RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

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LAWRENCE LAWRY/SPL

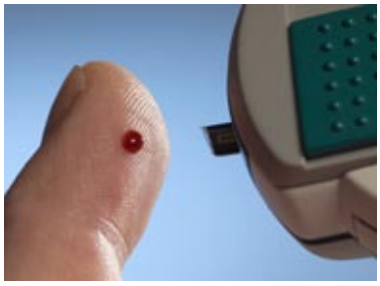
Utility of genetic and non-genetic risk factors in the prediction of type 2 diabetes

Around 300 people developed type 2 diabetes during 10 year follow-up in the Whitehall II study, a workplace based cohort study of 5535 initially healthy, white, middle aged civil servants. Would a comprehensive panel of genotypes associated with diabetes have helped to predict incident diabetes? The authors calculated the Cambridge type 2 diabetes risk score and the Framingham offspring study type 2 diabetes risk score for each participant and genotyped 20 single nucleotide polymorphisms associated with susceptibility to type 2 diabetes. They concluded that the genetic data added little (doi: 10.1136/bmj.b4838).

Ten steps towards improving prognosis research

Why does the scientific community generate, and apparently tolerate, prognosis research with so many limitations? Harry Hemingway and colleagues suggest 10 solutions for making prognosis research more effective at generating reliable new knowledge with benefits for patient outcomes, and more efficient, leading to less redundant or misleading research (doi: 10.1136/bmj.b4184).

Intensive control of blood sugar in type 2 diabetes



STEVE HORRELL/SPL

This week, two papers analyse data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study. This trial recruited more than 10 000 North Americans aged 40-79 with type 2 diabetes and high risk of cardiovascular disease. Participants were assigned to intensive or standard glycaemic control to see if reducing glycated haemoglobin levels to normal would cut rates of major cardiovascular events. The trial was meant to continue until June 2009, but in February 2008 it was interrupted for safety reasons. Compared with controls, the intensive therapy group had a relative increase in mortality of 22% and an absolute increase of 1.0%—equivalent to one extra death for every 95 patients treated for 3.5 years (*New Engl J Med* 2008; 358:2545-59). All participants were then switched to standard glycaemic control, while the other subcomponents of the trial, evaluating intensive versus standard treatments for hypertension and hyperlipidaemia, continued as planned. Editorialists Richard Lehman and Harlan M Krumholz advised last year that these same approaches should be widely used in type 2 diabetes: don't try to get HbA_{1c} to normal levels, focus on blood pressure and other cardiovascular risk factors, and help patients to live healthier lives (*BMJ* 2009;338:b800).

Academics are still unpicking data from the derailed part of ACCORD, to understand what went wrong in this huge trial and what it means for patients. We already know that deaths were not attributable to any particular hypoglycaemic drugs. Michael E Miller, Denise E Bonds, and colleagues have now done further multivariable analyses, finding that severe hypoglycaemia was more likely in trial participants with poorer baseline glycaemic control (regardless of treatment group), those who didn't respond quickly to intensive glucose lowering treatment, those also prescribed insulin, women, African Americans, older people, and those with lower educational achievement (p 138). And, although it may be unsurprising that death was more common among those who had severe hypoglycaemic events, mortality was unrelated to whether the patient was in the intensive or standard treatment arm of the trial, an answer that raises more questions (p 137).

The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study

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Cite this as: *BMJ* 2009;339:b4909
doi: 10.1136/bmj.b4909

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;339:b4909

STUDY QUESTION

Did participants in Action to Control Cardiovascular Risk in Diabetes (ACCORD) study who experienced one or more episodes of symptomatic, severe hypoglycaemia have an increased risk of death?

SUMMARY ANSWER

Symptomatic, severe hypoglycaemia was associated with an increased risk of death in both the intensive glucose control arm and the standard glucose control arm; however, among participants who experienced at least one episode of hypoglycaemia, the risk of death was lower in the intensive arm than in the standard arm.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Intensive glycaemia control is associated with increased rates of severe hypoglycaemia. This study demonstrates that patients with type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death, regardless of the intensity of glucose control.

Participants and setting

Patients were eligible for the ACCORD study if they had type 2 diabetes, a glycated haemoglobin concentration of 7.5% or more during screening, and were 40-79 years with established cardiovascular disease or 55-79 years with evidence of subclinical disease or two additional cardiovascular risk factors.

Design, size, and duration

This was a retrospective epidemiological analysis of data from the ACCORD study. A total of 10 194 participants with an average length of follow-up of 3.5 years were included.

Main results and the role of chance

Unadjusted annual mortality among patients in the intensive glucose control arm was 2.8% in those who had one or more episodes of hypoglycaemia requiring any assistance compared with 1.2% in those with no episodes (adjusted hazard ratio (HR) 1.41, 95% CI 1.03 to 1.93). A similar pattern was seen among participants in the standard glucose control arm (3.7% *v* 1.0%; adjusted HR 2.30, 95% CI 1.46 to 3.65). In participants who had experienced one or more episodes of severe hypoglycaemia, the risk of death was lower among those in the intensive arm than among those in the standard arm (adjusted HR 0.74, 95% CI 0.45 to 1.23).

Bias, confounding, and other reasons for caution

The protocol provided for differential monitoring of glucose, medication selection and titration, and tolerance for mild hypoglycaemia by the study clinicians; these factors could obscure the underlying cause of severe hypoglycaemia in this study. It is also difficult to assess the contribution of a specific drug or drug combination.

Generalisability to other populations

Patients with a recent history or frequent episodes of hypoglycaemia requiring medical assistance were excluded from the ACCORD trial. This approach may have resulted in somewhat lower estimates of absolute mortality risk owing to the relation between hypoglycaemia and mortality.

Study funding/potential competing interests

This study was supported by grants from the National Heart, Lung, and Blood Institute (N01-HC-95178, N01-HC-95179, N01-HC-95180, N01-HC-95181, N01-HC-95182, N01-HC-95183, N01-HC-95184, IAA-Y1-HC-9035, and IAA-Y1-HC-1010), by other components of the National Institutes of Health—including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute—by the Centers for Disease Control and Prevention, and by General Clinical Research Centers. The following companies provided study medications, equipment, or supplies: Abbott Laboratories, Amylin Pharmaceuticals, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi-Aventis, and Schering-Plough.

CRUDE, ANNUALISED MORTALITY RATES AND HAZARD RATIOS FOR HYPOGLYCAEMIC EVENTS REQUIRING ANY ASSISTANCE, MEDICAL OR NON-MEDICAL

	Mortality rate (n=451 deaths)		Adjusted hazard ratio for no previous events v at least one event* (HR (95% CI))
	No previous events	At least one previous event	
Intensive arm	1.2% a year (201 deaths/16 315 person years)	2.8% a year (53 deaths/1924 person years)	1.41 (1.03 to 1.93)
Standard arm	1.0% a year (176 deaths/17 297 person years)	3.7% a year (21 deaths/564 person years)	2.30 (1.46 to 3.65)

P=0.076 for interaction between history of hypoglycaemia and glycaemia intervention
*Hazard ratios are adjusted for the following baseline covariates: age, gender, smoking status, history of cardiovascular disease, history of heart failure, peripheral neuropathy, albumin to creatinine ratio, heart rate, QT score (from electrocardiology), visual acuity score, statin use, sulfonylurea use, glycaemia intervention, enrolled in lipid v blood pressure trial, intensive blood pressure control group, and fibrate group

The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study

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Cite this as: *BMJ* 2009;339:b5444
doi: 10.1136/bmj.b5444

This is a summary of a paper that was published in bmj.com as *BMJ* 2009;339:b5444

STUDY QUESTION

What factors increased the risk of severe hypoglycaemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, and was severe hypoglycaemia associated with levels of glycated haemoglobin (haemoglobin A_{1C}) achieved during therapy?

SUMMARY ANSWER

Participants with poorer glycaemic control had a greater risk of hypoglycaemia, irrespective of treatment group, and a greater drop in haemoglobin A_{1C} concentration from baseline to the four month visit was not associated with an increased risk for hypoglycaemia.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Intensive glycaemia control in patients with type 2 diabetes increases the risk of severe hypoglycaemia. Individuals started on intensive glycaemia treatment who do not respond promptly with a fall in haemoglobin A_{1C} concentration may be more likely to experience severe hypoglycaemia than those who respond promptly with a more rapid decline in haemoglobin A_{1C} level.

Participants and setting

Patients were eligible for the ACCORD study if they had type 2 diabetes, a haemoglobin A_{1C} concentration of 7.5% or more, and were aged 40-79 years with established cardiovascular disease or 55-79 years with evidence of subclinical disease or two or more cardiovascular risk factors.

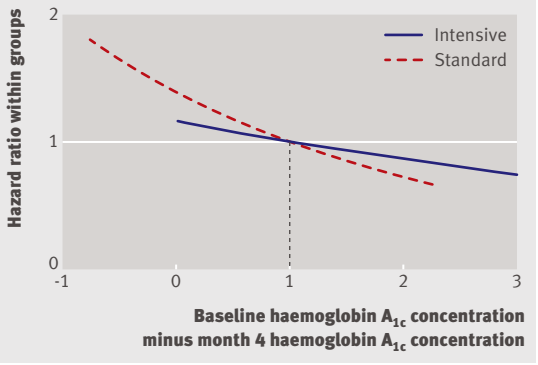
Design, size, and duration

This study is a post hoc epidemiological analysis of data from 10 209 participants in the ACCORD study. Participants were randomly allocated to intensive (haemoglobin A_{1C} <6.0%) or standard (haemoglobin A_{1C} 7.0-7.9%) glucose control and were followed up for an average of 3.4 years.

Main results and the role of chance

The annual incidence of hypoglycaemia was 3.14% in the intensive treatment group and 1.03% in the standard glycaemia group. We found significantly increased risks for hypoglycaemia among women (P=0.0300), African-Americans (P<0.0001 compared with non-Hispanic whites), those with less than a high school education (P<0.0500 compared with college graduates), aged participants (P<0.0001 per 1 year increase), and those who used insulin at trial entry (P<0.0001). For every 1% unit decline in the haemoglobin A_{1C} concentration from baseline to 4 months, the risk of hypoglycaemia requiring medical assistance fell by 28% (95% CI 19% to 37%) and 14% (4% to 23%) in the standard and intensive groups, respectively.

HAZARD RATIO FOR FOUR MONTH CHANGE IN HAEMOGLOBIN A_{1C} CONCENTRATION RELATIVE TO A 1% UNIT DECLINE



Bias, confounding, and other reasons for caution

Severe hypoglycaemia was self reported by participants, and individuals in the intensive control group had more frequent contact with study personnel so they had more opportunities to recall such episodes. It is difficult to assess the role that different medications may have played in the risk of severe hypoglycaemia.

Generalisability to other populations

Participants included in this study were selected on the basis of inclusion and exclusion criteria used in the ACCORD study. Our estimates of the incidence of severe hypoglycaemia may be lower than rates found in the general population because patients with a recent history or frequent episodes of hypoglycaemia requiring medical assistance at the time of enrolment were excluded from the ACCORD trial and special attention was given to monitoring and minimising severe hypoglycaemia during follow-up.

Study funding/potential competing interests

The authors were supported by contracts from the National Heart, Lung, and Blood Institute, by other components of the National Institutes of Health—including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute—by the Centers for Disease Control and Prevention, and by General Clinical Research Centers. The following companies provided study medications, equipment, or supplies: Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi-Aventis, and Schering-Plough.

Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe

The DIPART (vitamin D Individual Patient Analysis of Randomized Trials) group

EDITORIAL by Sahota
CLINICAL REVIEW, p 142

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Cite this as: *BMJ* 2010;340:b5463
doi: 10.1136/bmj.b5463

STUDY QUESTION

What individual participants' characteristics influence the anti-fracture efficacy of vitamin D, and what is the influence of dosing regimens and calcium co-administration?

SUMMARY ANSWER

Anti-fracture efficacy isindependent of age, sex, and fracture history; vitamin D given alone in doses of 10-20 µg/day is not effective in fracture prevention, but calcium and vitamin D given together reduce hip fractures and total fractures.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Vitamin D can reduce the risk of fractures in some groups of patients, but what dose is required and whether daily calcium co-supplementation is needed are unclear. Co-administration of 1000 mg c alcium/day is needed for fracture prevention with vitamin D oral doses of 10-20 µg/day.

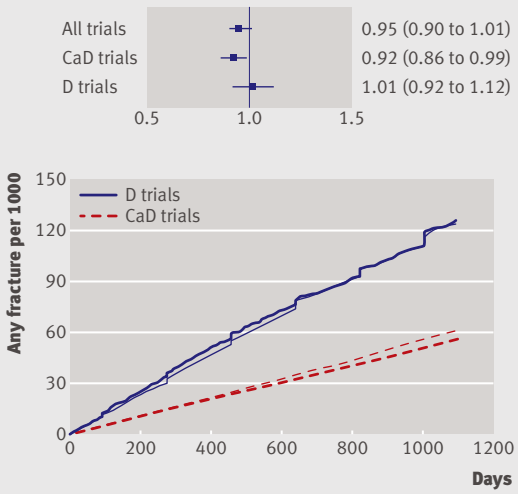
Selection criteria for studies

We included randomised studies (individual or cluster) with fracture as an outcome, at least one intervention arm in which vitamin D was given and one arm without vitamin D, and a study population of at least 1000 people.

Primary outcome(s)

The primary outcome was any fracture.

CUMULATIVE FRACTURE INCIDENCE FOR VITAMIN D (DARKER LINES) AND CONTROLS (LIGHTER LINES)



Inset shows treatment effect and 95% confidence intervals
CaD=calcium and vitamin D; D=vitamin D

Main results and role of chance

The analysis covered 7202 fractures over 177 203 person years. Trials using vitamin D with calcium showed a reduced risk of any fracture (hazard ratio 0.92, 95% confidence interval 0.86 to 0.99, P=0.025) and hip fracture (all studies: hazard ratio 0.84, 0.70 to 1.01, P=0.07; studies using 10 µg/day of vitamin D given with calcium: 0.74, 0.60 to 0.91, P=0.005). For any fracture, supplementation with calcium and vitamin D was associated with an absolute risk reduction of 0.5% over three years, corresponding to a number needed to treat of 213 people treated for three years to prevent a fracture. In patients with a previous fracture, the corresponding numbers were 1.2% and 82. For vitamin D alone, in daily equivalent doses of 10 or 20 µg/day, we found no significant effects. We found no interaction between history of fracture and response to treatment, nor any interaction with age, sex, or hormone replacement therapy. Results were unaffected by exclusion of users of hormone replacement therapy or bisphosphonates. We found no significant treatment by study interaction (calcium and vitamin D studies P=0.67 to 0.78, vitamin D studies P=0.14 to 0.44).

Bias, confounding, and other reasons for caution

Rates of fracture in the placebo group were higher in trials of vitamin D than in the trials combining vitamin D with calcium, as the former recruited older participants. We were unable to obtain data for four of the 11 identified studies that fulfilled the inclusion criteria, and we could not obtain sufficient information about compliance to do a pooled per protocol analysis. The effect size should be considered as worst case. In a sensitivity analysis, the Larsen trial was very influential in the analysis for hip fracture but not for any fracture. The hazard ratio for hip fracture was 0.97 (0.75 to 1.26, P=0.56) without the Larsen study.

Study funding/potential competing interests

AA acknowledges personal funding from the UK Medical Research Council and Chief Scientist Office of the Scottish Government Health Directorates. The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services. BA, TM, FHM, CC, DT, ALC, KB, and RMF have declared financial links with pharmaceutical companies (Amgen, Celltech, Eli Lilly, GlaxoSmithKline, Merck, Merck Sharp & Dohme, Novartis, Nycomed, Pfizer, Procter & Gamble, Osteologix, ProStrakan, Roche, Shire, Servier, and Sanofi-Aventis) and the Alliance for Better Bone Health (see online version for details).

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:b5463

Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial

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EDITORIAL by Cheville

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Cite this as: *BMJ* 2010;340:b5396
doi: 10.1136/bmj.b5396

This is a summary of a paper that was published on bmj.com as *BMJ* 2010:340:b5396

STUDY QUESTION Does early application of physiotherapy after breast cancer surgery reduce risk of lymphoedema?

SUMMARY ANSWER The early application of physiotherapy after breast cancer surgery with axillary lymph node dissection could be an effective measure to prevent secondary lymphoedema for at least one year.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Exercise and an educational strategy influences the occurrence and severity of secondary lymphoedema. In this study, early physiotherapy with an educational strategy after breast cancer surgery with axillary node dissection was associated with a lower risk of lymphoedema than the educational strategy alone after 12 months of follow-up.

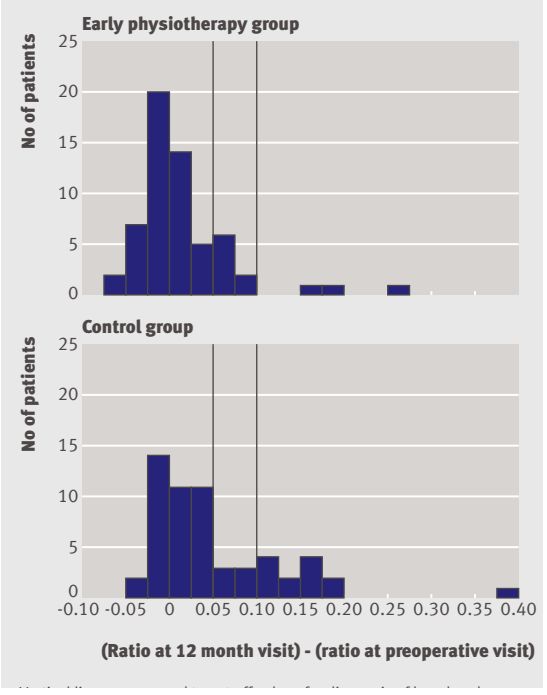
Design
Groups were randomised by computer to either intervention (early physiotherapy plus an educational strategy) or control (educational strategy alone). Researchers carrying out outcome assessment and data analysis were blinded to group allocation. Patients were followed up for 12 months.

Participants and setting
Participants were 120 women after surgery for breast cancer with axillary lymph node dissection at the Príncipe de Asturias University Hospital in Madrid in Spain, between May 2005 and June 2007.

Primary outcome(s)
We used binary criteria for diagnosing clinically significant secondary lymphoedema if the difference in circumference between both arms had increased by more than 2 cm at two adjacent points between the first visit (preoperative) and at 12 months of follow-up. We also measured the volume ratio between the arms (volume of affected arm/volume of unaffected arm) and calculated the increase in this ratio.

Main results and the role of chance
Of 116 women who completed the one year follow-up, 14 (25%) controls developed lymphoedema compared with four (7%) women in the early physiotherapy group (risk ratio 0.28, 95% confidence interval 0.10 to 0.79, P=0.01). The average increase in volume ratio in the control group was 5.1% (SE 1.01%) compared with 1.6% (SE 0.73%, P=0.0065 for difference) in the intervention group. A survival analysis showed a significant difference, with secondary lymphoedema being diagnosed four times earlier in the control than in the early physiotherapy group (hazard ratio 0.26, 95% confidence interval 0.09 to 0.79). Although the sample size was not large, the differences between groups were significant.

CHANGE IN VOLUME RATIOS OF ARMS BETWEEN PREOPERATIVE VISIT AND 12 MONTH FOLLOW-UP



Harms
No harms occurred during the study period.

Bias, confounding, and other reasons for caution
Body mass index was slightly higher in the intervention group, but after adjustment for body mass index the results remained unchanged. We looked at alternative diagnostic criteria for secondary lymphoedema on the basis of an increase in the volume ratio of 5% and 10%, as used in other analyses, and still found relevant differences between groups.

Generalisability to other populations
This study was carried out in one Spanish hospital only. Although we have no reason to suspect systematic differences between the care provided by this hospital and other regional hospitals or hospitals in other developed countries, this, together with the fact that physiotherapy was provided by trained physiotherapists, may limit the generalisability of this intervention to other settings.

Study funding/potential competing interests
All researchers are independent of the study funders, the Health Institute Carlos III of Spanish Health Ministry.

Trial registration number
Current Controlled Trials ISRCTN95870846.

Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis

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Cite this as: *BMJ* 2010;340:b5465
doi: 10.1136/bmj.b5465

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There is an interview with Professor Benjamin Wolozin in this week's podcast. http://podcasts.bmj.com/bmj/

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:b5465

STUDY QUESTION

Are angiotensin receptor blockers associated with protection against Alzheimer's disease or dementia?

SUMMARY ANSWER

Angiotensin receptor blockers are associated with a reduced incidence and progression of Alzheimer's disease and dementia compared with angiotensin converting enzyme inhibitors or other cardiovascular drugs in a predominantly male population.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Angiotensin receptor blockers are antihypertensive agents that offer superior protection against diabetes and stroke compared with other antihypertensive agents. We found that angiotensin receptor blockers are associated with a reduced incidence of Alzheimer's disease and dementia, as well as reduced rates of admission to a nursing home and death among people with Alzheimer's disease or dementia.

Participants and setting

The study sample comprised 819 491 predominantly male participants (98%) with cardiovascular disease, aged 65 years or more.

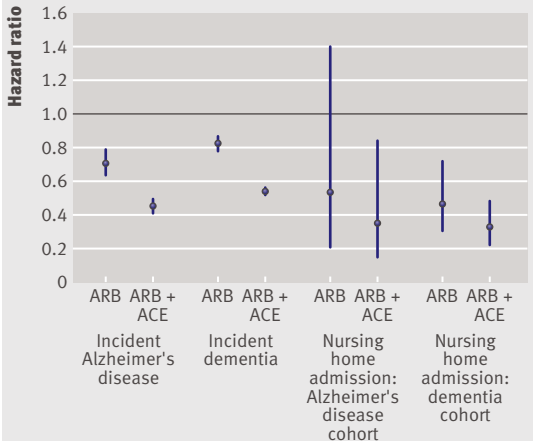
Design, size, and duration

Time to incident Alzheimer's disease or dementia was examined in three cohorts (angiotensin receptor blockers, lisinopril, and cardiovascular drugs) over a four year period (fiscal years 2003-6) using Cox proportional hazard models with adjustments for age, diabetes, stroke, and cardiovascular disease. Progression was studied by determining the time to nursing home admission or death among people with existing Alzheimer's disease or dementia.

Main results and the role of chance

Hazard rates for incident dementia in the angiotensin receptor blocker group were 0.76 (95% confidence interval 0.69 to 0.84) compared with the cardiovascular comparator and 0.81 (0.73 to 0.90) compared with the lisinopril group. Compared with the cardiovascular comparator, angiotensin receptor blockers in patients with pre-existing Alzheimer's disease were associated with a significantly lower risk of admission

EFFECT OF ANGIOTENSIN RECEPTOR BLOCKERS (ARB) ALONE OR WITH ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE) ON DEMENTIA OUTCOMES



to a nursing home (0.51, 0.36 to 0.72) and death (0.83, 0.71 to 0.97). Angiotensin receptor blockers exhibited a dose-response profile as well as additive effects in combination with angiotensin converting enzyme inhibitors. This combination compared with angiotensin converting enzyme inhibitors alone was associated with a reduced risk of incident dementia (0.54, 0.51 to 0.57) and admission to a nursing home (0.33, 0.22 to 0.49). Minor differences were shown in mean systolic and diastolic blood pressures between the groups. Similar results were observed for Alzheimer's disease.

Bias, confounding, and other reasons for caution

Misclassification, multiple indication bias, and differences in healthcare utilisation among the cohorts could be present. Quantification of nursing home admission depends on factors that are independent of dementia.

Generalisability to other populations

Our study examined a predominantly male population. Research needs to be extended to a mixed sex population.

Study funding/potential competing interests

This study was funded by grants from the Retirement Research Foundation (BW and RAW) and the Casten foundation (BW). We have no competing interests.

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