although 1 other patient had elective surgery (CABG was planned by the cardiologist after randomization without investigators' knowledge). There was 1 myocardial infarction in the chelation group and 9 patients were admitted at least once for worsening angina. None of these had angioplasty or CABG surgery associated with these events.

One of the chelation patients was withdrawn from therapy because of an elevation in serum creatinine. During the first 10 treatments the patient's serum creatinine level increased from 1.5 to 2.1 mg/dL (129 to 186 $\mu\text{mol/L}$, respectively). Treatment was stopped

Figure. Flow of Patients in the Trial



ECG indicates electrocardiogram.

and the serum creatinine level decreased to 1.6 mg/dL (138 μ mol/L) after 10 weeks. No other cause for the elevation in creatinine was found. In addition to the nonischemic events shown in the Figure leading to discontinuation of therapy, 3 additional placebo patients were hospitalized for nonischemic events: gout, lumbar back pain from a herniated disk, and gastrointestinal bleeding. These events did not interfere with completion of the treatment phase. There were no electrolyte results out of normal range during the study.

COMMENT

The main finding of this study was that chelation therapy had no beneficial effect on exercise time to ischemia, functional reserve for exercise, and quality of life in patients with proven ischemic heart disease, stable angina, and evidence of ischemia on treadmill examination. Accordingly, chelation therapy remains unproven in the treatment of ischemic heart disease.

EDTA is an amino acid complex with a high affinity for divalent and trivalent cations such as lead, magnesium, zinc, iron, and calcium. Conventional

chelation therapy involves multiple infusions of EDTA to chelate lead, iron, copper, calcium, and other metal ions in a redox inactive state. Chelated metal ions are then excreted from the body in the urine. For this reason EDTA has been used as a chelating agent in clinical situations in which these elements are found in excess.¹⁶

Because calcium is often found in atheromatous plaques, early proponents hypothesized that EDTA might be effective in treating ischemic heart disease by liberating plaque calcium with a subsequent favorable change in the properties of the plaque.^{3,4,17,18} Other hypotheses possibly accounting for the symptomatic improvement reported by many patients with ischemic heart disease include a free radical-scavenging function, inhibition of lipid oxidation (antioxidant), reduction of total body iron stores, cell membrane stabilization, arterial dilation due to possible calcium channel blocking actions, or stimulation of prostacyclin production and improvement in arterial wall elasticity.^{3,4,17-21} Oxidized cholesterol plays an important role in endothelial function and the formation of atherosclerotic plaque.²² There is at least some evidence, albeit controversial, that increased total body iron stores are associated with increased ischemic heart disease.²³ Therefore, some of these hypotheses about chelation having a potential mechanism for benefit in ischemic heart disease have plausibility. In the absence of studies confirming such effects and, more importantly, confirming a definite clinical benefit of chelation therapy, it remains possible that anecdotal reported improvements are simply due to the spontaneous fluctuations in symptoms frequently seen in ischemic heart disease.²⁴⁻²⁷ In our trial, the 1-minute increase in exercise time to ischemia and the improvement in the exertional capacity component of the Seattle Angina Questionnaire in both groups is consistent with a combination of placebo²⁴⁻²⁷ and training effects²⁸⁻³⁰ commonly seen in studies of angina patients. Another potential explanation for improvement is that both

Table 1. Baseline Characteristics of Patients Completing Treatment*

Variable	Placebo (n = 43)	Chelation (n = 41)	P Value
Age, mean (SD), y	65 (8.5)	66 (9.1)	.86
Male sex, No. (%)	32 (83.7)	33 (85.4)	.93
Left ventricular ejection fraction, mean (SD), %	58 (13.1)	62 (11.2)	.11
Extent of CAD, No. (%)			
Single vessel	17 (39.5)	21 (51.2)	.39
Multivessel	26 (60.5)	20 (48.8)	
CCS angina class, No. (%)			
Asymptomatic	14 (32.6)	12 (29.3)	.53
I	17 (39.5)	22 (53.7)	
II	9 (20.9)	5 (12.2)	
III	2 (4.7)	2 (4.9)	
IV	1 (2.3)	0 (0)	
Previous cardiac events, No. (%)			
Myocardial infarction	12 (27.9)	20 (48.8)	.08
Percutaneous coronary intervention	19 (44.2)	19 (46.3)	.98
Coronary artery bypass graft surgery	12 (27.9)	10 (24.4)	.91
Comorbid conditions, No. (%)			
Diabetes	6 (14.0)	7 (17.1)	.93
Hypertension	28 (65.1)	23 (56.1)	.53
Hyperlipidemia	34 (79.1)	34 (82.9)	.86
Laboratory values, mean (SD), mg/dL†			
Total cholesterol	185 (34.7)	185 (30.9)	.77
HDL cholesterol	43 (8.9)	45 (13.1)	.54
LDL cholesterol	106 (27.0)	107 (22.4)	.97
Triglycerides	177 (132.7)	177 (79.6)	.97
Creatinine	1.0 (0.20)	1.1 (0.23)	.19
Medication use, No. (%)			
β -Blockers	32 (74.4)	30 (73.2)	.90
Calcium channel blockers	23 (53.5)	19 (46.3)	.51
Nitrates	19 (44.2)	10 (24.4)	.06
Triple therapy‡	11 (25.6)	5 (12.2)	.12
ACE inhibitors	13 (30.2)	11 (26.8)	.73
Aspirin	41 (95.3)	38 (92.7)	.61
Lipid-lowering agents	37 (86.0)	28 (68.3)	.05

*CAD indicates coronary artery disease; CCS, Canadian Cardiovascular Society; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and ACE, angiotensin-converting enzyme. The CCS scale is measured from I to IV, with a higher score indicating greater severity.

†To convert cholesterol values to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.0113. To convert creatinine to μ mol/L, multiply values by 88.4.

‡Triple therapy includes β -blockers, calcium channel blockers, and nitrates.

Table 2. Exercise Times, Oxygen Consumption, and Quality of Life Scores at Baseline and 27 Weeks*

Measurement	Placebo Group				Chelation Group				Group Comparison	
	Baseline, Mean (SD)	27 Weeks, Mean (SD)	Change, Mean (95% CI)	P Value	Baseline, Mean (SD)	27 Weeks, Mean (SD)	Change, Mean (95% CI)	P Value	Difference in Mean Change	P Value
Time to ischemia, s	572 (172)	626 (186)	54 (23 to 84)	<.001	589 (176)	652 (174)	63 (29 to 95)	<.001	9 (–36 to 53)	.69
Time to anaerobic threshold, s	555 (151)	571 (195)	16 (–27 to 59)	.45	555 (164)	585 (140)	31 (–11 to 72)	.14	15 (–44 to 73)	.63
$\dot{V}O_2$ max, mL/min	1606 (484)	1646 (419)	40 (–53 to 134)	.39	1591 (468)	1675 (432)	84 (10 to 159)	.03	44 (–74 to 162)	.46
DASI	37.4 (13.4)	39.3 (14.5)	1.9 (–0.6 to 4.5)	.13	42.2 (12.5)	41.9 (14.2)	–0.2 (–3.2 to 2.7)	.87	–2.1 (–6.0 to 1.6)	.26
SAQ exertion	64.8 (20.3)	73.2 (17.8)	8.3 (3.9 to 12.8)	<.001	69.9 (22.5)	77.2 (18.2)	7.3 (2.2 to 12.5)	.006	–1.0 (–7.7 to 5.7)	.77
SF-36 mental component summary	48.3 (10.4)	50.4 (9.2)	2.1 (–0.4 to 4.5)	.09	52.6 (7.6)	54.6 (6.7)	2.1 (–0.4 to 4.6)	.10	0.01 (–3.4 to 3.4)	.99
SF-36 physical component summary	39.9 (11.0)	44.9 (10.7)	5.0 (2.7 to 7.3)	<.001	42.9 (10.1)	45.1 (10.0)	2.2 (–0.5 to 4.9)	.11	–2.8 (–6.3 to 0.6)	.11

*CI indicates confidence interval. Maximum score on the Duke Activity Status Index (DASI) is 58.2, with a higher score indicating better physiologic reserve. Scores on the Seattle Angina Questionnaire (SAQ) range from 1–100, with a higher score indicating better levels of functioning. Scores on the Short-Form 36 (SF-36) range from 0–100, with a higher score indicating better health-related quality of life. Mean change values were rounded.

groups were treated with optimal risk reduction therapy.

Chelation therapy is practiced and promoted as a form of complementary or alternative medicine in many developed countries. Additional vitamins and mineral supplements are recommended for patients undergoing chelation therapy. In our study, both groups received multivitamins; we cannot exclude the possibility that these supplements could be partially responsible for the improvement that we saw in both groups.

In the literature, numerous authors have reported positive results in uncontrolled studies.^{3–5,31} Very few randomized clinical trials have been published on the effects of chelation therapy, and those that have been published were performed in patients with peripheral arterial disease.^{1,2} Olszewer et al³² published a small trial of 10 men with peripheral arterial disease in which improvement was demonstrated in walking distance after 20 treatments, but there were only 5 patients in each group and therapy was not blinded. Guldager and colleagues¹ published a randomized, double-blind, placebo-controlled trial of 153 male patients with peripheral arterial disease (75 EDTA and 78 placebo), and during the 6-month follow-up no effect of EDTA on walking time or ankle-brachial blood pressure index was demonstrated. That trial has

been criticized for the high dropout rate (123 completed 6-month follow-up). van Rij et al² published the results of a similar randomized, double-blind, placebo-controlled trial of walking time and ankle-brachial blood pressure indices in 32 patients (15 EDTA and 17 placebo) with claudication, which also showed no effect of EDTA therapy.

There is even less evidence in patients with ischemic heart disease. Kitchell et al⁵ conducted a placebo-controlled, double-blind, crossover study of 9 patients with coronary heart disease and assessed performance on a treadmill. The authors documented that 2 of 4 EDTA-treated patients benefited at 12 weeks but only 2 patients volunteered to be treated in the second phase, and neither patient showed improvement. No statistical analyses were presented in that study.

As with all randomized clinical trials, our results can be applied to fit only a similar population to that studied: patients with stable angina who are not candidates for revascularization and can exercise on a treadmill. Our study showed that following 33 treatments with EDTA therapy, there was no evidence of any benefit compared with placebo in either objective measurements of exercise capacity or in measurements of patient-perceived well-being. One patient receiving EDTA had a transient increase in serum creatinine. There

was no difference in the number of clinical ischemic events, but our study was not powered to detect any such differences. According to our findings, the use of chelation therapy to increase ischemic threshold and improve quality of life cannot be supported for patients with ischemic heart disease. Larger trials with a broader range of patients will be needed to assess the safety and impact of EDTA therapy on clinical event rates.

Author Contributions: Study concept and design: Knudtson, Wyse, Galbraith, Brant, Hildebrand.

Acquisition of data: Knudtson, Wyse, Galbraith, Hildebrand, Paterson, Richardson, Burkart, Burgess.

Analysis and interpretation of data: Knudtson, Wyse, Galbraith, Brant, Burgess.

Drafting of the manuscript: Knudtson, Wyse, Galbraith, Brant, Hildebrand, Burgess.

Critical revision of the manuscript for important intellectual content: Knudtson, Wyse, Galbraith, Brant, Hildebrand, Paterson, Richardson, Burkart.

Statistical expertise: Wyse, Galbraith.

Obtained funding: Knudtson, Wyse, Galbraith, Brant, Hildebrand.

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Study supervision: Knudtson, Wyse, Galbraith, Paterson, Burkart, Burgess.

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PATCH Investigators: Clinical Steering Committee Members: Merril L. Knudtson, MD, D. George Wyse, MD, PhD, Rollin Brant, PhD, Ellen Burgess, MD, James Stone, MD, James Mayhew, MD, Jeanette Soriano, MD, Janet Hammond, P. Diane Galbraith, BN. **Safety Monitoring Committee Members:** Paul Armstrong, MD, University of Alberta; Koon Teo, MD, McMaster University; G. B. John Mancini, MD, University of British Columbia. **Substudy Committee:** Merril L. Knudtson, MD, D. George Wyse, MD, PhD, Rollin Brant, PhD, P. Diane Galbraith, BN, Todd Anderson, MD, Ellen Burgess, MD, and Derek Exner, MD, MPH.

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