Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study

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EDITORIAL by Mant and McManus

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Cite this as: *BMJ* 2015;350:h158
doi: 10.1136/bmj.h158

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h158

thebmj.com

- Analysis: Too Much Medicine: Mild hypertension in people at low risk (*BMJ* 2014;349:g5432)
- Analysis: Navigating the shoals in hypertension: discovery and guidance (*BMJ* 2012;344:d8218)
- Head to Head: Is systolic blood pressure all that matters? (*BMJ* 2009;339:b2665)

STUDY QUESTION

What blood pressure level should be targeted in the general population, and how soon should high blood pressure be treated?

SUMMARY ANSWER

A systolic blood pressure target higher than 150 mm Hg, delays of greater than 1.4 months before antihypertensive medication intensification after systolic blood pressure elevation, and delays of greater than 2.7 months before blood pressure follow-up after medication intensification are associated with an increased risk of an acute cardiovascular event or death from any cause.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

How soon patients with elevated blood pressure should be treated and what blood pressure levels should be targeted is not well understood. The findings of this study provide evidence that delays in treatment of high blood pressure are associated with increased risk of cardiovascular events and death.

Participants and setting

We included adults with a diagnosis of hypertension in primary care practices in the United Kingdom.

Design, size, and duration

We studied hypertension treatment strategies (defined by systolic medication intensification threshold, time to intensification after the first elevated blood pressure, and time to follow-up after medication intensification over the course of a 10 year treatment strategy assessment period) in 88 756 patients treated between 1986 and 2010 in a retrospective cohort analysis. We analyzed rates of acute cardiovascular events or death from any cause over the mean follow-up period of 37.4 months by using a Cox regression model.

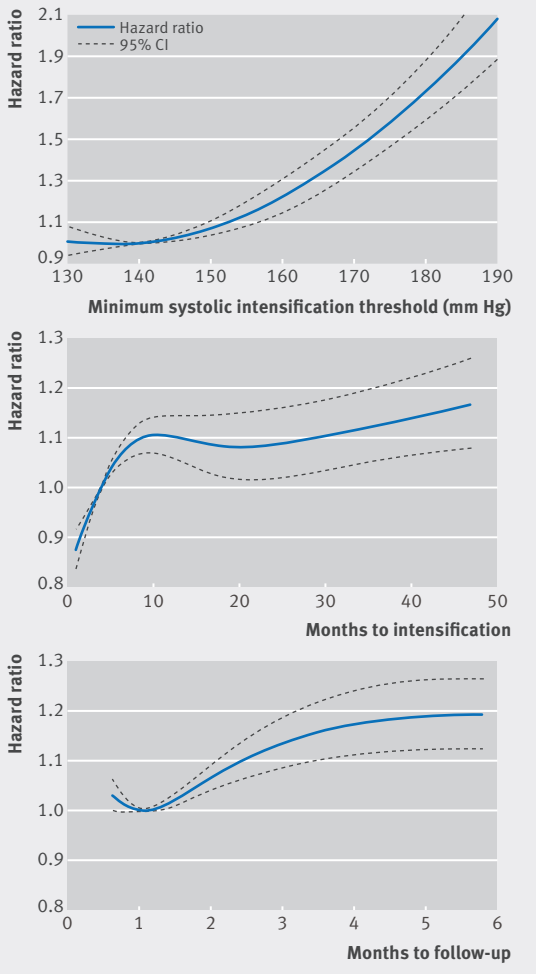
Main results and the role of chance

Over the follow-up period, 9985 (11.3%) participants had an acute cardiovascular event or died. We found no difference in the risk of the composite outcome between systolic intensification thresholds of 130 to 150 mm Hg, whereas systolic intensification thresholds greater than 150 mm Hg were associated with a progressively greater risk. Outcome risk increased progressively from the lowest (0-1.4 months) to the highest fifth of time to medication intensification. The highest fifth of time to follow-up (>2.7 months) was also associated with increased outcome risk.

Bias, confounding, and other reasons for caution

The multivariable analysis was adjusted for age; sex; smoking status; socioeconomic deprivation; history of diabetes, cardiovascular disease, or chronic kidney disease; Charlson comorbidity index; body mass index; medication possession ratio (a proxy for compliance); and baseline blood pressure. A higher risk of cardiovascular events and death at shorter time to follow-up may be explained by indication bias (patients with other life threatening comorbidities may have been seen sooner). Conclusions about causality cannot be drawn from this retrospective study.

Hazard ratios for cardiovascular event or death



Generalizability to other populations

The results may not be generalizable to patients who are at higher risk of cardiovascular events, adverse reactions to antihypertensive medications, or both (for example, older patients and those with diabetes or chronic kidney disease).

Study funding/potential competing interests

The study was funded by Harvard Medical School Center for Primary Care.

Alternate Healthy Eating Index 2010 and risk of chronic obstructive pulmonary disease among US women and men: prospective study

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Cite this as: *BMJ* 2015;350:h286
doi: 10.1136/bmj.h286

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h286

thebmj.com

- Research: Mediterranean diet and telomere length in Nurses' Health Study (*BMJ* 2014;349:g6674)
- Analysis: Food policies for healthy populations and healthy economies (*BMJ* 2012;344:e2801)
- Analysis: Potential causes and health effects of rising global food prices (*BMJ* 2009;339:b2403)

STUDY QUESTION

Does a longitudinal association exist between the Alternate Healthy Eating Index 2010 (AHEI-2010)—a measure of diet quality—and the risk of newly diagnosed chronic obstructive pulmonary disease (COPD)?

SUMMARY ANSWER

A higher AHEI-2010 diet score (reflecting high intakes of whole grains, polyunsaturated fatty acids, nuts, and long chain omega-3 fats and low intakes of red/processed meats, refined grains, and sugar sweetened drinks) was associated with a lower risk of COPD in both women and men.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The role of dietary scores in risk of chronic obstructive pulmonary disease (COPD) is unknown, but previous studies have found a lower risk of COPD associated with increased intake of antioxidants and a greater risk of COPD associated with increased intake of processed meats.
Although COPD prevention efforts should continue to focus on smoking cessation, these prospective findings support the importance of a healthy diet in multi-interventional programs to prevent COPD.

Participants and setting

We included 73 228 female nurses from the Nurses' Health Study (n=121 701 US women, 30-55 years old in 1976) and 47 026 men from the Health Professionals Follow-up Study (n=51 529 US health professionals, 40-75 years old in 1986). Follow-up questionnaires were sent every two years. Women completed a food frequency questionnaire in 1984 and men in 1986. Similar questionnaires were sent every two to four years thereafter.

Design, size, and duration

Over the study period, 723 cases of newly diagnosed COPD occurred in women (1984-2000) and 167 in men (1986-98). Eleven components are summed to obtain a total AHEI-2010 score, which ranges from 0 to 110, with a higher score representing a healthier diet. We identified the AHEI-2010 score from each food frequency questionnaire administered. To reduce measurement errors and to better represent long term dietary intake, we calculated the cumulative average of AHEI-2010, divided it into fifths, and used it as a time dependent variable. Multivariable hazard ratios were adjusted for age, physical activity, body mass index, total energy intake, smoking status, pack years of smoking, second hand tobacco exposure (women only), race/ethnicity, physician visits, US region, spouse's highest educational attainment (women only), and menopausal status (women only).

Association between Alternate Healthy Eating Index 2010 (AHEI-2010) and risk of newly diagnosed chronic obstructive pulmonary disease in women and men

AHEI-2010	No of cases	Person years	Hazard ratio† (95% CI)	P value‡
Lowest fifth*	251	324 879	1.00 (referent)	
Second fifth	195	330 995	0.81 (0.51 to 1.29)	0.07
Third fifth	195	332 405	0.98 (0.80 to 1.18)	0.50
Fourth fifth	137	334 571	0.74 (0.59 to 0.92)	0.33
Highest fifth*	112	336 022	0.67 (0.53 to 0.85)	0.63
P for trend			<0.001	

*Lowest fifth corresponds to least healthy diet according to AHEI-2010 diet score; highest fifth corresponds to healthiest diet.
†See text for adjustment variables.
‡Test for between studies heterogeneity.

Main results and the role of chance

In the pooled analysis, after control for several potential confounders, the risk of COPD was one third lower in participants who ate the healthiest diet according to the AHEI-2010 (highest fifth) compared with those who ate the least healthy diet (lowest fifth).

Bias, confounding, and other reasons for caution

Newly diagnosed COPD was defined by a self reported physician's diagnosis of COPD by the health professionals who comprise the two cohorts; lung function measures were not available. The main source of disease misclassification is probably a misdiagnosis with asthma, but our findings for AHEI-2010 and incident asthma were completely null. We acknowledge that the association between AHEI-2010 and COPD may be due, at least in part, to residual confounding by cigarette smoking.

Generalizability to other populations

The two cohorts comprise health professionals and, as such, are not necessarily generalizable to the general population. Health awareness, socioeconomic status, and smoking behavior might differ significantly between our study population and the general population. Moreover, our study population was mainly non-Hispanic white, which might limit generalizability of our results to other racial/ethnic populations.

Study funding/potential competing interests

The National Institute of Health (Bethesda, Maryland, United States) funded the study.

Labour induction with prostaglandins: a systematic review and network meta-analysis

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Cite this as: *BMJ* 2015;350:h217
doi: 10.1136/bmj.h217

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h217

thebmj.com

- Practice: What is the optimal pharmacological management of retained placenta? (*BMJ* 2014;349:g4778)
- Research News: Inducing labour reduces risk of caesarean delivery by 12% (*BMJ* 2014;348:g2960)
- Research: Outcomes of elective induction of labour compared with expectant management (*BMJ* 2012;344:e2838)

STUDY QUESTION

Which prostaglandins are most effective and safe for labour induction?

SUMMARY ANSWER

Titrated low dose oral misoprostol solution seems to be the safest in terms of caesarean section risk, while high dose vaginal misoprostol tablets (≥50 µg) are the most effective in achieving vaginal delivery within 24 hours of induction.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Various prostaglandins have been tested in randomised trials, but their relative effectiveness and safety have not been comprehensively compared in a single quantitative overview. This network meta-analysis simultaneously compares prostaglandin treatments in a coherent, methodologically robust manner, and suggests misoprostol is probably superior to dinoprostone (prostaglandin E_2) for labour induction.

Selection criteria for studies

We searched the Cochrane Pregnancy and Childbirth Group's Database of Trials. We included all randomised trials that compared a prostaglandin or prostaglandin analogue used for third trimester cervical ripening or labour induction with placebo or no treatment, with the same prostaglandin administered by a different route or dose, or with a different type of prostaglandin. We included only studies recruiting women with a viable fetus, but had no restrictions relating to indication for labour induction, language, or date of publication.

Primary outcome(s)

Vaginal delivery not achieved within 24 hours; caesarean section (any indication); serious neonatal morbidity or perinatal death; serious maternal morbidity or death; and uterine hyperstimulation with fetal heart rate changes.

Main results and role of chance

Relative to placebo, the odds of failing to achieve a vaginal delivery within 24 hours were lowest for vaginal misoprostol (≥50 µg) (odds ratio 0.06 (95% credible interval 0.02 to 0.12)), with a 39% absolute probability of event (95% credible interval 1% to 94%). Compared with placebo, the risk of caesarean section was lowest for titrated oral misoprostol solution (<50 µg) (odds ratio 0.64 (0.49 to 0.83)), with an absolute probability of event of 15% (3% to 40%).

Bias, confounding, and other reasons for caution

Analyses were restricted to trials at low risk of bias for allocation concealment. Findings from the analysis are more likely to be applicable to settings with cardiotocography and immediate access to caesarean section. Mortality and serious morbidity were rarely reported, and assessment of safety was therefore limited to caesarean section. All prostaglandins are known to cause uterine rupture, and findings must be interpreted in this context.

Study funding/potential competing interests

The work was supported by the National Institute for Health Research. DMC is supported by an MRC Population Health Scientist fellowship.

Ranking of treatments for risk of caesarean section and for failure to achieve vaginal delivery within 24 hours

	Caesarean section		No vaginal delivery within 24 hours	
Rank	Treatment	Rank 95% CrI	Treatment	Rank 95% CrI
1 (best)	Titrated oral misoprostol solution (<50 µg)	1 to 5	Vaginal misoprostol (≥50 µg)	1 to 4
2			Titrated oral misoprostol solution (<50 µg)	1 to 7
3	Vaginal misoprostol (≥50 µg)	1 to 7		
	Oral misoprostol tablet (≥50 µg)	1 to 7		
4	Vaginal misoprostol (<50 µg)	2 to 8	Vaginal PGE2 gel	2 to 8
			Vaginal misoprostol (<50 µg)	2 to 7
5			Vaginal PGE2 tablet	1 to 9
6	Vaginal PGE2 gel	3 to 9	Oral misoprostol tablet (>50 µg)	3 to 8
7	Intracervical PGE2	4 to 10	Vaginal PGE2 pessary (slow release)	3 to 10
			Misoprostol pessary sustained release	1 to 11
8	Vaginal PGE2 pessary (slow release)	2 to 11		
9	Vaginal PGE2 tablet	3 to 12	Intracervical PGE2	7 to 10
	PGF2 gel	1 to 12		
	Sustained release misoprostol pessary	1 to 12		
10	Vaginal PGE2 pessary	3 to 12	Oral misoprostol tablet (<50 µg)	4 to 11
11 (worst)	Oral misoprostol tablet (<50 µg)	3 to 12	Vaginal PGE2 pessary	6 to 11

95% CrI=95% credible interval. PGE2=prostaglandin E_2. PGF2=prostaglandin F_2.

The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study

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Cite this as: *BMJ* 2015;350:h246
doi: 10.1136/bmj.h246

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;350:h246

thebmj.com

- Analysis: Dabigatran, bleeding, and the regulators (*BMJ* 2014;349:g4517)
- Practice: Practical management of coagulopathy associated with warfarin (*BMJ* 2010;340:c1813)

STUDY QUESTION

How does kidney function affect the rate of major bleeding in older adults with atrial fibrillation starting warfarin?

SUMMARY ANSWER

Reduced kidney function was associated with an increased risk of major bleeding among older adults with atrial fibrillation starting warfarin. Excess risks from reduced kidney function were most pronounced during the first 30 days of treatment.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

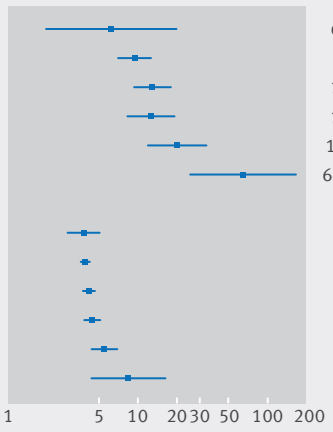
Although the risk of bleeding is considerably higher among patients who require dialysis than in the general population, there are limited data about the bleeding risk associated with warfarin treatment in people with different stages of chronic kidney disease. Our study suggests that the risk of warfarin treatment should be carefully weighed against the potential benefits based on the presence of comorbidities and the assessment of bleeding risk among patients with reduced kidney function (for example, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2); particularly in those with very reduced kidney function and during the first 30 days of treatment.

Participants and setting

Adults in Alberta, Canada, aged ≥66 years, with atrial fibrillation who started warfarin treatment between 1 May 2003 and 31 March 2010 and had a measure of kidney function at baseline.

Adjusted rates (per 100 person years) of major bleeding by estimated glomerular filtration rate

	No of events	Person years	Incidence rates per 100 person years (95% CI)	P value for trend
First 30 days of warfarin treatment				
≥90	3	47.2	6.1 (21.9 to 19.4)	0.001
60-89	55	500.1	9.2 (6.9 to 12.3)	
45-59	45	261.1	12.7 (9.2 to 17.6)	
30-44	29	147.2	12.4 (8.2 to 18.6)	
15-29	17	46.7	19.8 (11.7 to 33.5)	
<15	5	4.2	63.4 (24.9 to 161.6)	
After 30 days of warfarin treatment				
≥90	47	1450.6	3.7 (2.7 to 5.0)	0.002
60-89	585	15693.6	3.8 (3.5 to 4.1)	
45-59	353	8049.8	4.1 (3.7 to 4.5)	
30-44	213	4074.3	4.3 (3.7 to 5.0)	
15-29	82	1120.9	5.4 (4.3 to 6.8)	
<15	9	79.8	8.3 (4.2 to 16.1)	



Design, size, and duration

Retrospective cohort study of 12 403 older adults with atrial fibrillation followed up for a median duration of 2.1 years. Data obtained at baseline included an outpatient serum creatinine measurement for estimation of kidney function (primary exposure), sociodemographic information, comorbidities (diabetes, hypertension, myocardial infarction, congestive heart failure, cerebrovascular disease, and 12 other conditions), and drug use (antiplatelets, non-steroidal anti-inflammatory drugs, and proton pump inhibitors). The outcome measure was admission to hospital or visit to an emergency department for major bleeding (intracranial, upper and lower gastrointestinal, or other) reported as unadjusted and adjusted rates (per 100 person years) based on Poisson regression models.

Main results and the role of chance

Of 12 403 participants, 45% had an eGFR <60 mL/min/1.73m^2. Overall, 1443 (11.6%) experienced a major bleeding episode over the follow-up period. During the first 30 days of warfarin treatment, unadjusted and adjusted rates of major bleeding were higher at lower eGFR (P for trend <0.001 and 0.001, respectively). Adjusted bleeding rates per 100 person years were 63.4 (95% confidence interval 24.9 to 161.6) in participants with eGFR <15 mL/min/1.73m^2 compared with 6.1 (1.9 to 19.4) among those with eGFR >90 mL/min/1.73m^2 (adjusted incidence rate ratio 10.3, 95% confidence interval 2.3 to 45.5).

Bias, confounding, and other reasons for caution

We specifically focused on the safety, not efficacy, of warfarin treatment by kidney function in people with atrial fibrillation. Our results should be weighed against the potential benefit of warfarin treatment in this population. Our study included a large cohort of people with atrial fibrillation, but the number of participants with substantially reduced kidney function (<30 mL/min/1.73m^2) compared with those with normal or moderate kidney function, was small.

Generalisability to other populations

Our results are generalisable to most people who would be considered for warfarin to prevent stroke.

Study funding/potential competing interests

MTJ received an honorarium for presentation at an industry sponsored conference by Amgen. WCW serves on an event adjudication committee for a prospective study of an arrhythmia device in patients requiring haemodialysis sponsored by Medtronic. This study is based in part by data provided by Alberta Health and Alberta Health Services.