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RESEARCH


KAREN BRETT/SPL

THIS WEEK'S RESEARCH QUESTIONS

End of life care in older people

In the 1990s, the landmark SUPPORT trial found that documenting patient and family preferences for end of life care failed to improve care or patient outcomes (*JAMA* 1995;274:1591-8). Since then, studies of advance planning for end of life care have been inconclusive—but now Karen M Detering and colleagues' randomised controlled trial suggests that such planning may, after all, have a benefit (p 847).

They assessed 309 patients aged 80 or older who were being treated in a large university hospital in Melbourne, Australia. Among the 56 patients who had died by six months, end of life wishes were much more likely to be known and followed in the patients who had been randomly assigned to receive advance care planning. Furthermore, advance planning reduced stress, anxiety, and depression in family members of the deceased patients.

A large study of patients aged 60 and older, published this month in the *New England Journal of Medicine*, likewise found that those who had prepared advance directives received care that was strongly associated with their preferences (*N Engl J Med* 2010;362:1211-8).

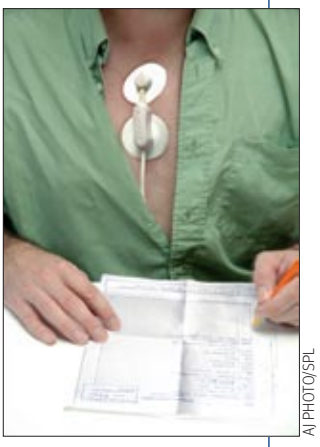
A poll of more than 4000 people conducted by BMJ Group found that palliative care at the end of life is the area in which doctors believe they can make the greatest difference to patient care (http://makingadifference.bmj.com). BMJ Group has committed to improving end of life care by commissioning and supporting work in this area through the Making a Difference campaign. This research will hopefully supplement such plans and help ensure that in the future the elderly receive care as much in line with their needs and wishes as possible.

Subgroup effects—true or false?

Researchers often split up trial data into subgroups to look for effects in particular segments of the study population. Such differences, if real, could be important for practice—but subgroup analyses are notoriously unreliable, and many proposed subgroup effects are later shown to be spurious.

In this week's Research Methods and Reporting article, Xin Sun and colleagues aim to help clinicians decide which subgroup analyses to believe (p 850). They suggest criteria that could improve existing measures of credibility, and they propose a restructured checklist of items addressing study design, analysis, and context.

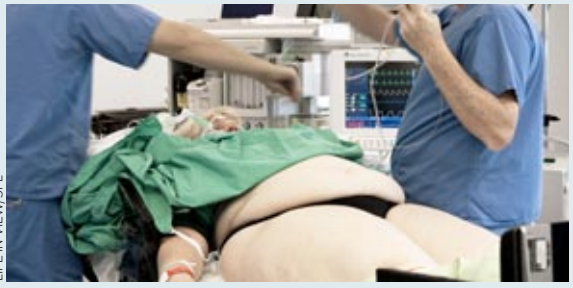
Blood pressure control


AJ PHOTO/SPL

Two studies in this week's journal look at the management of hypertension. Ambulatory blood pressure predicts cardiovascular outcomes better than clinic values, so Geoff Head and colleagues set out to determine the ambulatory equivalents of recognised clinic blood pressure thresholds used in the diagnosis and treatment of hypertension (p 849), using data from a cohort of patients with existing risk factors. The estimated ambulatory thresholds turned out to be slightly lower than the corresponding clinic values. Clinic values measured by doctors were higher than those measured by trained, non-medically qualified staff, and were not useful for predicting ambulatory thresholds.

Giuseppe Mancia and colleagues, meanwhile, contribute to the unsettled debate on whether statins work independently to reduce blood pressure (p 846). In their randomised, placebo controlled trial, statins seemed to offer no additional reduction in blood pressure for patients who were also taking antihypertensive drugs.

LATEST RESEARCH: For these and other new research articles see http://www.bmj.com/channels/research.dtl


LIFE IN VIEW/SPL

Impact of bariatric surgery on hypertension in pregnancy
Hypertension gets further attention online this week. Hypertensive disorders are a common cause of perinatal morbidity and mortality in the United States, and Wendy L Bennett and colleagues investigated whether weight loss surgery could reduce this problem in obese women. They found that women who underwent bariatric surgery before pregnancy had substantially lower rates of hypertensive disorders during pregnancy than those who had surgery after delivery, even after adjustment for other risk factors. This finding applied to all severities of hypertensive complication—pre-eclampsia and eclampsia, chronic hypertension, and gestational hypertension (doi:10.1136/bmj.c1662).

Statins, antihypertensive treatment, and blood pressure control in clinic and over 24 hours: evidence from PHYLLIS randomised double blind trial

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STUDY QUESTION In addition to their cholesterol lowering effect, do statins exert a blood pressure lowering effect?

SUMMARY ANSWER In patients with hypertension and hypercholesterolaemia whose blood pressure is effectively reduced by antihypertensive treatment, statins offer no additional blood pressure lowering effect over 24 hours.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Several studies have reported that statins exert a blood pressure lowering effect, which might be an additional protective mechanism of these drugs. In a long term prospective placebo controlled study, using ambulatory blood pressure monitoring in patients with hypercholesterolaemia and treated hypertension, no such effect was evident.

Study design

PHYLLIS (Plaque Hypertension Lipid-Lowering Italian Study) had a placebo controlled, double blind, double dummy factorial design. The participants were randomised to antihypertensive treatment (hydrochlorothiazide 25 mg or fosinopril 20 mg once daily) with the addition of pravastatin 40 mg once daily or placebo. Nifedipine GITS 30 mg could be added if systolic blood pressure was not reduced below 140 mm Hg.

Participants and setting

The study included 508 men and postmenopausal women aged 45-70 years, recruited in 13 Italian hospitals, with no history of cardiovascular events and with untreated or uncontrolled hypertension, hypercholesterolaemia, and asymptomatic carotid artery atherosclerosis.

Primary outcome(s)

The main outcome of this analysis was the comparison between the reduction in 24 hour ambulatory systolic blood pressure in the groups with and without pravastatin.

Main results and the role of chance

In each group a clear sustained reduction in clinic, 24 hour, daytime, and night-time systolic and diastolic blood pressure occurred. The pravastatin group performed slightly worse than the placebo group, and the between group differences did not exceed 1.9 (95% confidence interval −0.6 to 4.3, P=0.13) mm Hg throughout the treatment period. The sample size of the study was sufficient to detect a difference of 4.04 mm Hg in 24 hour average systolic blood pressure.

Harms

A previous publication from the PHYLLIS dataset did not report significant differences in safety profile between study groups.

Bias, confounding, and other reasons for caution

The main area of uncertainty was the possible influence of add-on nifedipine GITS. However, restricting the analysis to patients who remained on antihypertensive monotherapy throughout the study did not reveal any blood pressure lowering effect of pravastatin. The other possible source of error might have derived from differences in response size between patients with different baseline blood pressure levels. We found no interaction between baseline blood pressure and the effects of pravastatin on blood pressure, however.

Generalisability to other populations

The characteristics of PHYLLIS participants restrict our conclusions to patients with high blood pressure who receive effective antihypertensive treatment. On-treatment ambulatory and clinic blood pressure remained well above normal values, however, leaving potential for a further reduction in blood pressure. Most cardiovascular effects of statins are reported to be common to the class, and the lipid lowering efficacy of this statin is in line with the results of other studies, suggesting that the lack of blood pressure lowering effect of pravastatin in PHYLLIS might be extrapolated to other statins.

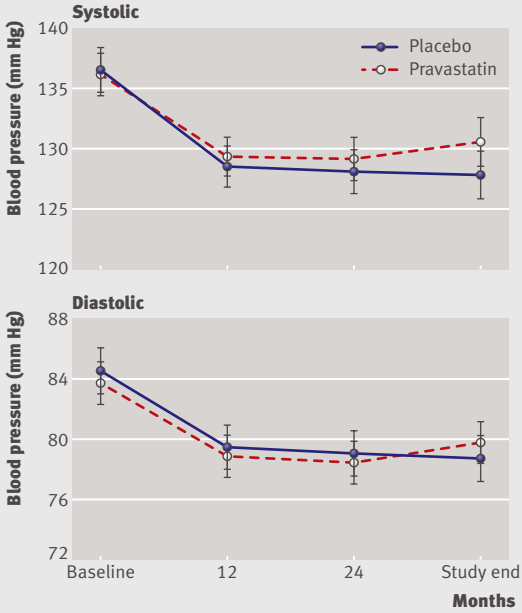
Study funding/potential competing interests

PHYLLIS was an investigator generated trial sponsored by Bristol-Myers Squibb Italy, Rome, and Menarini, Florence. All authors carried out this research project in full independence from funders. GC, GM, AZ, GP, and FV have received research grants or honorariums for lectures from the sponsors.

Trial registration number

BRISQUI_*IV_2004_001 (registered at Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali—National Monitoring Centre on Clinical Research with Medicines).

MEAN 24 HOUR SYSTOLIC AND DIASTOLIC BLOOD PRESSURE



All values during treatment were always significantly different from those at baseline (P<0.001); baseline and on-treatment values were not significantly different between treatment groups

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1197

The impact of advance care planning on end of life care in elderly patients: randomised controlled trial

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STUDY QUESTION What is the impact of coordinated advance care planning on end of life care?

SUMMARY ANSWER Coordinated advance care planning ensures that patients' end of life wishes are known and respected and improves end of life care from the perspective of both patients and their relatives.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS End of life care is often poor and is not improved by focusing on completion of advance directives only. Coordinated, systematic patient centred advance care planning improved end of life care and reduced the incidence of anxiety, depression, and post-traumatic stress in surviving relatives.

Design
This was a prospective randomised controlled trial of a coordinated approach to advance care planning. Participants were randomised to receive usual care or usual care plus facilitated advance care planning. Advance care planning aimed to assist patients to reflect on their goals, values, and beliefs; to consider future preferences for medical treatment; to appoint a surrogate; and to document their wishes. Randomisation was carried out using sealed envelopes containing allocation cards assigned by random number.

Participants and setting
Participants were competent, English speaking, medical inpatients (internal medicine, cardiology, or respiratory medicine) aged 80 or more. This study was carried out in a university hospital in Melbourne, Australia.

Primary outcome(s)
The primary outcome was whether a patient's end of life wishes were known and respected. Other outcomes included patient and family satisfaction with hospital stay and levels of stress, anxiety, and depression in relatives of patients who died.

Main results and the role of chance
We enrolled 309 patients: 125 of 154 (81%) assigned to advance care planning received the intervention. Of these, 108 (84%) expressed wishes, appointed a surrogate, or both. Only one patient in the control group received advance care planning. Fifty six patients had died at six months. End of life wishes were more likely to be known and followed in the intervention group (25/29, 86%) compared with the control group (8/27, 30%; P<0.001).

Harms
No harms were identified in this study.

Bias, confounding, and other reasons for caution
There is no known bias or confounding factors or other reasons for caution.

Generalisability to other populations
Although this was a single centre study of a complex intervention, therefore potentially influenced by local cultural and systemic factors, our model of advance care planning is none the less likely to be generalisable to other healthcare settings. The Respecting Patient Choices model of advance care planning is derived from Respecting Choices, a programme that has been successfully implemented in multiple health services in the United States, as well as Canada, Germany, Spain, and Singapore. Furthermore, the Respecting Patient Choices programme has been implemented into health services in each Australian state and territory.

Study funding/potential competing interests
No funding was received for this study. We have no competing interests.

Trial registration number
Australian New Zealand clinical trials registry ACTRN12608000539336.

OUTCOMES IN PATIENTS WHO DIED

	No (%) of patients		
Outcomes	Intervention (n=154)	Control (n=155)	P value of difference
Deaths (n=56)	29	27	0.75
Patients with advance care planning	25 (86)*	0	<0.001
Patients with wishes known and followed	25 (86)	8 (30)	<0.001
Patients with wishes unknown	3 (10)	17 (63)	<0.001
Patients with wishes known but not followed	1 (3)	2 (7)	0.51

Surviving relatives in intervention group had significantly less stress (P<0.001), anxiety (P=0.02), and depression (P=0.002) compared with control group. Patient and family satisfaction was higher in intervention group.

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1345

WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense *Plasmodium falciparum* transmission: prospective study

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STUDY QUESTION Does the World Health Organization's "Guideline for care at the first-referral level in developing countries" provide appropriate advice for prescribing antibiotics to febrile children in an area of intense malaria transmission?

SUMMARY ANSWER WHO guidelines failed to identify almost a third of children with invasive bacterial disease, and more than half of the organisms isolated were not susceptible to currently recommended antimicrobials.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Overlapping clinical features of malaria and bacterial disease create difficulties in distinguishing between invasive bacterial disease and malaria in African children. The addition of simple and available clinical criteria may significantly increase detection of invasive bacterial disease in African children with severe or fatal illness.

Participants and setting

The study took place in a district hospital in an area of Tanzania that has intense transmission of malaria. We included all children aged 2 months to 13 years admitted for febrile illness with fever or a history of fever in the previous 48 hours and no obvious non-infectious cause for the fever.

Design, size, and duration

The study ran from June 2006 to May 2007. All children admitted to the paediatric ward during study hours were given emergency treatment as necessary and then screened for eligibility for the study. Clinical officers used a standard medical history and examination based on the WHO criteria to assess children admitted to the study. Blood was drawn for culture, haemoglobin, glucose concentrations, serum lactate, rapid diagnostic test for *Plasmodium falciparum*, and a full blood count. We tested all children for HIV by antibody tests with polymerase chain reaction when indicated.

Main results and the role of chance

We enrolled 3639 children, of whom 184 (5.1%) died; 2195 (60.3%) were blood slide positive for *Plasmodium falciparum*, 341 (9.4%) had invasive bacterial disease, and 142 (3.9%) were seropositive for HIV. Mortality was significantly higher among children with invasive bacterial disease (58/341; 17%) than in children without invasive bacterial disease (126/3298; 3.8%) (P<0.001), and this was true regardless of the presence of *P falciparum* parasitaemia. The sensitivity and specificity of the WHO criteria in identifying invasive bacterial disease in slide positive children were 60.0% (95% confidence interval 58.0% to 62.1%) and 53.5% (51.4% to 55.6%), compared with 70.5% (68.2% to 72.9%) and 48.1% (45.6% to 50.7%) in slide negative children. In children with WHO criteria for invasive bacterial disease, only 99/211(47%) of isolated organisms were susceptible to the first recommended antimicrobial.

Bias, confounding, and other reasons for caution

This was a single site study in an area with a very high malaria transmission rate. The intensity of malaria transmission varies over time and place, and this will affect the applicability of the results.

Generalisability to other populations

Consistency of the findings with other studies suggests that these results are generalisable to other areas of Africa that have high rates of malaria transmission.

Study funding/potential competing interests

Core funding for the study was provided by European Commission (Europaid) grant code SANTE/2004/078-607. BN was supported by grants from the Berkeley Fellowship, Sir Halley Stewart Trust, and Pfizer Pharmaceuticals. Pfizer Pharmaceuticals provided equipment and consumables for microbiology. Abbott Pharmaceuticals provided reagents for HIV testing. Netspear funded the E-tests performed at the KEMRI/Wellcome Trust Centre for Geographic Medicine (Coast), Kilifi, Kenya. None of the funders had a role in the design, analysis, or interpretation of results.

SENSITIVITY AND SPECIFICITY OF WHO CRITERIA FOR ANTIMICROBIAL TREATMENT IN IDENTIFYING CHILDREN WITH INVASIVE BACTERIAL DISEASE

	Total cases (No; % died)	No (%) with IBD	Sensitivity—% (95% CI)	Specificity—% (95% CI)	PPV (%)	NPV (%)	NNT*	% fatal cases with IBD treated†
RDT and slide negative‡	943 (56; 5.9)	143 (15.2)	72.7 (69.9 to 75.6)	47.3 (44.1 to 50.4)	19.8	90.6	5.1	88.9
RDT positive, slide negative§	501 (33; 6.6)	98 (19.6)	67.3 (63.2 to 71.5)	49.9 (45.5 to 54.3)	24.6	86.3	4.1	83.3
Slide positive <5000/µl	405 (19; 4.7)	33 (8.1)	60.6 (55.9 to 65.4)	51.9 (47.0 to 56.8)	10.1	93.7	10.1	80.0
Slide positive 5000-50 000/µl	917 (33; 3.6)	31 (3.4)	67.7 (64.7 to 70.8)	55.9 (52.7 to 59.1)	5.1	98.0	19.6	66.7
Slide positive >50 000/µl	873 (43; 4.9)	36 (4.1)	52.8 (49.5 to 56.1)	51.6 (48.3 to 54.9)	4.5	96.2	22.3	60.0

IBD=invasive bacterial disease; NPV=negative predictive value; PPV=positive predictive value; RDT=rapid diagnostic test.
*Number needed to treat presumptively with antimicrobials to correctly treat one child with IBD.
†Proportion of all IBD associated fatalities with "guidelines for care at first-referral level" indication for antimicrobial treatment.
‡56 children were RDT negative and blood slide positive and are included in slide positive data (sensitivity of RDT compared with slide reading was 97.4%).
§Assumed to indicate recent infection with *P falciparum*.

Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: a prospective cohort study

Ambulatory Blood Pressure Working Group of the High Blood Pressure Research Council of Australia

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STUDY QUESTION What are the ambulatory blood pressure equivalents of thresholds for clinic blood pressure in the diagnosis and treatment of hypertension?

SUMMARY ANSWER Thresholds for daytime ambulatory blood pressure are slightly lower than clinic values.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Ambulatory blood pressure predicts cardiovascular outcome better than clinic blood pressure and equivalent thresholds for the diagnosis of mild hypertension have been established. However, ambulatory equivalents have not been defined for patients with existing cardiovascular disease or risk factors. We provide equivalent daytime ambulatory blood pressure measurements for recognised diagnostic thresholds and targets.

Participants and setting

Participants (n=8529) from 11 Australian centres referred by physicians for 24 hour blood pressure recordings, including individuals with known or suspected hypertension, and healthy people recruited from the general population by advertising. Average age 56 years (SD 16), 54% female (n=4626), mean body mass index 28.9 kg/m^2 (SD 5.5).

Design

Ambulatory blood pressure was recorded during a typical day with validated devices. Clinic blood pressure was measured by trained, non-medically qualified professional staff; data from four centres also included clinic blood pressure measured by referring doctor.

Primary outcome

Diurnal ambulatory blood pressure equivalents for a range of target clinic blood pressures used in the management of hypertension.

Main results

Based on regression analysis, the ambulatory equivalent for a clinic threshold of 140/90 mm Hg (lower limit of grade 1 hypertension) was 4/3 mm Hg lower, for 130/80 mm Hg (target upper limit for hypertension with associated condition) was 2/2 mm Hg lower, and for 125/75 mm Hg was 1/1 mm Hg lower. Ambulatory equivalent thresholds were 1/2 mm Hg lower for women than men and 3/1 mm Hg lower in people older than 65 than in the combined group (table). Clinic blood pressure measured by staff was 9/7 mm Hg lower than that measured by doctors (P<0.001), showing that doctors' measurements are inappropriate for use in the estimation of ambulatory thresholds.

Bias, confounding, and other reasons for caution

We used a mainly hypertensive population, with and without co-morbidities, to predict target values.

Generalisability to other populations

Restriction of the dataset to individuals not treated for hypertension did not significantly change the predicted values, suggesting that the findings are widely applicable to other populations.

Study funding/potential competing interests

Financial sponsorship for data analysis was from the High Blood Pressure Research Council of Australia. No authors had support from any company or had any non-financial interests that might be relevant to this work.

SYSTOLIC/DIASTOLIC AMBULATORY BLOOD PRESSURES PREDICTED FROM CLINIC LEVELS MEASURED BY TRAINED STAFF (MM HG)

	Seated clinic blood pressure threshold	Predicted daytime ambulatory equivalent	Predicted 24 hour ambulatory equivalent
Grade 3 (severe) hypertension	180/110	168/105	163/101
Grade 2 (moderate) hypertension	160/100	152/96	148/93
Grade 1 (mild) hypertension	140/90	136/87	133/84
Target blood pressure plus one condition	130/80	128/78	125/76
Target blood pressure with proteinuria	125/75	124/74	121/71
Normal blood pressure	120/80	120/78	117/76