RESEARCH

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STEVE HORRELL/SPL

THIS WEEK'S RESEARCH QUESTIONS

Supplements and stroke

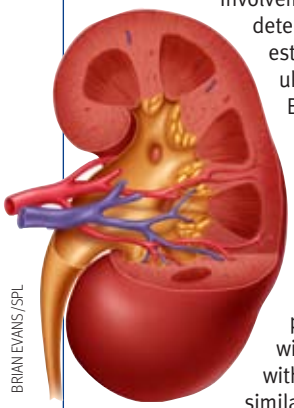
Up to 12.7% of adults in the United States take vitamin E supplements in the hope of staving off cardiovascular disease, but Markus Schürks and colleagues have found that these supplements increase the risk of haemorrhagic stroke by more than 20% (p 1033). Interestingly, their meta-analysis of almost 120 000 patients also found that supplementation reduced the risk of ischaemic stroke by 10%.

The authors stress that the absolute risks are small: vitamin E could cause one additional haemorrhagic stroke for every 1250 people taking the supplement but would prevent one ischaemic stroke per 476 people. However, given that haemorrhagic stroke is associated with worse outcomes and the risk reduction for ischaemic stroke is modest, they caution against indiscriminate widespread use of vitamin E supplements and recommend other strategies to prevent ischaemic stroke, such as blood pressure and cholesterol lowering drugs and having a healthy lifestyle.

Peter Coleman, deputy director of research at the Stroke Association, told BBC news: "This is a very interesting study that shows that the risk of haemorrhagic stroke can be slightly increased by high levels of orally taken vitamin E, although what is a high level has not clearly been ascertained. More research is required to discover the mechanism of action and the level at which vitamin E can become harmful" (http://bbc.in/a9yaqU).

Population screening for chronic kidney disease

The 2008 NICE guideline on chronic kidney disease (CKD) says, "Offer people testing if they have any of the following risk factors: diabetes, hypertension, cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease), structural renal tract disease, renal calculi or prostatic hypertrophy, multisystem diseases with potential kidney involvement, family history of stage 5 CKD or hereditary kidney disease, or opportunistic detection of haematuria or proteinuria," and recommends annual testing with estimated glomerular filtration rate (eGFR) for all of these groups (www.nice.org.uk/nicemedia/live/12069/42119/42119.pdf).



BRIAN EVANS/SPL

But is there also a case for population based screening? It seems not, as 16-21 people would have to be screened to detect one case of disease, and this would not be cost effective. But studies so far have been based on screening with urinalysis for proteinuria and macroalbuminuria, and now Braden Manns and colleagues have brought the evidence up to date by modelling the cost effectiveness of screening in primary care with a one off test for eGFR (p 1036). They found that, in a cohort of 100 000 people, screening and subsequent treatment with angiotensin blockade would cut the number of people developing end stage renal disease over their lifetime from 675 to 657, with an unfavourable incremental cost per QALY of more than £62 000. For people with diabetes, however, routine screening looks promising and has a cost per QALY similar to other publicly funded interventions.

Spotting subarachnoid haemorrhage

DAVID MALAN/GETTY

How do you know when a headache is a sign of something more serious, like intracranial bleeding? Identifying subarachnoid haemorrhage in patients who present to the emergency department can be tricky (particularly in patients who are "neurologically intact") and can involve expensive medical imaging and invasive procedures such as dural and lumbar puncture.

Jeffrey Perry and colleagues looked at nearly 2000 patients presenting with severe headache at six university teaching hospitals in Canada to see whether any clinical characteristics might predict a diagnosis of subarachnoid haemorrhage (p 1035). They identified seven variables strongly and reliably associated with the condition: age ≥40, witnessed loss of consciousness, complaint of neck pain or stiffness, onset with exertion, arrival by ambulance, vomiting, and raised diastolic (≥100 mm Hg) or systolic (≥160 mm Hg) blood pressure.

The authors of this study are now carrying out prospective validation of three clinical decision making rules formulated on the basis of their findings. "Since 4% of all emergency department visits are for headache and everyone is worried about missing subarachnoid haemorrhage, this is a potentially important paper," says Elizabeth Loder, clinical epidemiology editor at the *BMJ*.

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Detecting endobronchial intubation Endotracheal intubation is routinely performed by clinicians with different levels of experience, but misplacement of an endotracheal tube in a mainstem bronchus can lead to serious complications. Christian Sitzwohl and colleagues did a randomised trial to determine which bedside method of detecting inadvertent endobronchial intubation in adults was most sensitive and specific. Clinicians were randomly assigned to perform bilateral auscultation of the chest (the currently recommended method); observation and palpation of symmetrical chest movements; estimation of the tube position by the insertion depth; or all three. When using auscultation, doctors with limited experience missed over half of endobronchial intubations, and even experienced anaesthetists were often unable to detect the problem. When tube insertion depth was used, sensitivity was 85% in first year residents and 90% in experienced anaesthetists; optimal tube depth was 20 cm for women and 22 cm for men. The highest sensitivity and specificity were achieved by combining all three methods (doi:10.1136/bmj.c5943).

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials

Markus Schürks,[1 6] Robert J Glynn,[1 3] Pamela M Rist,[1 2] Christophe Tzourio,[4 5] Tobias Kurth[1 2 4 5]

[1]Division of Preventive Medicine, Department of Medicine; Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215-1204, USA
[2]Department of Epidemiology, Harvard School of Public Health, Boston
[3]Department of Biostatistics, Harvard School of Public Health, Boston
[4]INSERM Unit 708 - Neuroepidemiology, Paris, France
[5]UPMC Univ Paris 06, F-75005, Paris
[6]Department of Neurology, University Hospital Essen, Germany

Correspondence to: M Schürks **mschuerks@rics.bwh.harvard.edu**, T Kurth **tobias.kurth@upmc.fr**

Cite this as: *BMJ* 2010;341:c5702
doi: 10.1136/bmj.c5702

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c5702

Response on bmj.com

"I think it would be wise to study how vitamin E may affect the risk of hemorrhagic stroke when combined with drugs that may affect platelet activity or in poorly controlled hypertension."
Edoardo Cervoni, United Kingdom

To submit a rapid response, go to any article on bmj.com and select "Respond to this article"

STUDY QUESTION What is the effect of vitamin E supplementation on total, haemorrhagic, and ischaemic stroke?

SUMMARY ANSWER Vitamin E intake increased the risk of haemorrhagic stroke by 22% and reduced the risk of ischaemic stroke by 10%.

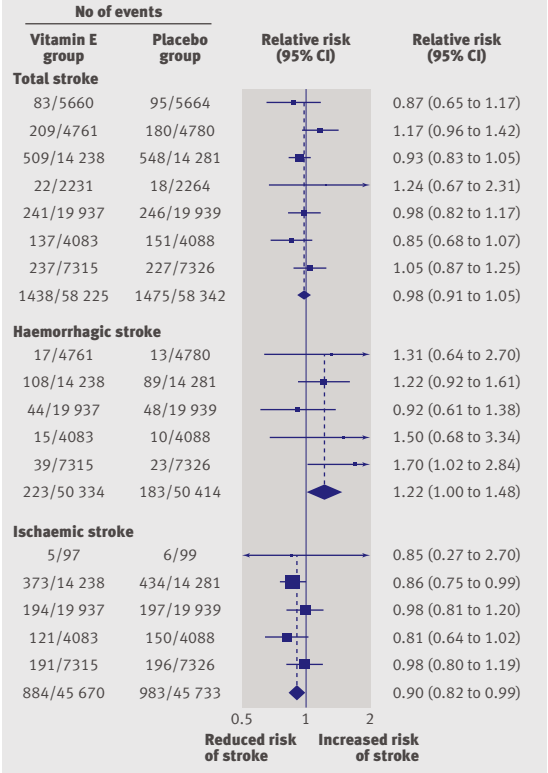
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Randomised controlled trials reported no effect of vitamin E on risk of cardiovascular disease and high dose of vitamin E may increase the risk of all-cause mortality. This study adds that vitamin E intake increases the risk of haemorrhagic stroke and decreases the risk of ischaemic stroke.

Selection criteria for studies

We followed the guidelines of the PRISMA statement for reporting our meta-analysis. Two investigators independently searched Medline and Embase (from inception to January 2010) as well as the Cochrane Central Register of Controlled Trials (CENTRAL) (issue 1, 2010). We a priori defined the following inclusion criteria: (i) randomised, placebo controlled design with a follow-up of ≥1 year; (ii) investigating the effect of vitamin E on stroke incidence (total stroke or stroke subtypes); (iii) trial participants must have been selected on clinical grounds; (iv) if multiple papers reported on a trial, we chose either the original report or the report that was most informative with regard to stroke and stroke subtypes. Data were extracted by two independent investigators. Within each study, we calculated the risk ratio as a measure for the relative risk for total stroke, haemorrhagic stroke, and ischaemic stroke based on the reported events in the treatment and placebo groups.

EFFECT OF VITAMIN E ON RISK OF TOTAL STROKE AND STROKE SUBTYPES



Data sources

Primary outcome(s)

Incidence of total, haemorrhagic, or ischaemic stroke.

Main results and the role of chance

Nine trials investigating the effect of vitamin E on incident stroke were included, totalling 118 765 participants (59 357 randomised to vitamin E and 59 408 to placebo). Seven of the trials reported data for total stroke and five trials each reported on haemorrhagic and ischaemic stroke. Vitamin E had no effect on the risk for total stroke (pooled relative risk 0.98 (95% confidence interval 0.91 to 1.05), P=0.53). In contrast, the risk for haemorrhagic stroke was increased (pooled relative risk 1.22 (1.00 to 1.48), P=0.045), while the risk of ischaemic stroke was reduced (pooled relative risk 0.90 (0.82 to 0.99), P=0.02). There was little evidence for heterogeneity among studies. Meta-regression did not identify blinding strategy, vitamin E dose, or morbidity status of participants as sources of heterogeneity. In terms of absolute risk, these results translate into one additional haemorrhagic stroke for every 1250 individuals taking vitamin E, and one ischaemic stroke prevented for every 476 individuals taking vitamin E.

Bias, confounding, and other reasons for caution

We decided a priori to include only trials that investigated the effect of "pure" vitamin E on stroke. Included trials were considered irrespective of blinding and morbidity status of participants. This approach increases the total sample size and thus the power to detect a potential effect of vitamin E on stroke subtypes and also allows for greater flexibility at the analysis level by performing sensitivity analyses.

Generalisability to other populations

Participants of clinical trials are selected based on certain inclusion and exclusion criteria, which reflect the risk status of only a subgroup of the general population and may limit generalisability.

Study funding/potential competing interests

This study had no specific funding.

Outcome selection and role of patient reported outcomes in contemporary cardiovascular trials: systematic review

Kazem Rahimi,[1] Aneil Malhotra,[1] Adrian P Banning,[1] Crispin Jenkinson[2]

[1]Department of Cardiology, Oxford Heart Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK
[2]Department of Public Health, Health Services Research Unit, University of Oxford

Correspondence to: K Rahimi
kazem.rahimi@orh.nhs.uk

Cite this as: *BMJ* 2010;341:c5707
doi: 10.1136/bmj.c5707

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c5707

STUDY QUESTION

How relevant are patient reported outcomes to the clinical interpretation of findings from contemporary cardiovascular trials, and do investigators use them appropriately?

SUMMARY ANSWER

Although patient reported outcomes were judged to be of little or no relevance to a large proportion of, mostly explanatory, cardiovascular trials, still more than two thirds of trials in which patient reported outcomes were judged to be important or crucial for clinical decision making failed to report such outcomes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Patient reported outcomes help to assess the impact of interventions from the patients' perspective and can be particularly useful in trials of interventions that aim to improve symptoms or functional status. Two other major but less well known areas where patient reported outcomes were underused are trials that assess the effect of interventions with a considerable potential for causing harm that is not meaningfully measured, and trials with composite outcomes that are dominated by outcomes of questionable importance to patients.

Selection criteria for studies

We searched Embase and Medline for randomised trials of treatment for or prevention of cardiovascular disease published in 10 leading general medical and cardiology journals between January 2005 and December 2008.

Primary outcome(s)

We extracted information about the type of outcomes selected and prevalence of patient reported outcomes. Based on literature recommendations and experts' opinion, we devised a tool for ranking the relevance of patient reported outcomes, taking account of key characteristics of trials, and applied it to 413 randomly selected trials.

Main results and role of chance

Primary outcomes were patient important (death, morbidity, or patient reported outcomes) in only 93 trials (23%, SE 2%), whereas another 92 (22%, SE 2%) combined these outcomes with other less important outcomes into a composite. Sixty five trials (16%; SE 2%) used at least one instrument to measure patient reported outcomes, mostly in trials where such information would have been important or crucial for clinical decision making (52 trials). We judged patient reported outcomes to be of little incremental value to a large number of, mostly explanatory, cardiovascular trials (152 trials). However, many trials in which patient reported outcomes would have been important or crucial for clinical decision making did not report such outcomes (122 of 174 trials, 70%). These included several trials that primarily aimed to improve symptoms or functional status, trials that tested interventions with a considerable potential for causing harm (mainly bleeding) that was not meaningfully measured, and trials with composite outcomes that were dominated by outcomes of questionable importance to patients.

REPORTING OF PATIENT REPORTED OUTCOMES (PROS) BY LEVEL OF RELEVANCE OF SUCH OUTCOMES TO INDIVIDUAL TRIALS

Relevance of PROs to clinical decision making	No of evaluated trials	No (%) of trials that reported PRO*
Crucial	93	37 (40)
Important	81	15 (19)
Potentially relevant	59	3 (5)
Irrelevant	93	2 (2)
Uncertain	87	8 (9)

*P<0.001 for trend across categories of trials (excluding trials where level of relevance was uncertain).

Bias, confounding, and other reasons for caution

Despite our systematic approach, a certain degree of judgment in grading the relevance of patient reported outcomes was inevitable. We did not evaluate the feasibility of use of patient reported outcomes and were unable to fully investigate the underlying causes for their underuse.

Study funding/potential competing interests

We received no funding for this study and have no competing interests.

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High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study

Jeffrey J Perry,[1] Ian G Stiell,[1] Marco L A Sivilotti,[2] Michael J Bullard,[3] Jacques S Lee,[4] Mary Eisenhauer,[5] Cheryl Symington,[1] Melodie Mortensen,[1] Jane Sutherland,[6] Howard Lesiuk,[7] George A Wells[8]

EDITORIAL by Rinkel

[1]Department of Emergency Medicine, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada K1Y 4E9
[2]Department of Pharmacology and Toxicology, Queen's University, Kingston, Ontario
[3]Division of Emergency Medicine, University of Alberta, Edmonton, Alberta
[4]Division of Emergency Medicine, University of Toronto, Toronto, Ontario
[5]Division of Emergency Medicine, University of Western Ontario, London, Ontario
[6]University of Ottawa, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario
[7]Division of Neurosurgery, Ottawa Hospital Research Institute, Ottawa, Ontario
[8]Department of Epidemiology and Community Medicine, Ottawa Hospital Research Institute, Ottawa, Ontario
Correspondence to: J Perry
jperry@ohri.ca

Cite this as: *BMJ* 2010;341:c5204
doi: 10.1136/bmj.c5204

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c5204

STUDY QUESTION

What clinical characteristics are sensitive and reliable enough to combine into a clinical decision rule to rule out subarachnoid haemorrhage in neurologically intact emergency patients with acute headache?

SUMMARY ANSWER

Age 40 and over, arrival by ambulance, onset with exertion, complaint of neck stiffness or pain, raised blood pressure, loss of consciousness, or vomiting are predictive for subarachnoid haemorrhage.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

It is currently recommended that all emergency patients with abrupt onset headache undergo lumbar puncture followed by computed tomography to exclude subarachnoid haemorrhage. This high stakes-low yield strategy is inefficient. We derived three clinical decision rules, which use clinical findings to rule out subarachnoid haemorrhage. If prospectively validated, these rules could allow clinicians to be more selective and accurate when investigating patients with acute headache.

Participants and setting

This study enrolled alert, neurologically intact adults presenting to one of six tertiary care emergency departments for a non-traumatic headache that peaked within one hour.

Design, size, and duration

This five year prospective cohort study enrolled 1999 patients including 130 with confirmed subarachnoid haemorrhage.

Main results and the role of chance

We derived three related clinical decision models, based on recursive partitioning and using only highly reliable variables (κ >0.6). All three rules have retrospective sensitivity of 100% (95% confidence interval 97.1% to 100.0%). The specificity of the models ranged from 28.4% to 38.8%, with corresponding investigation rates from 63.7% to 73.5%, lower than the observed rate of 82.9%.

Bias, confounding, and other reasons for caution

Twenty six patients were lost to active follow-up by telephone, although we searched coroner records and return to regional neurosurgical centres. Forty eight enrolled patients had another serious cause of headache identified on computed tomography, and physicians may be more willing to forgo lumbar puncture than imaging based on a clinical decision rule. While we enrolled patients with non-thunderclap headaches, the reported time to peak headache intensity was up to several minutes even among those with subarachnoid haemorrhage. The proposed clinical rules need to be validated before being incorporated fully in clinical practice.

VARIABLES INCLUDED IN EACH OF THREE PROPOSED RULES TO IDENTIFY PATIENTS AT HIGH RISK FOR SUBARACHNOID HAEMORRHAGE

For each rule, patients should be investigated if one or more of the variables are present

Rule 1
- Age ≥40
- Complaint of neck pain or stiffness
- Witnessed loss of consciousness
- Onset with exertion

Sensitivity 100% (95% confidence interval 97.1% to 100.0%)
Specificity 28.4% (26.4% to 30.4%)

Rule 2
- Arrival by ambulance
- Age ≥45
- Vomiting at least once
- Diastolic blood pressure ≥100 mm Hg

Sensitivity 100% (97.1% to 100.0%)
Specificity 36.5% (34.4% to 38.8%)

Rule 3
- Arrival by ambulance
- Systolic blood pressure ≥160 mm Hg
- Complaint of neck pain or stiffness
- Age 45-55

Sensitivity 100% (97.1% to 100.0%)
Specificity 38.8% (36.7% to 41.1%)

Generalisability to other populations

We excluded patients with a history of three or more similar headaches, and our rules should not be applied to such patients. We remain concerned that arrival by ambulance might not extrapolate to regions with different cultural traditions or funding models for ambulance services.

Study funding/potential competing interests

This study was funded by Ontario Ministry of Health and Long Term Care, physicians of Ontario through the Physician's Services Incorporated Foundation (grant No 01-39), the Canadian Institutes for Health Research (grant No 67107). JJP was funded as a career scientist by the Ontario Ministry of Health and is now funded by a Canadian Institutes for Health Research New Investigator Award. IGS is a University Health Research Chair, University of Ottawa.

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Population based screening for chronic kidney disease: cost effectiveness study

Braden Manns,[1234] Brenda Hemmelgarn,[1234] Marcello Tonelli,[45] Flora Au,[24] T Carter Chiasson,[4] James Dong,[45] Scott Klarenbach,[45] on behalf of the Alberta Kidney Disease Network

EDITORIAL by Kiberd

[1]Department of Medicine, University of Calgary, Calgary, Alberta, Canada
[2]Community Health Sciences, University of Calgary, Calgary
[3]Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary
[4]Alberta Kidney Disease Network, Calgary
[5]Department of Medicine, Division of Nephrology, University of Alberta, Edmonton, Alberta
Correspondence to: B Manns, Foothills Medical Centre, 1403 29th St. NW Calgary, Alberta Canada T2N 2T9 Braden.Manns@albertahealthservices.ca

Cite this as: *BMJ* 2010;341:c5869
doi: 10.1136/bmj.c5869

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c5869

STUDY QUESTION

What is the cost effectiveness of one-off screening with estimated glomerular filtration rate for chronic kidney disease in the general population and in subgroups defined by age, diabetes, and hypertension?

SUMMARY ANSWER

Population based screening with estimated glomerular filtration rate is not cost effective, though targeted screening of people with diabetes has a similar cost per quality adjusted life year (QALY) gained to other publicly funded interventions.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Chronic kidney disease is common and effective treatments are available, and screening could be useful. Population based screening, however, is not cost effective, though targeted screening of people with diabetes seems attractive.

Main results

We assessed incremental costs, quality adjusted life years (QALYs), and cost per QALY gained of screening compared with no formal screening for the general population and defined subgroups. In a cohort of 100 000 people, screening for chronic kidney disease would reduce the number of people developing end stage renal disease over their lifetime from 675 to 657. In a cohort of 100 000 people with diabetes, screening would be expected to reduce the number of people developing end stage renal disease from 1796 to 1741. Population based screening with estimated glomerular filtration rate has an unfavourable incremental cost per QALY of >$104 900 (2009 Canadian dollars; equivalent to about £62 000, €70 300, $101 540). Targeted screening of people with diabetes has a cost per QALY similar to other publically funded interventions ($C22 600 per QALY).

Design

A validated Markov model was constructed incorporating health states of no chronic kidney disease, non-dialysis chronic kidney disease, and end stage renal disease. Identification of undiagnosed chronic kidney disease would result in treatment with angiotensin blockade. The model accounted for adherence with screening and angiotensin blockade, as well as incidental case finding. Extensive sensitivity analysis, including probabilistic sensitivity analysis, was conducted on key variables over their plausible ranges.

Source of effectiveness

Effectiveness of angiotensin blockade was taken from high quality meta-analyses and randomised trials in people with chronic kidney disease, stratified by diabetes and proteinuria status.

Data sources

The prevalence of undiagnosed chronic kidney disease was determined from the National Health and Nutrition Examination Survey (NHANES) III, while the natural course of the disease, including progression to end stage renal disease, mortality, and other model parameters were obtained from the Alberta Kidney Disease Network, a contemporary population based cohort followed over five years. Resource use for management of non-dialysis and dialysis chronic kidney disease was obtained from the network data and relevant costing studies. Resource use for screening and associated investigations and subsequent treatment with angiotensin blockade was estimated, and unit costs were assigned from local Canadian cost lists. Analyses were from the perspective of healthcare funders, and we used a lifetime time horizon.

Results of sensitivity analysis

The cost per QALY of screening with estimated glomerular filtration rate in people with diabetes was robust in one way sensitivity analysis, with a 99% probability that the cost per QALY gained is under $C50 000. Screening those without diabetes resulted in cost per QALY gained of about $C50 000 only in scenarios where treatment was assumed to improve survival by 15% or when the risk of progression to end stage renal disease in untreated patients was assumed to be substantially increased.

Limitations

We compared only screening estimated glomerular filtration rate with no screening; other comparators, including screening with urinalysis, were not considered. Model parameters and estimates of effectiveness are limited by availability of data, although high quality data were identified and incorporated.

Study funding/potential competing interests

This study was supported by an operating grant from Alberta Heritage Foundation for Medical Research (now Alberta Innovates-Health Solutions).

COST EFFECTIVENESS OF POPULATION BASED AND TARGETED SCREENING FOR CHRONIC KIDNEY DISEASE

Outcome	Incremental cost ($C)	Incremental QALYs	Cost ($C) per QALY
Overall	463	0.0044	104 900
Age <65	148	0.0007	200 100
Age ≥65	997	0.0106	93 700
With diabetes	578	0.0256	22 600
Without diabetes	440	0.0008	572 000
Without diabetes, without hypertension	350	0.0003	1 411 100
Without diabetes, with hypertension	470	0.0014	334 000