RESEARCH

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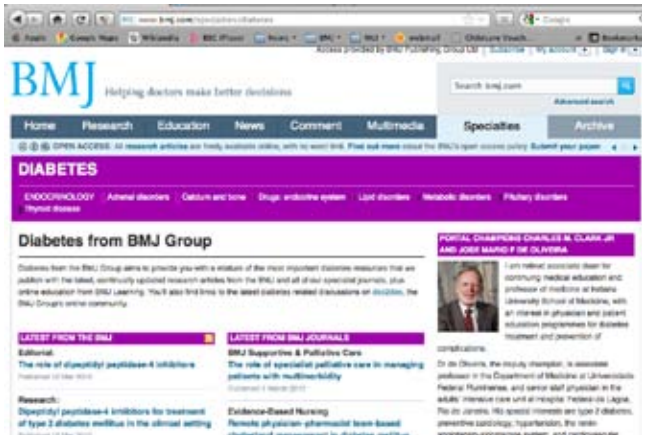


Recently published

Use of pioglitazone and risk of bladder cancer in people with type 2 diabetes
http://www.bmj.com/content/344/bmj.e3645

Metformin is not significantly different from insulin in preventing fetal macrosomia in women with gestational diabetes
http://ebm.bmj.com/content/17/3/88

Diabetic ketoacidosis and hyperosmolar non-ketotic state
http://learning.bmj.com/learning/module-intro/.html?channelCode=hospitaldoctor&channelFamilyConfig=bmj&moduleId=6050648

What our readers think

Effectiveness and cost effectiveness of dark chocolate consumption as prevention therapy in people at high risk of cardiovascular disease [http://www.bmj.com/content/344/bmj.e3657]

This study (see p 18) was published on bmj.com on 31 May and triggered a heated debate in the media. Here's what some of our rapid responders said:

"The study did not look at the practicalities of substituting the rest of the daily diet for this 100 g consumption. In reality, if the 100 g is palatable the majority are going to add this to the diet, not substitute it. The study, far from solving some of our obesity and cardiovascular time bombs, seems to be adding to the weight of these problems on the health profession."

"This study tried to specify effects: polyphenols without considering the diet as a whole, relate to changes in blood parameters. This means ignoring underlying variables that could change the interpretation of the results both quantitatively and qualitatively . . . The blood parameters adjusted for in the classification, but not the dietary habits, could interfere and hence may not allow the extra contribution of chocolate to be addressed."

"The authors list $42 (£25) as a pure cost. However, unlike medications that provide no benefit to patients beyond the hoped for reduction in non-fatal and fatal events, consumption of dark chocolate has intrinsic value to most patients. As a result, the cost attributed to the prevention strategy is too high and dark chocolate consumption should be even more cost effective than predicted by the authors."

Read more at http://www.bmj.com/content/344/bmj.e3657?tab=responses

RESEARCH ONLINE: For this and other new research articles see www.bmj.com/research

Mortality and implant revision rates of hip arthroplasty in patients with osteoarthritis

This registry based cohort study found a small but significantly increased risk of revision with uncemented rather than cemented total hip replacement, and a small but significantly increased risk of death with cemented procedures. It is not known whether these are causal relations or caused by residual confounding, say the authors.

Ursodeoxycholic acid versus placebo, and early term delivery versus expectant management, in women with intrahepatic cholestasis of pregnancy: semifactorial randomised clinical trial

Lucy C Chappell,[1] Vinita Gurung,[2] Paul T Seed,[1] Jenny Chambers,[3] Catherine Williamson,[3] James G Thornton,[4] on behalf of the PITCH Study Consortium

[1]Women's Health Academic Centre, King's Health Partners, UK
[2]Birmingham City Hospital, Birmingham, UK
[3]Department of Surgery and Cancer, Imperial College London, UK
[4]Nottingham Clinical Trials Unit, Nottingham Health Science Partners, Queen's Medical Centre, Nottingham NG7 2UH, UK
Correspondence to: J G Thornton
jim.thornton@nottingham.ac.uk

Cite this as: *BMJ* 2012;344:e3799
doi: 10.1136/bmj.e3799

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e3799

STUDY QUESTION

Does ursodeoxycholic acid reduce itching in intrahepatic cholestasis of pregnancy, and what is the effect of early term delivery on caesarean section rates?

SUMMARY ANSWER

Ursodeoxycholic acid significantly reduces pruritus, but the size of the benefit may be too small for most doctors to recommend it or for most women to want to take it. Individual women are likely to differ in whether they consider the benefit to be worthwhile. Planned early term delivery seems not to increase caesarean section rates.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Intrahepatic cholestasis of pregnancy is associated with preterm birth and fetal asphyxial events. Ursodeoxycholic acid and early delivery are widely used interventions of unproved efficacy. This study, the largest of ursodeoxycholic acid in intrahepatic cholestasis of pregnancy, shows that the drug significantly reduces itching but that the size of the benefit is small.

Design

A semifactorial randomised controlled trial of ursodeoxycholic acid versus placebo, and of delivery by 38 weeks' gestation or expectant management, for intrahepatic cholestasis of pregnancy.

Participants and setting

125 women with intrahepatic cholestasis of pregnancy recruited after 24 weeks' gestation in nine UK maternity units. 109 women participated in the ursodeoxycholic acid comparison, and 62 in the timed delivery comparison.

Primary outcomes

For the ursodeoxycholic acid comparison, the mean of all measures of itch assessed on a 100 mm visual analogue scale between randomisation and delivery. For the timing of delivery comparison, caesarean section rates.

Main results and the role of chance

Ursodeoxycholic acid reduced itching by −16 mm (95% confidence interval −27 mm to −6 mm). This was less than the 30 mm difference prespecified by clinicians and women as clinically meaningful. Seven of 30 (23%) women were delivered by caesarean section in the early term delivery group compared with 11 of 32 (33%) in the expectant group (relative risk 0.70, 95% confidence interval 0.31 to 1.6).

Harms

No perinatal deaths occurred. 13 (23%) adverse events occurred in the ursodeoxycholic acid arm versus 10 (18%) in the placebo arm. None was severe. In two cases (one per group) the trial drug was stopped.

Bias, confounding, and other reasons for caution

The risk of bias in the estimate of the effect of ursodeoxycholic acid on itching is low. The study was originally designed as the initial phase of a larger definitive trial to test the effect of both interventions on fetal outcomes. The latter is not yet funded, so a prespecified analysis plan for testing the effect of ursodeoxycholic acid on itching was drawn up before unblinding, with a clinically meaningful effect size based on surveys of women and doctors. The precision of the effect of early delivery on caesarean delivery is low because of the small sample size.

Generalisability to other populations

Participants in the present trial had the same spectrum of disease severity as non-participants. Women with intrahepatic cholestasis of pregnancy in other populations would be expected to respond to ursodeoxycholic acid similarly.

Study funding/potential competing interests

Research for patient benefit programme from the National Institute for Health Research. JC founded the Obstetric Cholestasis Support Group (www.ocsupport.org).

Trial registration number

Current Controlled Trials ISRCTN37730443.

Effect of ursodeoxycholic acid versus placebo on secondary outcomes

Outcomes	Ursodeoxycholic acid group (n=56)	Placebo group (n=55)	Effect (95% CI)
Mean (SD) gestational age at delivery (weeks)	38 (1.9)	37 (2.0)	Difference 0.29 (−0.40 to 0.95)
No (%) with delivery <37 weeks	14 (23)	26 (41)	Risk ratio 0.65 (0.35 to 1.22)
No (%) with caesarean section	21 (35)	20 (31)	Risk ratio 1.26 (0.70 to 2.26)
No (%) with meconium stained amniotic fluid	5 (8)	13 (20)	Relative risk 0.39 (0.16 to 0.97)

The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study

Laurent Azoulay,[1 2] Hui Yin,[1] Kristian B Filion,[1 3] Jonathan Assayag,[1] Agnieszka Majdan,[4] Michael N Pollak,[2] Samy Suissa[5]

EDITORIAL by Hillaire-Buys and Faillie

[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Côte Sainte-Catherine, H-425.1, Montreal, Quebec, Canada, H3T 1E2
[2]Department of Oncology, McGill University, Montreal, Quebec, Canada
[3]Division of Clinical Epidemiology, McGill University, Montreal
[4]Division of Endocrinology, Jewish General Hospital, Montreal
[5]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal
Correspondence to: L Azoulay
laurent.azoulay@mcgill.ca

Cite this as: *BMJ* 2012;344:e3645
doi: 10.1136/bmj.e3645

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e3645

STUDY QUESTION

Is the use of pioglitazone associated with an increased risk of incident bladder cancer in people with type 2 diabetes?

SUMMARY ANSWER

The use of pioglitazone is associated with an increased risk of bladder cancer. The risk is greatest after more than 24 months of use and at cumulative dosages above 28 000 mg.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

This study provides additional evidence that the use of pioglitazone is associated with an increased risk of bladder cancer.

Participants and setting

Using the UK general practice research database, we identified a cohort of people with type 2 diabetes newly treated with oral hypoglycaemic agents between 1 January 1988 and 31 December 2009.

Design, size, and duration

A nested case-control analysis was carried out within a cohort of 115 727 users of oral hypoglycaemic agents, followed for an average of 4.6 years. All incident cases of bladder cancer occurring during follow-up were identified and matched to up to 20 controls on year of birth, year of cohort entry, sex, and duration of follow-up. Exposure was defined as ever use of pioglitazone, along with measures of duration and cumulative dosage.

Primary outcomes, risks, exposures

Incident cases of bladder cancer diagnosed beyond one year of follow-up to account for latency.

Main results and the role of chance

A total of 376 cases of bladder cancer diagnosed beyond one year of follow-up were matched to 6699 controls. Overall, compared with never use of any thiazolidinediones, ever use of pioglitazone was associated with an increased rate of bladder cancer (rate ratio 1.83, 95% confidence interval 1.10 to 3.05). The rate increased as a function of duration of use, with the highest rate observed in patients exposed for more than 24 months (1.99, 1.14 to 3.45) and in those with a cumulative dose greater than 28 000 mg (2.54, 1.05 to 6.14). No associations were observed with rosiglitazone, the other thiazolidinedione available in the United Kingdom during the study period.

Bias, confounding, and other reasons for caution

The general practice research database does not have information on certain bladder cancer risk factors, such as exposure to arsenic, occupational exposures, race/ethnicity, and family history of bladder cancer. Thus, residual confounding is possible.

Generalisability to other populations

The results of this study can be generalised to populations where pioglitazone is used as a second line and third line treatment in people with type 2 diabetes.

Study funding/potential competing interests

This study was supported by grants from the Canadian Institutes of Health Research and the Canadian Foundation for Innovation. The funding sources had no role in the design, analysis, and interpretation of the results, and thus the authors were independent from the funding source. MNP served as a consultant for Novo Nordisk and Sanofi-Aventis and received research funding from Novo Nordisk.

Pioglitazone cumulative duration of use and cumulative dosage and risk of bladder cancer among cases of bladder cancer and matched controls

Variables	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)
Never use of any thiazolidinediones	1.00 (reference)	1.00 (reference)
Cumulative duration of pioglitazone (months):		
≤12	0.69 (0.09 to 5.11)	0.56 (0.07 to 4.42)
13-24	2.99 (0.61 to 14.59)	3.03 (0.63 to 14.52)
>24	2.00 (1.16 to 3.45)	1.99 (1.14 to 3.45)
		P=0.050 for trend
Cumulative dosage of pioglitazone (mg):		
≤10 500	1.63 (0.72 to 3.69)	1.58 (0.69 to 3.62)
10 501-28 000	1.75 (0.75 to 4.07)	1.66 (0.70 to 3.94)
>28 000	2.44 (1.02 to 5.84)	2.54 (1.05 to 6.14)
		P=0.030 for trend

Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study

Leif Friberg,[1] Lina Benson,[2] Mårten Rosenqvist,[3] Gregory Y H Lip[4]

EDITORIAL by Prescott and Sørensen

[1]Karolinska Institute, Danderyd Hospital, Stockholm, Sweden
[2]Karolinska Institute, Department of Clinical Science and Education, Södersjukhuset, Stockholm
[3]Karolinska Institute, Department of Clinical Science and Education, Cardiology Unit, Södersjukhuset
[4]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK
Correspondence to: L Friberg
leif.friberg@ki.se

Cite this as: *BMJ* 2012;344:e3522
doi: 10.1136/bmj.e3522

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e3522

STUDY QUESTION

Do women with atrial fibrillation have a higher risk of stroke than men?

SUMMARY ANSWER

Women with atrial fibrillation have an increased risk of stroke compared with men, although those women younger than 65 years and with no other risk factors have a low risk for stroke and do not need anticoagulant treatment.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous studies have shown higher rates of stroke among women than men with atrial fibrillation, but since these women tend to be older and have more comorbidities than men, it has been difficult to assess female sex as a true risk factor for atrial fibrillation related stroke. The present study, with its large cohort, indicated a moderately increased risk of stroke in women with atrial fibrillation compared with men.

Participants and setting

All patients with a diagnosis of atrial fibrillation in a hospital, or a hospital affiliated outpatient clinic, in Sweden between 1 July 2005 and 31 December 2008. We excluded patients with warfarin at baseline, mitral stenosis, previous valvular surgery, or who died within 14 days from baseline.

Design, size, and duration

We included 50 135 men and 50 667 women with non-valvular atrial fibrillation who did not have oral anticoagulant treatment at baseline, who had records in the nationwide Swedish hospital discharge register. We also used this register to obtain information about comorbidities and stroke events. Information about drug exposure was obtained from the Swedish drug register, which includes information about all drugs sold in pharmacies throughout the country. Median follow-up was 1.2 years (total 139 504 years at risk).

Main results and the role of chance

We recorded 7221 ischaemic strokes during follow-up, with an annual stroke rate of 6.2% in women and 4.2% in men (P<0.0001). After multivariable adjustment for 35 cofactors, a higher risk of stroke in women than in men remained (hazard ratio 1.18, 95% confidence interval 1.12 to 1.24). Among patients with "lone atrial fibrillation" (that is, age <65 years and no other risk factors), the absolute incidence of stroke each year was similar in men and women (0.7% *v* 0.5%, P=0.09).

Bias, confounding, and other reasons for caution

Some comorbidities could have been under-reported in the national register. Women were older and generally had poorer health than men. Some residual confounding could have been present that we were unable to adjust for. We selected patients on the basis that they did not use warfarin at baseline, but since more men than women received warfarin, this difference could have resulted in a selection bias.

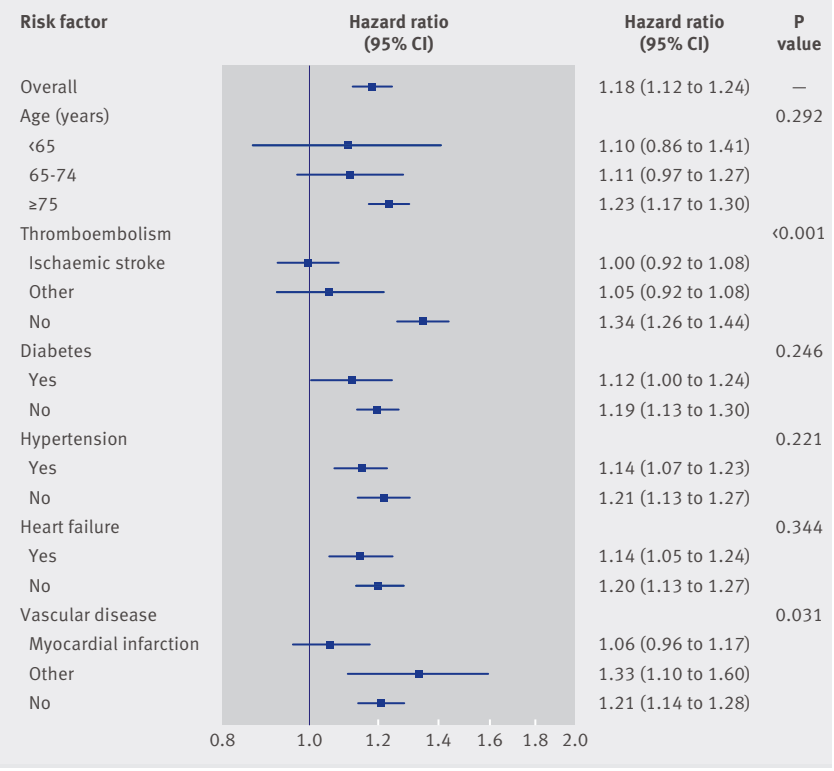
Generalisability to other populations

Our findings were derived from a hospital based population and might not be representative of a population managed exclusively in primary care.

Study funding/potential competing interests

The study was supported by the Swedish Heart and Lung Foundation, Stockholm County Council, and Board of Benevolence of the Swedish Order of Freemasons. LF is a consultant to Sanofi-Aventis, Boehringer-Ingelheim, and Bristol-Myers Squibb. LB has nothing to declare. MR is a consultant to Sanofi-Aventis and Nycomed, and was national coordinator for the RECORD, REALISE, and ARISTOTLE studies. GYHL has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis.

Risk of ischaemic stroke in women compared with men



Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis

Tessa S S Genders,[1 2] Ewout W Steyerberg,[3] M G Myriam Hunink,[1 2 4] On behalf of the CAD consortium collaborators

[1]Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, Netherlands
[2]Department of Radiology, Erasmus University Medical Centre
[3]Department of Public Health, Erasmus University Medical Centre
[4]Department of Health Policy and Management, Harvard School of Public Health, Harvard University, Boston, MA, USA
Correspondence to: M G M Hunink Departments of Epidemiology and Radiology, Erasmus University Medical Centre, PO Box 2040, 3000 CA Rotterdam, Netherlands
m.hunink@erasmusmc.nl

Cite this as: *BMJ* 2012;344:e3485
doi: 10.1136/bmj.e3485

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e3485

STUDY QUESTION How accurate are prediction models for estimating the pretest probability of obstructive coronary artery disease, and can they be further improved?

SUMMARY ANSWER Updated prediction models including age, sex, symptoms, and cardiovascular risk factors estimated the probability of coronary artery disease accurately in low prevalence populations, and improved on current estimates.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Guidelines from the National Institute for Health and Clinical Excellence require physicians to estimate the pretest probability of coronary artery disease in patients with recent onset chest pain. The currently recommended method, the Duke clinical score, overestimates the probability; we updated and validated a prediction model that improves the estimate.

Participants and setting

We analysed individual patient data from 18 hospitals in Europe and the United States. Patients with stable chest pain without evidence of previous coronary artery disease were eligible if they were referred for computed tomography (CT) based coronary angiography or catheter based coronary angiography.

Design, size, and duration

We did a retrospective pooled analysis. Outcome was obstructive coronary artery disease (≥50% diameter stenosis in one or more vessels shown on catheter based coronary angiography). We did multiple imputation to account for missing predictors and outcomes, owing to the strong correlation between the two different angiography procedures. We used three predictive models that are available online (http://rcc.simpal.com/NpfpV5): the basic model (including age, sex, symptoms, and setting), clinical model (basic model plus diabetes, hypertension, dyslipidaemia, and smoking), and extended model (clinical model plus the CT based coronary calcium score). We assessed discrimination (c statistic), calibration, and continuous net reclassification improvement by cross validation for the four largest low prevalence datasets separately and the smaller remaining low prevalence datasets combined.

Random effects logistic regression analysis in the low prevalence setting

	Prediction model (odds ratio (95% CI))		
	Basic	Clinical	Extended
Age (per 10 years)	1.89 (1.74 to 2.04)	1.85 (1.70 to 2.02)	1.11 (0.99 to 1.25)
Male sex	3.89 (3.24 to 4.66)	3.79 (3.13 to 4.58)	2.19 (1.75 to 2.75)
Chest pain (*v* non-specific chest pain)			
Atypical	1.93 (1.48 to 2.52)	1.88 (1.44 to 2.46)	2.05 (1.50 to 2.80)
Typical, if diabetes is absent	7.21 (5.64 to 9.22)*	7.36 (5.64 to 9.61)	7.57 (5.56 to 10.3)
Typical, if diabetes is present	—	4.91 (3.16 to 7.63)	3.46 (2.12 to 5.63)
Diabetes	—	2.29 (1.72 to 3.04)	1.93 (1.41 to 2.65)
Hypertension	—	1.40 (1.18 to 1.67)	1.26 (1.04 to 1.54)
Dyslipidaemia	—	1.53 (1.25 to 1.86)	1.20 (0.95 to 1.53)
Smoking	—	1.59 (1.30 to 1.93)	1.23 (0.97 to 1.55)
Coronary calcium score, log transformed score (per standard deviation)	—	—	4.69 (3.76 to 5.84)

Data are odds ratio (95% confidence interval); all odds ratios showed significant associations (P<0.05) apart from age, dyslipidaemia, and smoking in the extended model.
*Irrespective of diabetic status, since basic model does not include diabetes.

Main results and the role of chance

We included 5677 patients (3283 men, 2394 women), of whom 1634 had obstructive coronary artery disease on catheter based coronary angiography. All predictors were significantly associated with the presence of disease. The clinical model improved the prediction of disease compared with the basic model (cross validated c statistic improved from 0.77 to 0.79, net reclassification improvement 35%), although the coronary calcium score in the extended model was a major predictor (0.79 to 0.88, 102%). Calibration for low prevalence datasets was satisfactory.

Bias, confounding, and other reasons for caution

Only 2062 (36%) patients underwent catheter based coronary angiography. Because an analysis restricted to patients undergoing catheter based coronary angiography could be influenced by verification bias, we imputed missing data for results from catheter based coronary angiography by using CT based coronary angiography as an auxiliary variable in addition to all other predictors. Furthermore, the current analysis was not the main purpose of the data collection, resulting in considerable heterogeneity across hospitals with respect to patient selection, data availability, and predictor definitions.

Generalisability to other populations

Patients were selected on the basis of referral to CT based coronary angiography, catheter based coronary angiography, or both; however, not all patients presenting with chest pain in practice will be referred for one procedure or the other. After graphical assessment, calibration could be considered satisfactory, suggesting that the model is generalisable, although further external validation of our model in other populations is needed.

Study funding/potential competing interests

This research was supported by a healthcare efficiency grant from the Erasmus University Medical Centre. The funding organisations had no involvement in the study design and conduct; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to publish the manuscript. The authors have no conflicts of interest. The main paper includes full disclosures of all consortium members.

The effectiveness and cost effectiveness of dark chocolate consumption as prevention therapy in people at high risk of cardiovascular disease: best case scenario analysis using a Markov model

Ella Zomer,[1] Alice Owen,[1] Dianna J Magliano,[2] Danny Liew,[3] Christopher M Reid[1]

[1]CCRE Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Centre, Melbourne, Victoria, Australia
[2]Baker IDI Heart and Diabetes Institute, Melbourne
[3]Melbourne EpiCentre, Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Melbourne
Correspondence to: C M Reid
Chris.Reid@monash.edu

Cite this as: *BMJ* 2012;344:e3657
doi: 10.1136/bmj.e3657

This is a summary of a paper that was published on bmj.com as *BMJ* 2012;344:e3657

STUDY QUESTION Does dark chocolate consumption represent an effective and cost effective means of preventing cardiovascular disease among patients with the metabolic syndrome (without diabetes)?

SUMMARY ANSWER The blood pressure lowering and lipid effects of dark chocolate could represent an effective and cost effective strategy for the prevention of cardiovascular disease in patients with the metabolic syndrome (and no diabetes).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In short term trials, dark chocolate consumption has been shown to reduce systolic blood pressure by 5 mm Hg (interquartile range 2-8 mm Hg) and total cholesterol levels by 0.21 mmol/L (0.05-0.36 mmol/L). Our modelling analysis translates these benefits to potential reduction in cardiovascular events and death, and estimates how much could be spent on this as a preventive health strategy for it to remain cost effective.

Main results

Among patients with the metabolic syndrome (but without diagnosed diabetes and cardiovascular disease at baseline), dark chocolate consumption over 10 years could potentially avert 70 (interquartile range 55-85) non-fatal cardiovascular events and 15 (5-20) fatal cardiovascular events per 10 000 population. Up to $A40 (£25; €31; $42) could be spent per person per year for a dark chocolate prevention strategy to remain cost effective.

Design

A Markov model was constructed to assess the health effects and associated costs of daily consumption of plain dark chocolate versus no chocolate.

Sources of effectiveness

The study population comprised individuals from the Australian Diabetes Obesity and Lifestyle study classified as having the metabolic syndrome. All participants entered the Markov model in the "alive without cardiovascular disease" health state. With each annual cycle, we used prediction algorithms and population life tables to determine the probability of transitioning to other health states—that is, developing non-fatal cardiovascular disease, dying from cardiovascular disease, or dying from non-cardiovascular causes. We calculated changes in cardiovascular risk associated with the consumption of dark chocolate by application of expected effects of dark chocolate on systolic blood pressure and lipid levels. The number of cardiovascular events prevented (non-fatal and fatal), years of life saved, and potential monies available for the prevention strategy to be considered cost effective were calculated over 10 years.

Data sources

Changes in systolic blood pressure and lipid levels associated with the consumption of dark chocolate were informed by data from meta-analyses. Costs of cardiovascular events comprised direct costs of myocardial infarction and stroke, measured for the first year of the event and after the first year, as well as fatal cardiovascular events. All costs were inflated to reflect 2012 costs according to the Australian national health price index.

Results of sensitivity analysis

The main areas of uncertainty were in treatment effects, costing data, and adherence to treatment. Lower compliance levels showed decreased numbers of cardiovascular events prevented. In turn, the amount of funding required for prevention strategies to be considered cost effective decreased.

Limitations

Using modelling to predict long term effects of interventions, for which no data exist from long term clinical trials, has inherent limitations. The beneficial effects of dark chocolate have been observed in relatively short term trials, and herein these have been assumed to extend throughout the life of the model with no diminution of effect. In addition, there is currently no algorithm available for risk prediction of cardiovascular events specifically in patients with the metabolic syndrome. The Framingham algorithm (validated in "general" populations) was chosen as it was likely to represent a conservative estimate of risk. The additional caloric and glycaemic load imposed by dark chocolate is not able to be accounted for in this model, but dark chocolate has been found to increase satiety, potentially countering the caloric load of the intervention.

Study funding/potential competing interests

This study was supported by an Australian Research Council linkage grant (LP0775329) with Sanofi-Aventis Australia as the linkage partner.

Effectiveness and cost effectiveness of dark chocolate consumption. Values are base cases (interquartile ranges)

Compliance level	Cardiovascular events prevented/ 10 000 population		Years of life saved	Monies available annually per person ($)*
	Non-fatal	Fatal		
100%	70 (55-85)	15 (5-20)	40 (15-60)	42 (31-58)
90%	60 (50-80)	10 (5-20)	35 (5-35)	39 (27-54)
80%	55 (40-70)	10 (5-15)	30 (10-50)	34 (23-47)

$0.99 (£0.62; €0.77; $A1.00).
*Potential monies available to make intervention cost effective.