Cost-Effectiveness of Maintaining Daily Intake of Oat β-Glucan for Coronary Heart Disease Primary Prevention

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ABSTRACT

Purpose: Oat β-glucan reduces cholesterol levels and thus reduces the risk for coronary heart disease (CHD). However, its economic impact has not been well studied. We examined the economic impact of daily intake of ≥3 g of oat β-glucan in primary prevention of CHD in patients receiving statins or no pharmacologic treatment.

Methods: A decision model was developed to compare costs and outcomes associated with lowering cholesterol levels with no pharmacologic treatment and normal diet, no pharmacologic treatment plus ≥3 g/d of oat β-glucan, and statin therapy plus ≥3 g/d of oat β-glucan. The population comprised men 45, 55, or 65 years of age with no history of cardiovascular disease and a 10-year risk for CHD of 5%, 7.5%, or 10%. Clinical efficacy data were gathered from meta-analyses; safety data, costs, and utilities were gathered from published literature. Cost per quality-adjusted life years and number of first events were reported.

Findings: Maintaining ≥3 g/d of β-glucan may be cost-effective in men aged 45, 55, and 65 years with 10-year CHD risks of 5.0%, 7.5%, and 10.0% taking no pharmacologic treatment or on statins. It may also reduce first events of myocardial infarction and CHD death. Results are sensitive to oat β-glucan cost but insensitive to changes in other parameters. Maintaining ≥3 g of oat β-glucan daily remains cost-effective within plausible range of values.

Implications: β-glucan may be cost-effective for preventing CHD events in middle-aged men with no history of cardiovascular events whose 10-year CHD risk is ≥5%. Maintaining daily β-glucan intake may have considerable impact on first events. (*Clin Ther.* 2017;∎:∎∎∎–∎∎∎) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: β-glucan, cholesterol, coronary heart disease, cost-effectiveness, fiber, primary prevention.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally. Total direct medical costs associated with CVD may reach as high as $918 billion by 2030 in the United States.[1] A major risk factor for CVD is high cholesterol levels, for which statins are a primary prevention therapy. In an analysis of the National Health and Nutrition Examination Survey, the number of individuals eligible for statin therapy could rise from 37.5% to 48.6% for those assuming treatment according to practice guidelines. Thus, use of pharmacotherapy is increasing.

Primary prevention is aimed at reducing risk factors for coronary heart disease (CHD) in individuals who have no previous CHD events.[2] Lifestyle changes including dietary modifications are one of the first recommendations for lowering cholesterol levels in

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adults. Claims that dietary modification is associated with cholesterol-lowering effects are based on a diet of at least 3 g/d of β-glucan, a soluble fiber found in oats.[3] Although meta-analyses have examined the effect of β-glucan on cholesterol,[4–6] until recently, these analyses included older studies with intakes <3 g of β-glucan daily and/or did not consider β-glucan molecular weight. A recent meta-analysis of randomized controlled trials was performed to examine the impact of daily intake of at least 3 g of high-molecular-weight β-glucan on cholesterol levels.[7] Given this recent evidence, it is important to understand the economic impact of maintaining a diet of oat β-glucan. We performed an economic evaluation of adding 3 g of oat β-glucan daily to the diet of men with no history of CHD who are either receiving no pharmacologic treatment or who are taking statins.

PATIENTS AND METHODS

We updated a Markov model (University of North Carolina and Research Triangle Institute CVD Primary Prevention model)[8–12] to examine cost and outcomes associated with consumption of oat β-glucan. The model was programmed in Microsoft Excel 2010 for Windows (Microsoft Corporation, Redmond, Washington). The model was designed to simulate cohorts of healthy middle-aged men with no history of cardiovascular events and with various levels of 10-year risk for CHD (Figure 1). The model assumes all men begin in the healthy state (possible candidates for statin therapy with no history of CVD events) and then either begin treatment and/or supplement current treatment with a 3-g/d intake of β-glucan. Men transition through the model based on treatment type, and they accrue costs and utilities associated with each health state. Men who experience a CVD event transition to a postevent health state, in which they receive optimal secondary prevention. These men remain in the respective postevent health state until death.

Because the present analysis focused on primary CHD prevention, optimal secondary prevention was modeled by using increased costs, decreased utility preference, and increased risk of death, which were determined from published literature and applied to postevent health states. Men with myopathy are presumed to discontinue statin treatment and progress to postmyopathy, in which they advance through the model with the same CVD event risk

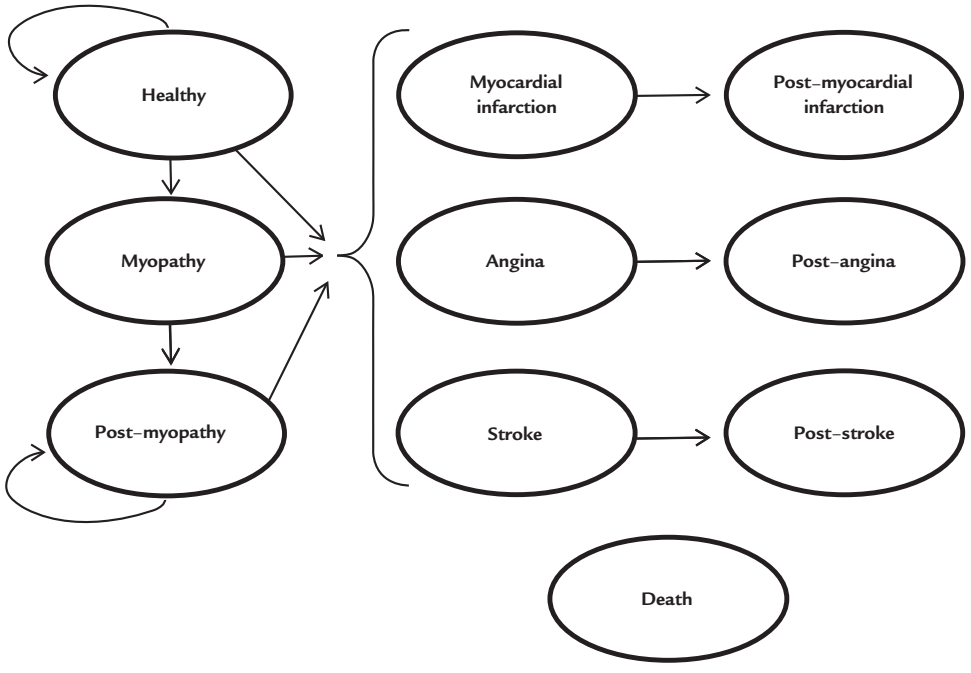

Figure 1. Model structure. Patients may progress to "death" from any health state.

as men with or without a purposefully increased intake of β-glucan.

Men were followed annually for the remainder of their lifetime. The model was populated with data from the published literature. The analysis was performed from a societal perspective, in which indirect costs were not considered. All costs and outcomes were discounted at 3% per annum.[13] Good modeling research practices and consolidated health economic evaluation reporting standards were followed.[14,15]

Patient Population

Patients in the base analysis were assumed to be healthy, middle-aged men with a starting age of 45 years, no history of CHD events, and a 7.5% 10-year CHD risk (eg, nonsmoker, no diabetes, systolic blood pressure of 120 mm Hg, total cholesterol level of 240 mg/dL, HDL level of 40 mg/dL). Analyses were also performed in men with starting ages of 55 and 65 years and 10-year CHD risk of 5.0%, 7.5%, and 10.0%.

Comparators

Men in the β-glucan and no pharmacologic treatment arm received at least 3 g of β-glucan daily via an intake of 75 g of oats daily.[7,16] Men treated with statins were assumed to receive 40 mg of generic simvastatin daily.[17] Men on a combination of β-glucan and statins received a minimum of 3 g of β-glucan through an intake of 75 g of oats daily and 40 mg of generic simvastatin daily. Other CHD preventive strategies, such as smoking cessation or hypertension treatment, were not considered. After 10 years of treatment, men were assumed to be receiving optimal primary preventive care, which may include 81 mg daily of generic aspirin and statins.

Baseline Event Probabilities

Baseline risks of initial CHD events (myocardial infarction [MI], angina, and CHD death) and stroke among patients receiving no pharmacotherapy were estimated from the Framingham risk equations using hypothetical scenarios of nonsmoking men without diabetes with varying levels of total cholesterol, HDL cholesterol, and systolic blood pressure risk factors.[18] Men aged 45, 55, and 65 years with 10-year CHD risks of 5.0%, 7.5%, and 10.0% were examined in model scenarios. These 10-year risks were translated into annual, event-related transition probabilities, assuming an exponential distribution. Probabilities were adjusted annually to reflect age-related increases in CHD and stroke risk. Baseline risk of myopathy was assumed to be zero.

Treatment Efficacy

Table I presents the base case clinical and mortality values and ranges.[7,19–30] The impact of statins on cardiovascular events was estimated by applying relative risks from published meta-analyses of randomized controlled trials, systematic synthesis of the literature, and trials to the age-based risks derived from the Framingham equations.[19–23]

Maintaining a daily dietary intake of fiber has been associated with a positive impact on CHD risks.[1] However, evidence of an impact of fiber intake on hard events (ie, MI, stroke, angina, CHD death, CVD death) is limited,[31] whereas the impact of β-glucan on cholesterol levels has been studied more thoroughly.[7,32,33] Therefore, the impact of at least 3 g/d of β-glucan was estimated from recently published meta-analyses[7] and was expected to reduce total cholesterol levels, with the majority of the effect due to reductions in LDL levels. To translate this effect of β-glucan on the risk of CHD hard events, we applied the change in total cholesterol levels to baseline patient characteristics (ie, age, sex, systolic blood pressure, HDL cholesterol level, smoker status, diabetes status, left ventricular hypertrophy status) used by the Framingham equations to generate risks for patients with no pharmacologic treatment and risk of CHD events for patients receiving β-glucan.

Among patients receiving both β-glucan and statins, the effects of β-glucan and statins were assumed to be independent (ie, additive). This assumption was examined in sensitivity analyses.

Adverse Events

An absolute risk of myopathy was applied for men taking statins.[19,24] β-glucan intake was not associated with a risk of myopathy, and no adverse events due to the consumption of β-glucan were assumed.

Mortality

Men in our population were assumed to have a mortality prevalence similar to that of the general population. Thus, age- and sex-specific all-cause mortality from the National Vital Statistics System life tables[34] was applied. Mortality was adjusted for changes in cardiovascular death, as estimated from the Framingham equations, to estimate cardiovascular

Table I. Base case clinical and mortality values and ranges.

Parameter	Base Case Estimate (Range)	Source/Assumption
Change in total cholesterol due to β-glucan intake, mmol/L	−0.30 (−0.35 to −0.24)	Whitehead et al (2014)[7]
Myopathy risk on statin therapy	0.001 (0.005 to 0.05)	Graham et al (2004)[24]; Pignone et al (2001)[19]
Relative risk of angina on statin therapy	0.68 (0.49 to 0.95)	Downs et al (1998)[20]
Relative risk of stroke on statin therapy	0.85 (0.57 to 1.28)	White et al (2000)[21]; Briel et al (2004)[22]
Relative risk of MI on statin therapy	0.70 (0.62, 0.79)	Pignone et al (2000)[23]
Mortality		
Increase in mortality due to stroke	0.144	Antithrombotic Trialists' (ATT) Collaboration et al (2009)[25]
Absolute risk of death due to myopathy	0.0016 (0.000001 to 0.0001)	Law and Rudnicka (2006)[26]
Relative risk of CHD death on statin therapy	0.80 (0.76 to 0. 85)	Cholesterol Treatment Trialists' (CTT) Collaborators et al (2012)[27]
All-cause reduction in death on statin therapy	0.79 (0.72 to 0.86)	LaRosa et al (1999)[28]
Increase in risk of death after MI	3.7 (3.0 to 4.7)	Lampe et al (2000)[29]
Increase in risk of death after angina	3.0 (2.1 to 4.2)	Lampe et al (2000)[29]
Increase in risk of death after stroke	2.3 (1.0 to 4.6)	Dennis et al (1993)[30]

CHD = coronary heart disease; MI = myocardial infarction.

and noncardiovascular death. Mortality increased as men aged in the model.

Mortality for patients taking statins was adjusted by using statin-specific relative risks of CHD death obtained from the literature (Table I).[25,27,28] The impact of β-glucan on CHD death was accounted for in the cardiovascular death risks generated by the β-glucan–specific Framingham equations. Increased risk of death after a CVD event was estimated by adjusting all-cause mortality according to hazard ratios obtained from the literature for secondary prevention patients.[29,30]

Costs

Table II presents base case cost and utility values and ranges.[2,16,17,26,36–52] Costs in the model included drug acquisition, oats, primary care, events, and postevent care costs.[17,26,35–47] Acquisition costs for generic statins were based on wholesale acquisition costs.[40] Men were assumed to be adherent to their statin treatment 69% of the time.[53] Purposeful maintenance of 3 g of β-glucan intake daily was estimated at $0.18 daily based on a cost of 75 g of oats daily, which is the amount of oats needed to obtain a minimum of 3 g of β-glucan daily.[7,16] We also examined the impact of a daily intake of 3 g of β-glucan at $0.00 daily, in which it was assumed there is no additional cost to individuals because consumption of oats should be part of an individual's normal daily diet.

Healthy men receiving no pharmacotherapy were assumed to incur 1 outpatient physician visit per year. Men receiving statins (alone or in combination with β-glucan) were assumed to incur 1 additional outpatient

Table II. Base case cost and utility values and ranges.

Parameter	Base Case Estimate (Range)	Source/Assumption
Costs		
Oats (per day)	$0.18	Estimated from costs of 42-ounce container and a need for 75 g/d of oats to achieve intake of 3 g/d of β-glucan (Rebello et al [2014][16]; Walmart [2015][36]; Walmart [2015][37]; Safeway [2015][38]; Harris Teeter [2015][39])
Statin (per day)	$0.0464	Micromedex 2.0. Red Book Online (2015)[40]; Simvastatin prescribing information (2009)[17]
Physician visit	$73.30	CPT code 99213[35]; Ingenix Inc (2015)[43]
Lipid panel	$26.95	CPT code 80061[35]; Ingenix Inc (2015)[43]
Annual health state costs		
Healthy, maintaining oat β-glucan diet	$114.99	National Cholesterol Educational Program Guidelines (2002)[2]; CPT codes 99213, 83701, and 84478[35]; Ingenix Inc (2015)[43]
Healthy, on statin therapy	$173.56	CPT code 80061 and (2) 99213; Ingenix Inc (2015)[43]
Myopathy*	$306.82	Law and Rudnicka (2006)[26]; Ingenix Inc (2015)[43]; HCUPnet (2015)[41]; US Bureau of Labor Statistics (2015)[44]
Angina*	$14,102	HCUPnet (2015)[41]; Russell et al (1998)[42]; US Bureau of Labor Statistics (2015)[44]
Post-angina	$7525	Russell et al (1998)[42]; US Bureau of Labor Statistics (2015)[44]
MI*	$26,458	HCUPnet (2015)[41]; Ingenix Inc (2015)[43]; Menzin et al (2008)[47]; US Bureau of Labor Statistics (2015)[44]
Post-MI	$5232	Menzin et al (2008)[47]; US Bureau of Labor Statistics (2015)[44]
Stroke*	$40,753	HCUPnet (2015)[41]; Ingenix Inc (2015)[43]; Leibson et al (1996)[45]; Lloyd-Jones et al (2010)[46]; US Bureau of Labor Statistics (2015)[44]
Post-stroke	$17,128	Ingenix Inc (2015)[43]; Leibson et al (1996)[45]; Lloyd-Jones et al (2010)[46]; US Bureau of Labor Statistics (2015)[44]
Utilities		
Healthy	1.0	Assumption
On statin therapy	0.9972 (0.9962 to 0.9980)	Hutchins et al (2015)[48]
Myopathy	0.983 (0.79 to 1.0)	Law and Rudnicka (2006)[26]
Post-myopathy	1.000	Assumption
Angina	0.929 (0.923 to 1.00)	Nease et al (1995)[49]
Post-angina	0.997 (0.997 to 1.00)	Nease et al (1995)[49]
MI	0.87 (0.82 to 0.92)	Tsevat et al (1993)[50]
Post-MI	0.91 (0.86 to 0.96)	Tsevat et al (1993)[50]
Stroke	0.61 (0.48 to 0.83)	Augustovski et al (1998)[51]
Post-stroke	0.830	Gore et al (1995)[52]
Death	0.0	Assumption

CPT = Current Procedural Terminology; HCUP = Healthcare Cost and Utilization Project; MI = myocardial infarction.
*Event health state costs represent the cost of the acute event and ongoing care.

physician visit and 1 additional serum lipid level test each year. Costs of events were obtained from the Healthcare Cost and Utilization Project database. Ongoing postevent care costs were estimated from the published literature.

All costs were reported in 2015 US dollars. Costs obtained for earlier years were converted to 2015 US dollars by using the Medical Consumer Price Index.[44]

Utilities

Utility weights, associated with each health state, were obtained from the published literature and were used to calculate quality-adjusted life years (QALYs). Utility weights measure a person's perception of well-being under certain health states. Utility weights ranged from 0.0 to 1.0, in which a utility of 1.0 represents perfect health and a value of 0.0 represents death (Table II).[26,48–52]

Model Calculations

For each treatment strategy, the following were derived: lifetime drug and other medical costs; life years; QALYs; number of first MI, first angina, and first stroke events and CHD deaths; and the incremental cost per QALY. The incremental cost per QALY, or incremental cost-effectiveness ratio, was calculated as follows:

$$\text{ICER} = (C_1 - C_2) \div (Q_1 - Q_2),$$

where C_1 is total cost incurred by men receiving the treatment of interest, C_2 is total cost incurred by men receiving status quo treatment, Q_1 is total QALYs accrued by men receiving the treatment of interest, and Q_2 is total QALYs accrued by men receiving status quo treatment. Treatment was considered cost-effective if the incremental cost per QALY was $50,000 or less, based on the World Health Organization's definition of an intervention being very cost-effective if the incremental cost-effectiveness ratio is <1 times the gross domestic product and the current gross domestic product of the United States.[54,55]

Analyses were run for men aged 45, 55, and 65 years at different levels of 10-year risk for CHD (5.0%, 7.5%, and 10.0%). Additional scenario analyses were performed to examine the effect if the cost of oats was assumed to be $0 daily. Break-even analyses were performed to estimate the daily cost of oats that would be required to maintain β-glucan intake at 3 g daily such that it was cost saving (incremental cost per QALY, $0 or less) and cost-effective (incremental cost per QALY, $50,000 or less).

Sensitivity Analyses

To test the robustness of model assumptions and specific parameters, we examined the effect of changing several parameters in both one-way and probabilistic (ie, second-order Monte Carlo simulation) sensitivity analyses. In one-way sensitivity analysis, the effect of varying individual parameters was examined by using plausible ranges of values (Tables I and II) from the literature with the use of 95% CIs of published values or by varying estimates by up to 50% in each direction. Parameters were ranked from most sensitive to least sensitive and plotted in a tornado diagram. Although all parameters were examined in sensitivity analyses, only the top 10 most sensitive parameters are presented graphically.

Probabilistic sensitivity analyses in which all parameters were varied simultaneously were also performed. We assumed parameter estimates followed a gamma distribution for relative risks of events, increases in mortality, and costs. Health-state utilities followed a beta distribution. Analyses were run 10,000 times to capture stability in results. Scatter plots were developed to represent uncertainty.

RESULTS

Base Case Analysis

Maintaining a diet of 3 g/d of β-glucan at a cost of $0.18 daily was a good value (incremental cost per QALY, $50,000 or less) for middle-aged men (ages 45, 55, and 65 years; 10-year CHD risk, 5.0%, 7.5%, or 10.0%) who were candidates for primary prevention and were receiving either no pharmacologic treatment or statins (Table III). If an individual's current diet was replaced (ie, daily cost of $0.00) with 3 g/d of β-glucan, β-glucan was cost saving (ie, more effective and less costly). Break-even analyses revealed that an individual's daily cost for maintaining a 3-g/d β-glucan intake could increase to $0.04 to $0.08 and remain cost saving, or to $0.44 to $0.78 and remain cost-effective (Supplemental Table A.I).

Maintaining 3 g daily of β-glucan was shown to reduce first MIs by up to 17% and CHD deaths by up to 18%. Younger and higher risk men were more likely to experience greater reductions.

Table III. Incremental cost per quality-adjusted life years in men aged 45, 55, and 65 years with 5.0%, 7.5%, and 10.0% risk of coronary heart disease (CHD).

	CHD Risk Level		
Comparison/Age Group	5.0%	7.5%	10.0%
β-glucan cost of $0.18 per day, $			
β-glucan vs no pharmacologic treatment			
45 years	12,666	14,252	11,885
55 years	10,459	7614	8588
65 years	8826	10,458	8556
β-glucan and statin vs statin only			
45 years	15,437	16,880	13,879
55 years	13,235	9684	10,624
65 years	11,704	13,507	10,946
β-glucan cost of $0.00 per day, $			
β-glucan vs no pharmacologic treatment			
45 years	−9097	−6533	−3769
55 years	−7189	−5710	−4585
65 years	−5886	−4939	−3940
β-glucan and statin vs statin only			
45 years	−8894	−6399	−3646
55 years	−7346	−5843	−4712
65 years	−6401	−5374	−4292

Table IV. Base case results: 45-year-old men with 7.5% 10-year risk of coronary heart disease (CHD).

Outcome	β-Glucan	No Pharmacologic Treatment	Absolute Difference	Relative Difference
Drug costs (per patient)	$2268	$972	$1296	133.35%
Other medical costs (per patient)	$17,313	$17,723	−$409	−2.31%
Total costs (per patient)	$19,581	$18,695	$887	4.74%
Life years	31.0	30.9	0.13	0.42%
Quality-adjusted life years	19.6	19.5	0.06	0.32%
Outcomes per 10,000 patients				
First angina	711.4	694.5	16.9	2.43%
First stroke	496.2	491.2	5.1	1.03%
First MI	1215.1	1300.6	−85.5	−6.57%
First CHD death	578.6	621.3	−42.7	−6.88%
Incremental cost-effectiveness ratio			$14,252	

MI = myocardial infarction.

Reductions were similar for men currently taking statins and men receiving no pharmacologic treatment (Supplemental Table A.II). As an example, in 45-year-old men with a 7.5% 10-year CHD risk (Table IV), 3 g/d of β-glucan reduced first MIs and CHD deaths by 6.0% (85 per 10,000 and 42 per 10,000 men, respectively) over their remaining lifetime. Although the occurrence of first stroke increased, this finding may be due to men living longer.

Sensitivity Analyses

Using 45-year-old men with a 7.5% 10-year CHD risk, we examined the sensitivity of results in response to changes in various input assumptions. The first assumption tested was the independent effect of β-glucan and statins among individuals taking statins who increased their intake of β-glucan to 3 g/d. Even when the combined effect was reduced such that only 10% of the benefit of β-glucan was incurred, maintaining a diet of 3 g/d of β-glucan remained cost-effective.

In men receiving no pharmacologic treatment who increased their intake of β-glucan to 3 g/d, the one-way sensitivity analysis revealed that results were most sensitive to changes in the daily cost of oats (Figure 2**A**). However, adding β-glucan remained cost-effective when changing the cost within a reasonable range. Changes in all other parameters within their plausible ranges did not change the direction of the results. Similar results were observed among men currently taking statins who increased their intake of β-glucan to 3 g/d (Figure 2**B**).

When varying all parameters simultaneously, the probabilistic sensitivity analysis revealed a cost-effective result in 99.99% of simulations in men who were not taking pharmacologic treatment and maintained 3 g of β-glucan intake daily compared with men receiving pharmacologic treatment alone (Supplemental Figure). Similarly, 100% of simulations were cost-effective in men who were taking statins and maintained 3 g of β-glucan intake daily compared with men taking statins alone.

DISCUSSION

The present study examined the cholesterol-lowering effects of maintaining 3 g/d of oat β-glucan on costs and outcomes in middle-aged men with no previous cardiovascular events and with 10-year risks of CHD of 5.0%, 7.5%, and 10.0%. We found that purposeful maintenance of 3 g/d of oat β-glucan would be cost-effective in men currently taking statins and in those receiving no pharmacologic treatment.

To the best of our knowledge, this study is the first to model the direct impact of maintaining a daily intake of 3 g of oat β-glucan on total cholesterol. Although other studies have examined the impact of various dietary changes on CHD,[56–60] none have explicitly examined the effects of oat β-glucan. Prosser et al[56] examined the impact on primary prevention of National Cholesterol Education Program Step 1 diet therapy, assuming the diet reduced total cholesterol levels by 6.5 mg/dL, compared with no treatment or treatment with statins. In contrast, a recent meta-analysis by Whitehead et al[7] revealed a reduction in total cholesterol levels of ~11.6 mg/dL when maintaining intake of 3 g of oat β-glucan daily. Results of our analysis of oat β-glucan versus no pharmacologic treatment are consistent with the findings of Prosser et al.

Using updated meta-analysis results for the effects of 3 g/d of oat β-glucan, we observed that maintaining adequate levels of oat β-glucan may have a more significant impact on costs and outcomes. Unlike Prosser et al,[56] however, we examined the impact of adding oat β-glucan to a diet in individuals already taking a statin, whereas Prosser et al compared the use of a statin with National Cholesterol Education Program Step 1 diet therapy. This comparison was likely to be highly relevant in 2000, as individuals were more likely to monitor their diet than take medication. In contrast, statin use has become significantly more prevalent in recent years due to inexpensive and effective pharmacotherapy to treat cholesterol levels. Our study, therefore, addresses an important question by determining the economic impact of maintaining daily consumption of oat β-glucan in addition to current care.

One limitation of our analysis is the assumption that the cholesterol-lowering effect of oat β-glucan translates into a reduction in hard clinical events. Although we used the effect of oat β-glucan on total cholesterol to determine the effect on the risk of CHD events, Whitehead et al[7] showed that most, if not all, of the effect of β-glucan on total cholesterol was due to reduced LDL cholesterol levels. Although there

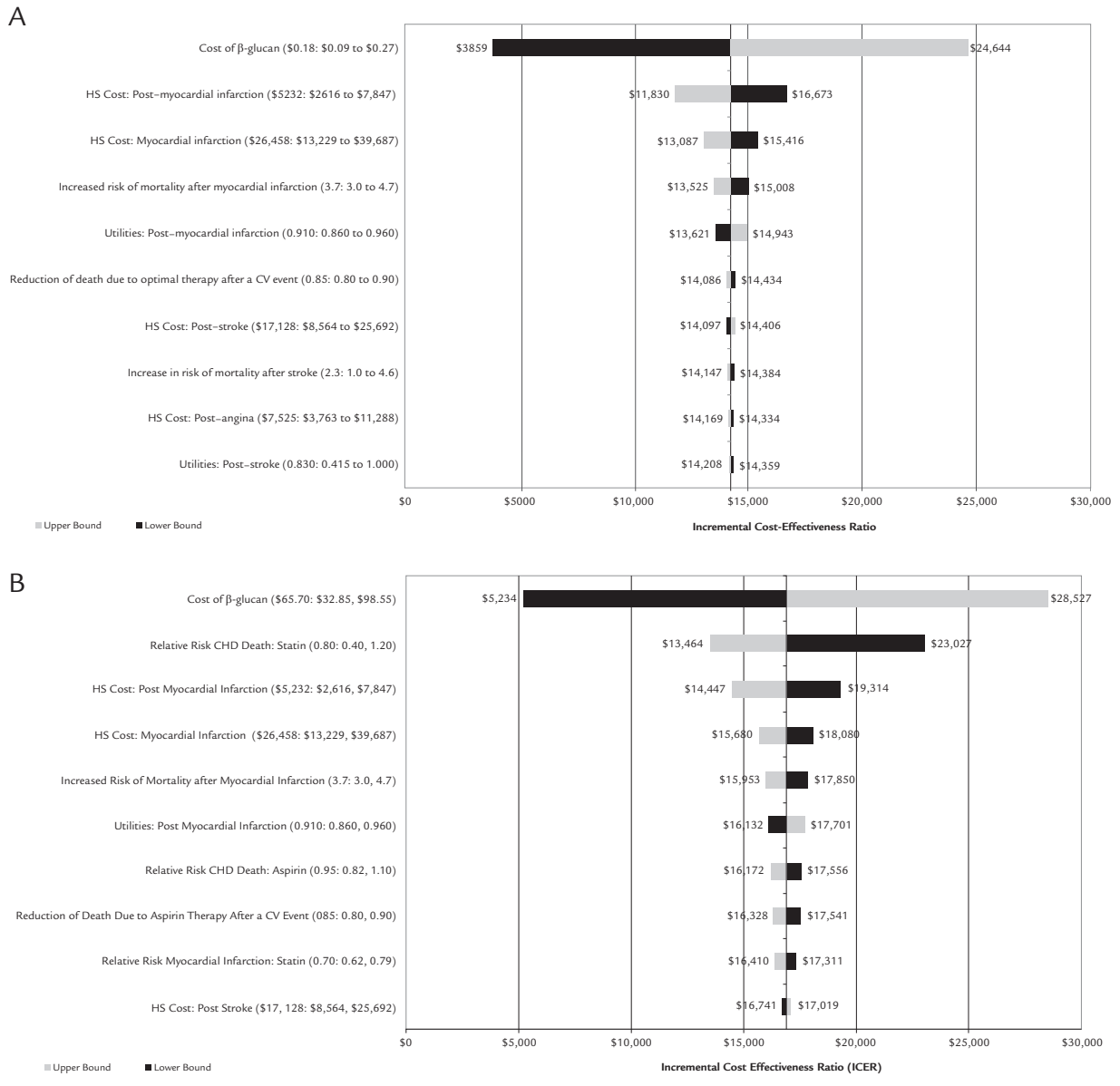

Figure 2. Results of one-way sensitivity analysis in 45-year-old men with 7.5% 10-year coronary heart disease (CHD) risk. (A) Sensitivity of results to changes in parameters when adding β-glucan to no pharmacologic treatment. The graphic presents the results of the one-way sensitivity analysis for men undergoing no pharmacologic treatment with a 7.5% 10-year risk of CHD when maintaining β-glucan intake at 3 g/d. Gray-shaded bars represent the upper bound of the parameter, and black-shaded bars represent the lower bound of the parameter. Baseline incremental cost per quality-adjusted life year on the x-axis is $14,252. (B) Sensitivity of results to changes in parameters when adding β-glucan to statin therapy. The graphic presents the results of the one-way sensitivity analysis for men on statin therapy with a 7.5% 10-year risk of CHD when maintaining β-glucan intake at 3 g/d. Gray-shaded bars represent the upper bound of the parameter, and black-shaded bars represent the lower bound of the parameter. Baseline incremental cost per quality-adjusted life year on the x-axis is $16,880. CV = cardiovascular.

remains strong evidence to support the LDL cholesterol hypothesis from large pooled analyses of statins[61] and statin plus ezetimibe trials,[62] and now preliminary data from early trials using the proprotein convertase subtilisin-kexin type 9 inhibitors,[63,64] not all pharmacologic methods for lowering LDL cholesterol have shown benefit.[65] The same is true for dietary strategies to reduce LDL cholesterol levels and CHD risk through a reduction in saturated fats, wherein the benefit seems restricted to replacement with mixed omega-3/omega-6 sources[66,67] or for carbohydrates to whole grains and low-glycemic foods.[68,69]

Although the direct impact of oat β-glucan on CHD events was not the focus of the present study, we believe these results are robust. First, a meta-analysis by Gordon[70] showed that lowering cholesterol levels via dietary modification reduces CHD risk to the same degree as pharmacotherapy. Second, in a more recent meta-analysis, Tang et al[31] reported that the highest amounts of whole grain intake were associated with a reduction in the risk of CHD. We were unable to include this effect in our analysis because highest whole grain intake was not explicitly defined. However, this finding suggests that dietary modification is associated with CHD events.

Another limitation is that the present analysis was limited to middle-aged men. Because CHD risk differs between men and women, these modeled results should not be generalized to women. It will be important to expand this analysis to include women and younger individuals. Further limitation of this simulation is the major assumption of daily consumption and consistent impact of β-glucan on cholesterol lowering. Its chemical structure and physiologic properties vary depending on plant source, variety, food processing, and preparation. Thus, its effect on cholesterol lowering is heterogeneous and premised on frequency of consumption not commonly attained. Lastly, studies on the cholesterol-lowering effect of oat β-glucan are of short duration compared with the 10-year exposure modeled here.

Further limitations include that utility values for estimating QALYs were drawn from different studies using various elicitation methods and with differences in the patient populations. Although not an optimal approach to deriving QALYs, sensitivity analyses showed that the results were relatively insensitive to changes in these values. The analysis also explicitly excludes indirect costs. These costs were excluded because of the limited availability of data. Including these costs and others would accurately represent the societal reference case as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine[71] and likely bolster the cost-effectiveness/cost savings.

There has been a shift toward more dietary pattern–based approaches to cardiovascular risk reduction,[72] which is reflected in recent general dietary guidelines.[73] Foods are not consumed in isolation, and healthy eating patterns that consist of multiple interacting food components are associated with a reduced risk of CVD. If one takes advantage of these interactions by creating a dietary portfolio of cholesterol-lowering foods that include β-glucan from oats along with other sources of viscous fibers, vegetable protein, nuts, and plant sterols, there is then evidence from randomized controlled trials that it is possible to achieve meaningful reductions in LDL cholesterol similar to that seen with early generation statins[74] and sustainable in an adherence-dependent manner for up to 6 months.[75] Future research will need to assess whether the addition of oats to other healthy dietary patterns that include foods with complementary mechanisms for lowering cholesterol will continue to exhibit an additive effect on cholesterol lowering.

CONCLUSION

A majority of American's intake of foods and food components associated with reduced risk of CVD, such as whole grains, legumes, fruit vegetables, and fiber, is below recommended levels of intake.[76] Therefore, opportunity exists to promote healthy eating patterns, rich in cholesterol-lowering foods, with few side effects and little or no harm. Patient values and preferences may preclude or lead to discontinuation of lipid-lowering drugs. As the population ages and the use of low-cost statins grows, statin intolerance will also become more prevalent, and some patients will continue to have suboptimal responses. As such, not all patients will reach their target with the use of drugs alone. A healthy diet should continue to be the cornerstone of therapy and an important add-on therapy for primary prevention.

Maintaining β-glucan intake of at least 3 g/d is not only beneficial for lowering total and LDL cholesterol levels, but maintaining this level of intake may have

considerable impact on events in middle-aged men whose 10-year risk for CHD is $\geq 5\%$ and with no history of cardiovascular events, regardless of whether they are currently taking statins. Our analysis suggests this beneficial effect translates to β-glucan intake being good value for money (ie, cost-effective). As a result, a positive public health effect both from the outcomes and economic perspective could result.

CONFLICTS OF INTEREST

Dr. Earnshaw and Ms. McDade are employees of RTI Health Solutions, an independent contract research organization that has received research funding for this and other studies from PepsiCo and pharmaceutical companies that market drugs to prevent cardiovascular events and other conditions. Ms. Fleige and Dr. Chu are employees of PepsiCo, which manufactures Quaker Oats, a product that contains β-glucan.

Dr. Sievenpiper is an employee of the University of Toronto and St. Michael's Hospital. He has received research support from the Canadian Institutes of health Research (CIHR), Canadian Diabetes Association (CDA), PSI Foundation, Banting and Best Diabetes Centre (BBDC), Canadian Nutrition Society (CNS), American Society for Nutrition (ASN), Calorie Control Council, INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Coca-Cola Company (investigator initiated, unrestricted), Dr. Pepper Snapple Group (investigator initiated, unrestricted), and The Tate and Lyle Nutritional Research Fund at the University of Toronto. He has received speaker fees and/or honoraria from the Canadian Diabetes Association (CDA), Canadian Nutrition Society (CNS), University of Alabama at Birmingham, Dr. Pepper Snapple Group, Dairy Farmers of Canada, Nutrition Foundation of Italy (NFI), C3 Collaborating for Health, Sprim Brasil, WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, and Pulse Canada. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of the Canadian Diabetes Association (CDA), European Association for the study of Diabetes (EASD), and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the American Society for Nutrition (ASN). He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Unilever Canada.

Employees of PepsiCo were involved in the conduct of the study, interpretation of the data, and review and approval of the manuscript. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Dr. Earnshaw and Ms. McDade were involved in the conceptual design; acquisition, analysis, and interpretation of data; drafting and critical revision of the manuscript; statistical analysis; and obtaining funding. Ms. Fleige and Dr. Chu were involved in the conceptual design; acquisition, analysis, and interpretation of data; critical revision of the manuscript; obtaining funding; and supervision. Dr. Sievenpiper was involved in the acquisition, analysis, and interpretation of data; critical revision of the manuscript; statistical analysis; administrative, technical, and material support; and supervision.

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Note that the sponsors of these personnel awards require that this last disclosure be included as part of the acknowledgement or funding statement. Please do not expand the abbreviation "CIHR INMD/CNS..." (as this is the exact name of the award). This statement does not need to be replicated in Dr. Sievenpiper's COI statement,

as all sources have been included separately in his COI statement as part of his research support disclosure.

SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.012.

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SUPPLEMENTARY MATERIAL

See Figs A.1A and A.1B.
Appendix Tables A.I. and A.II.

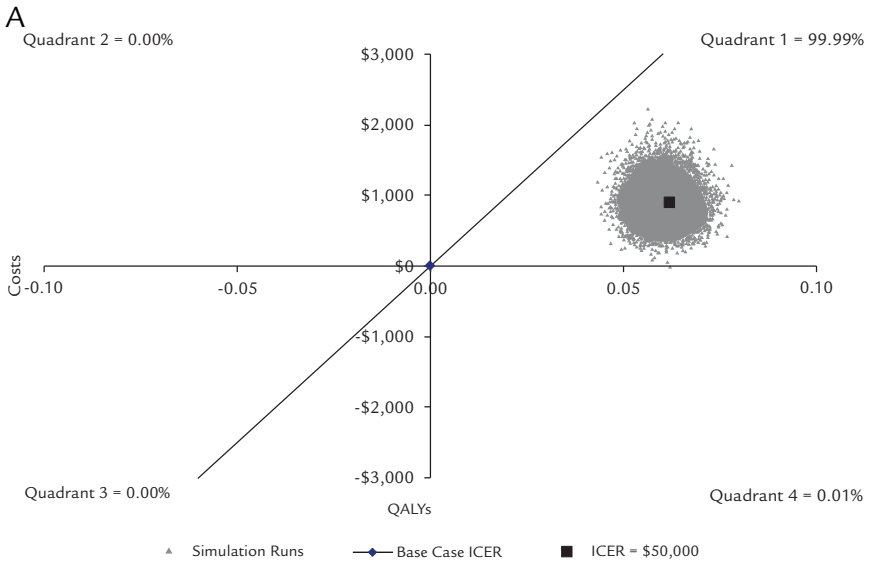

Fig A.1A. Probabilistic sensitivity analysis results in 45-year old men with 7.5% 10-year CHD risk. The diagonal line represents the ICER of 50,000. Individual dots represent results for each of 10,000 iterations of the model.

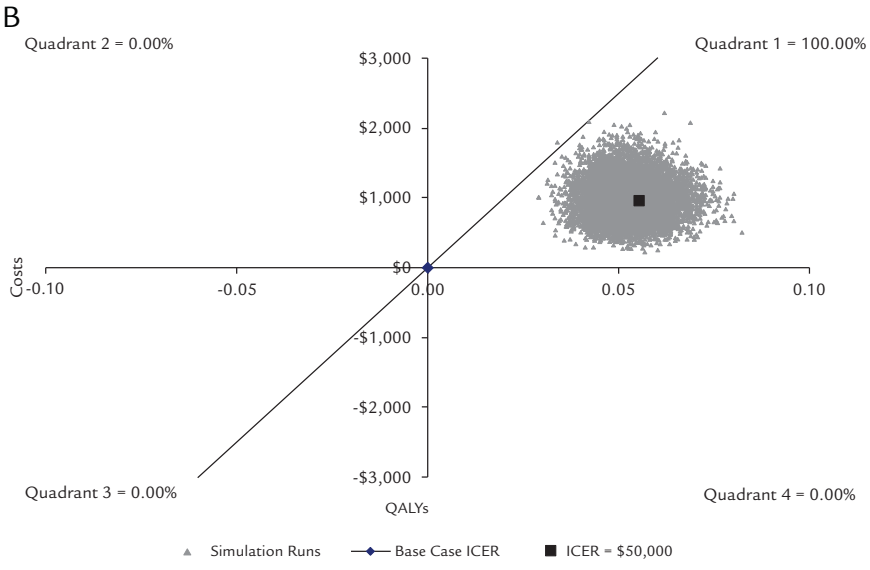

Fig A.1B. Probabilistic results when adding β-glucan to status therapy. The diagonal line represents the ICER of 50,000. Individual dots represent results for each of 10,000 iterations of the model.

Appendix Table A.I. Break-even Costs for Maintaining 3 g per Day of β-glucan.

Comparison/Age Group	CHD Risk Level 5.0%	7.5%	10.0%
Break-even cost to maintain cost savings (incremental cost per QALY ≤ $0)			
β-glucan vs. no pharmacologic treatment			
45 years	$0.08	$0.06	$0.04
55 years	$0.07	$0.08	$0.06
65 years	$0.07	$0.06	$0.06
β-glucan and statin vs. statin only			
45 years	$0.07	$0.05	$0.04
55 years	$0.06	$0.07	$0.06
65 years	$0.06	$0.05	$0.05
Break-even cost to remain cost-effective (incremental cost per QALY ≤ $50,000)			
β-glucan vs. no pharmacologic treatment			
45 years	$0.49	$0.49	$0.62
55 years	$0.58	$0.75	$0.75
65 years	$0.68	$0.64	$0.78
β-glucan and statin vs. statin only			
45 years	$0.44	$0.44	$0.55
55 years	$0.50	$0.65	$0.64
65 years	$0.56	$0.53	$0.64

CHD = coronary heart disease; QALY = quality-adjusted life year.

Appendix Table A.II. Avoided Myocardial Infarction and CHD Deaths.

Comparison/Age Group	CHD Risk Level 5.0%	7.5%	10.0%
Myocardial infarctions avoided per 10,000 (relative reduction)			
β-glucan vs. no pharmacologic treatment			
45 years	86.6 (11.14%)	85.5 (6.57%)	109.8 (6.52%)
55 years	71.5 (13.63%)	92.4 (11.09%)	89.3 (7.73%)
65 years	58.6 (18.38%)	58.5 (11.53%)	70.4 (9.07%)
β-glucan and statin vs. statin only			
45 years	82.8 (11.08%)	81.7 (11.05%)	104.7 (6.51%)
55 years	66.6 (13.56%)	86.0 (11.05%)	83.1 (7.73%)
65 years	52.5 (18.32%)	52.4 (11.53%)	63.2 (9.09%)
CHD deaths avoided per 10,000 (relative reduction)			
β-glucan vs. no pharmacologic treatment			
45 years	41.9 (11.56%)	42.7 (6.88%)	61.3 (7.42%)
55 years	41.0 (13.73%)	55.3 (11.53%)	56.0 (8.31%)
65 years	38.6 (17.98%)	38.0 (11.22%)	48.8 (9.33%)
β-glucan and statin vs. statin only			
45 years	41.2 (11.51%)	41.9 (11.44%)	60.0 (7.38%)
55 years	39.2 (13.63%)	52.7 (11.44%)	53.3 (8.25%)
65 years	35.4 (17.83%)	34.7 (11.12%)	44.6 (9.27%)

CHD = coronary heart disease.