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Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis

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STUDY QUESTION Do differences exist among the effects of various renin-angiotensin system blockers and other antihypertensive treatments, alone or combined, on survival and major renal outcomes in patients with diabetes?

SUMMARY ANSWER Available evidence shows the renoprotective effects and superiority of angiotensin converting enzyme (ACE) inhibitors in patients with diabetes but is not able to distinguish the protective effects of angiotensin receptor blockers (ARBs) from ACE inhibitors in either monotherapy or combination therapy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Guidelines suggest ACE inhibitors or ARBs as first line treatment in hypertensive patients with diabetes when cost is not a concern, but the difference in protective effects between these drugs remains inconclusive, and consensus is lacking about the choice of treatments in combination with renin-angiotensin system blockers. This study supports the use of ACE inhibitors as the first line antihypertensive agent in consideration of the cost; calcium channel blockers might be the preferred treatment in combination with ACE inhibitors if adequate blood pressure control is unachievable by ACE inhibitors alone.

Results of network meta-analysis for treatments compared with placebo

Treatment	Odds ratio (95% CrI)
All cause mortality:	
ACE inhibitor+CCB	0.51 (0.15 to 1.35)
ACE inhibitor+diuretic	0.86 (0.59 to 1.26)
ACE inhibitor	0.99 (0.73 to 1.26)
CCB	1.02 (0.74 to 1.46)
ARB	1.08 (0.87 to 1.39)
Diuretic	2.19 (0.17 to 55.70)
β blocker	7.13 (1.37 to 41.39)*
End stage renal disease:	
ACE inhibitor	0.71 (0.39 to 1.28)
ARB	0.73 (0.43 to 1.25)
β blocker	0.87 (0.10 to 6.34)
CCB	1.01 (0.54 to 1.90)
ACE inhibitor+diuretic	1.20 (0.50 to 2.93)
Doubling of serum creatinine level:	
ACE inhibitor	0.58 (0.32 to 0.90)*
ARB	0.76 (0.47 to 1.32)
CCB	1.18 (0.57 to 2.54)
ACE inhibitor+diuretic	1.22 (0.49 to 3.03)
β blocker	4.87 (0.77 to 34.61)

CrI=credible interval; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CCB=calcium channel blocker.
*Statistically significant difference.

Selection criteria for studies
We searched PubMed, Medline, Scopus, and the Cochrane Library for studies published up to December 2011. Eligible studies had to be randomised clinical trials of antihypertensive therapy (ACE inhibitors, ARBs, α blockers, β blockers, CCBs, diuretics, and their combinations with each other) in adults (>18 years) with diabetes, with a follow-up of at least 12 months, reporting all cause mortality, requirement for dialysis, or doubling of serum creatinine level.

Primary outcomes
The primary outcomes were all cause mortality, end stage renal disease, and doubling of serum creatinine level, assessed with bayesian random effects odds ratios and 95% credible intervals, as well as the probabilities of ranking, for treatments based on their protective effects.

Main results and role of chance
63 trials with 36 917 participants were identified, including 2400 deaths, 766 patients requiring dialysis, and 1099 patients with a doubled serum creatinine level. Compared with placebo, only ACE inhibitors were associated with a significant reduction in the doubling of serum creatinine (odds ratio 0.58, 95% credible interval 0.32 to 0.90), and only β blockers showed a significant difference in mortality (odds ratio 7.13, 95% credible interval 1.37 to 41.39). Comparisons among all treatments showed no statistical significance in the outcome of dialysis. Although the beneficial effects of ACE inhibitors compared with ARBs did not reach statistical significance, ACE inhibitors consistently showed higher probabilities of being in the superior ranking positions among all three outcomes. While the protective effect of ACE inhibitors plus CCB compared with placebo was not statistically significant, this combination therapy showed the greatest probability (73.9%) for being the best treatment on reducing mortality, followed by ACE inhibitor plus diuretic (12.5%), ACE inhibitors (2.0%), CCBs (1.2%), and ARBs (0.4%). These estimates are fairly robust and changed little in sensitivity analyses.

Bias, confounding and other reasons for caution
The strength of evidence was affected by potential risk of bias in the included studies and the sparseness of data for some outcomes of treatment comparisons, which limited the precision and statistical power of the estimates across studies.

Study funding/potential competing interests
None.

Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial

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EDITORIAL by Jordan et al

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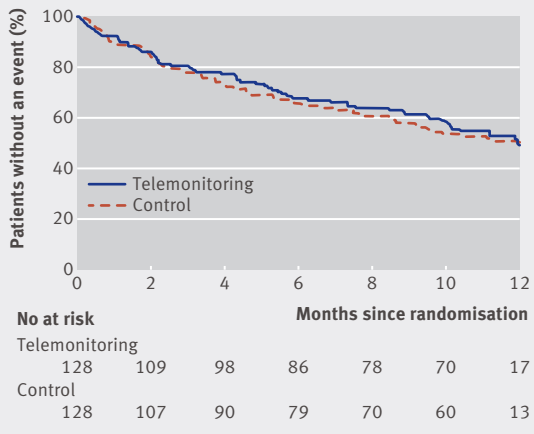
STUDY QUESTION Does telemonitoring, integrated into existing clinical services such that intervention and control groups have access to the same clinical care, reduce the time to hospital admission with exacerbation of chronic obstructive pulmonary disease (COPD)?

SUMMARY ANSWER In participants with a history of admission for exacerbations of COPD, telemonitoring was not effective in postponing hospital admissions.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Previous trials of telemonitoring in COPD have introduced telemonitoring as part of complex packages of enhanced care including case management, pulmonary rehabilitation, or integrated care programmes, which potentially reduce hospital admissions. When integrated into existing clinical services, telemonitoring had no effect on time to hospital admission for exacerbations of COPD.

Design
In a 12 month, researcher blind, multicentre randomised controlled trial, participants were centrally randomised to telemonitoring or control groups with a 1:1 allocation using randomised blocks of two or four and stratified by the clinical service providing COPD care. Using a touch screen, telemonitoring participants recorded a daily questionnaire about symptoms and treatment use, and monitored oxygen saturation using linked instruments. Algorithms, based on the symptom score, generated alerts if readings were omitted or breached thresholds.

Time to first admission with an exacerbation of COPD



Participants and setting
Participants were adults in UK primary care (Lothian, Scotland) with at least one admission for COPD in the year before randomisation.

Primary outcome
Time to first hospital admission with a diagnosis of an exacerbation of COPD up to one calendar year after randomisation.

Main results and the role of chance
Of 256 patients completing the study, 128 patients were randomised to telemonitoring and 128 to usual care; baseline characteristics of each group were similar. Median time to first COPD admission was 362 days (interquartile range 131 to >365) in the telemonitoring group and 361 days (113 to >365) in the control group. The number of days to admission did not differ significantly between groups (adjusted hazard ratio 0.98, 95% confidence interval 0.66 to 1.44).

Harms
We recorded 16 and 21 deaths in the telemonitoring and control groups, respectively. This difference was not significant (adjusted odds ratio 0.66 (95% confidence interval 0.29 to 1.48)).

Bias, confounding, and other reasons for caution
The confidence intervals for our primary outcome were wide and we cannot rule out a clinically meaningful smaller difference than the one we were powered to study. Blinding of participants and researchers was not possible, but central randomisation ensured concealment and the primary outcome was assessed by two clinicians unaware of allocation. Outcome data were collected by a blinded member of the research team, although inadvertent mention of telemonitoring could have revealed allocation during some data collection visits.

Generalisability to other populations
The clinical context—with established community specialist respiratory teams, specialist nurses in long term conditions, and primary care teams—enabled us to integrate telemonitoring within existing services, which may not be possible in other healthcare systems. Most participants lived within 10 miles of secondary care facilities; outcomes might be different in rural areas.

Study funding/potential competing interests
See full version of paper on bmj.com.

Updates on nutrition from the *BMJ* are at bmj.com/specialties/nutrition-and-metabolism

Palm oil taxes and cardiovascular disease mortality in India: economic-epidemiologic model

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STUDY QUESTION What is the potential effect of a palm oil tax on hyperlipidemia and cardiovascular disease mortality rates in India?

SUMMARY ANSWER Curtailing palm oil intake through taxation may modestly reduce hyperlipidemia and cardiovascular mortality, but with potential distributional consequences differentially benefiting male and urban populations, as well as affecting food security.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Palm oil has a very high saturated fat content and has been significantly associated with increased mortality rates for myocardial infarction in low and middle income countries. Although palm oil taxation may modestly reduce hyperlipidemia and cardiovascular mortality, it may also indirectly reduce food security among some groups

Main results

A 20% tax on palm oil purchases would be expected to avert approximately 363 000 (95% confidence interval 247 000 to 479 000) deaths from myocardial infarctions and strokes in India over the period 2014-23 (1.3% reduction in age standardized cardiovascular deaths), after dynamic trends in risk factors have been accounted for.

Design

We used a mathematical model incorporating nationally representative data on cardiovascular disease risk factors, palm oil consumption, substitution of palm oil with other oils, and changing trends in disease risk over time.

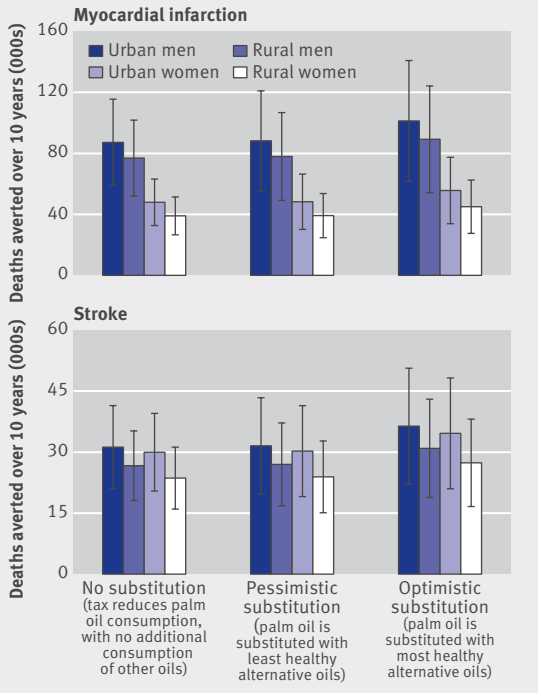
Source(s) of effectiveness

We used international meta-analyses to capture the relative risk reduction for myocardial infarctions and strokes associated with changes in consumption of palm and other oils.

Data sources

We projected 10 year outcomes by using population representative data from the World Health Organization's household surveys and prevalence metrics, describing cardiovascular risks (including systolic blood pressure, total cholesterol, tobacco use, prevalence of diabetes, and pre-existing coronary heart disease and cerebrovascular disease) among both men and women aged 20 to 79 years in urban and rural locations.

Estimated deaths from myocardial infarction and stroke averted in India from palm oil tax, 2014-25



Results of sensitivity analysis

Among the various oils that may be substituted for palm oil, an increase in soybean oil consumption conferred the greatest cardiovascular benefit because it contains the highest quantity of polyunsaturated fat. A 1% rise in the consumption of soybean oil increased the number of averted myocardial infarctions and strokes by 0.5%.

Limitations

The model uses total cholesterol rather than a complete lipid profile to predict risk of cardiovascular disease. Complex mechanistic understandings of low density lipoprotein profiles, high density lipoprotein profiles, and ultimate outcomes are not accounted for in this model, as nationally representative data on these cholesterol components are unavailable for India.

Study funding/potential competing interests

The study was funded by the National Institute on Aging, the Stanford Woods Institute for the Environment, and the International Development Research Centre of Canada.

Tamsulosin treatment for benign prostatic hyperplasia and risk of severe hypotension in men aged 40-85 years in the United States: risk window analyses using between and within patient methodology

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EDITORIAL by Ramirez

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STUDY QUESTION What is the risk of severe hypotension needing hospital admission in middle aged and older men treated with tamsulosin for benign prostatic hyperplasia?

SUMMARY ANSWER We observed a temporal association between tamsulosin and severe hypotension during the first eight weeks after initiating tamsulosin treatment and during the first eight weeks after restarting tamsulosin treatment in repeat users.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Non-selective α adrenergic antagonists are known to increase the risk for dizziness and orthostatic hypotension. We identified that tamsulosin, a selective α1a receptor antagonist, shows a substantial "first dose phenomenon" in relation to hypotension needing hospital admission; physicians should focus on improving counseling strategies to warn patients regarding the first dose phenomenon with tamsulosin.

Participants and setting
Men aged 40-85 years with private US healthcare insurance entered the cohort at their first dispensing for tamsulosin (297 596) or a 5α reductase inhibitor (n=85 971) between January 2001 and June 2011 after a minimum of six months of healthcare enrolment. Healthcare claims data were obtained from the IMS Lifelink database in the United States.

Design, size, and duration
Population based retrospective cohort study (between patient methodology) and self controlled case series (within patient methodology).

Main results and the role of chance
Among 383 567 new users of study drugs, 2562 admissions to hospital for hypotension were identified. The incidence of severe hypotension was higher for tamsulosin (42.4 events per 10 000 person years) than for 5ARIs (31.3 events per 10 000 person years) or all accrued person time (29.1 events per 10 000 person years). Tamsulosin resulted in a roughly doubled risk for hypotension needing hospital admission during the first eight weeks after tamsulosin initiation and first weeks after restarting tamsulosin treatment. The self controlled case series gave similar results as the cohort analysis.

Risk of hypotension with tamsulosin treatment

	Rate ratio (95% CI)	
Time varying risk window	Cohort analysis	Self controlled case series
New use (weeks 1-4)	2.12 (1.29 to 3.04)	2.56 (2.15 to 3.05)
New use (weeks 5-8)	1.51 (1.04 to 2.18)	1.66 (1.30 to 2.11)
New use (weeks 9-12)	1.16 (0.83 to 1.61)	1.54 (1.19 to 2.01)
Restarting treatment (weeks 1-4)	1.84 (1.46 to 2.33)	1.58 (1.24 to 2.01)
Restarting treatment (weeks 5-8)	1.85 (1.45 to 2.36)	1.60 (1.25 to 2.05)
Restarting treatment (weeks 9-12)	1.34 (0.97 to 1.84)	1.19 (0.86 to 1.64)
Maintenance treatment	1.19 (1.07 to 1.32)	1.38 (1.21 to 1.57)

Bias, confounding, and other reasons for caution
We did not have access to information on ethnicity, socioeconomic status, or lifestyle factors in our data. The close temporality of hypotension risk to tamsulosin initiation and similar results in a self controlled analysis suggest this confounding could have been minimal. Resultant rate ratios must be interpreted within the context of prescribing practice: rate ratios for hypotension in later risk windows (for example, weeks 5-8, 9-12) represent hypotension risk among patients who probably tolerated earlier risk windows of exposure (such as weeks 1-4) without having a hypotension event that led to hospital admission. Patients compliant with tamsulosin treatment may also achieve better control of lower urinary tract symptoms, which could result in a lower risk of falls, supporting the importance of optimizing drug adherence.

Generalisability to other populations
This analysis is generalisable to men aged 40-85 years with private healthcare insurance (including Medicare Advantage) who initiate tamsulosin treatment.

Study funding/potential competing interests
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the McGill University Health Center, Fonds de la Recherche en Santé du Québec, and the Ministère de la Santé et des Services Sociaux for the submitted work; JMB has received peer review financial support from le Fonds de la Recherche en Santé du Québec, JACD has a research grant from the Agency for Healthcare Research and Quality, AGH is a principal investigator for the Observational Medical Outcomes Partnership, a private-public partnership designed to help improve drug safety monitoring, and STB is employed by the US Food and Drug Administration; no other relationships or activities that could appear to have influenced the submitted work.