In a randomised, double-blind, placebo-controlled trial, Michael Weber and colleagues[1] claim that darusentan is effective in lowering both clinic and ambulatory blood pressure in patients with resistant hypertension. This may well be, but one must be forgiven for being at least sceptical in the absence of detail on the method of blood-pressure measurement on which the results are totally dependent.

We are simply told that "Clinic blood-pressures were measured... in the seated position by standard sphygmomanometry. Ambulatory blood pressure monitoring was done for all patients... Automated readings were obtained every 20 min throughout the 24-h observations." What is "standard sphygmomanometry"? Was a mercury or automated device used? Were the observers trained in sphygmomanometry? Which bladders were used for obese patients? What device was used for ambulatory blood-pressure measurement? Had it been independently validated for accuracy according to a standard protocol? The issue of device accuracy is such as to justify a website that gives consumers who may wish to purchase devices, and researchers who may wish to check the validation status of devices used in studies, up-to-date information on all devices on the market.

For the **website on device accuracy** see http://www.dableducational.org/

This is not the first time that I have had to deplore the lack of methodological detail on blood-pressure measurement in elaborate studies in high-impact scientific journals,[2,3] and unfortunately I suspect it will not be the last.

I declare that I have no conflicts of interest.

Eoin O'Brien
eobrien@iol.ie

Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Ireland

1 Weber MA, Black H, Bakris G, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 1423–31.

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I wish to provide a brief comment on the impressive randomised trial by Michael Weber and colleagues,[1] which shows that the endothelin-receptor antagonist darusentan provides additional reductions in blood pressure in patients who have not attained their treatment goals with three or more antihypertensive drugs.

When awake, sympathetic activity is high and when asleep sympathetic activity is reduced and renin secretion increases.[2] Hermida and Ayala[3] have shown that a greater reduction in blood pressure can be achieved with night-time administration of ramipril (an angiotensin-converting-enzyme [ACE] inhibitor) than with morning dosing; the same effect may apply to angiotensin II antagonists.[4]

From a clinical practice point of view, it is worth discussing with patients when they take their specific antihypertensive medications and adjust the timing, if appropriate, before starting additional ones. In the case of ACE inhibitors, those that have shorter half lives or uncertain duration of action might be best given at night.[5]

I declare that I have no conflicts of interest.

Mark Naunton
mark.naunton@cdu.edu.au

Charles Darwin University, School of Environmental and Life Science, Darwin, NT 0909, Australia

1 Weber MA, Black H, Bakris G, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 1423–31.

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4 Hermida RC, Ayala DE, Fernández JR, Calvo C. Comparison of the efficacy of morning versus evening administration of telmisartan in essential hypertension. *Hypertension* 2007; **50:** 715–22.

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Authors' reply

In the doses described in our paper, darusentan provided clear efficacy in patients with treatment-resistant hypertension. Neeraj Dhaun and colleagues speculate that the flat dose response seen in the study could reflect on the selectivity of this antagonist of endothelin A receptors. Just as likely, however, is that we used doses that were at or above the maximum; as discussed in our paper, earlier experience has suggested that lower doses are associated with a dose response. We agree with Dhaun and colleagues that blood pressure reduction could partly explain the albuminuria-reducing effects of darusentan, although it is interesting that the higher drug doses seemed to produce a greater reduction than the lower dose despite similar blood pressure effects.

As Bhavneet Bharti and Sahul Bharti point out, there were more adverse events reported with the active drug than placebo, chiefly due to some occurrences of fluid retention. We concur with the conclusion of Dhaun and colleagues that this problem responds well to diuretic intervention. Further experience in patients with differing levels of renal function should provide guidance as to which types and doses of diuretics could be recommended as concomitant therapy with darusentan to prevent fluid retention.

Bharti and Bharti also enquire about certain confounders that might have affected our results. In fact, the use of non-steroidal anti-inflammatory drugs was prohibited during the study; moreover, we did account for diabetes in our analysis, and patients with secondary forms of hypertension, including hyperaldosteronism, were excluded from the trial. We acknowledge that future comparisons of darusentan with other potential treatments in patients with resistant hypertension would be of interest.

Eoin O'Brien asks for more information about blood pressure measurements. Indeed, we should have explained in our paper that all investigators undertook a rigorous training and certification programme in sphygmomanometry provided by external consultants. Ambulatory blood pressure was monitored with SpaceLabs devices; this manufacturer is one of the sponsors of the website recommended by O'Brien.

Mark Naunton raises the interesting idea that the antihypertensive efficacy of shorter-acting agents that interrupt the renin-angiotensin system might be enhanced if they are taken at night when activity of this system is greatest. Thus, it is possible that switching drug dosing from morning to evening could be beneficial in some patients with treatment-resistant hypertension and should be considered by practitioners.

MAW serves as a consultant to Gilead, the sponsor of the trial. JVL is an employee of Gilead.

*Michael A Weber, Jennifer V Linseman, Lars H Lindholm, for the authors
michaelwebermd@cs.com

Health Science Center at Brooklyn, State University of New York, Brooklyn, NY 11203, USA (MAW); Gilead Sciences, Foster City, CA, USA (JVL); and Umea University Hospital, Umea, Sweden (LHL)

The need for new antibiotics

Your call for the urgent development of new antibiotics (Dec 5, p 1868)[1] must be coupled with an even more urgent one for careful and appropriate use of available antimicrobials. Antibiotics are overused by doctors,[2] both in outpatient and inpatient settings, and self-medication is common, especially in developing countries.[3] These things favour the continuing emergence of resistance.[4]

We must reverse the increasing trend of physicians to prescribe defensively, treating with antibiotics any suspected inflammatory process, and using broad-spectrum antimicrobials unnecessarily. Physicians at large must be educated urgently in antimicrobial therapy, thus restricting the targeting of clinicians' limited knowledge and growing insecurity by pharmaceutical company marketing. Doctors should remember that antibiotic use can increase even the burden of infection: in a study done in Scotland many years ago, all antibiotics were proscribed while trying to control a multiresistant *Klebsiella aerogenes* outbreak in a neurosurgical unit; the pathogen disappeared, and the incidence of infection decreased strikingly.[5]

How to limit antimicrobial resistance? General practitioners should curb antibiotic prescribing or reduce the duration of prescriptions for upper-respiratory-tract infections and uncomplicated urinary-tract infections; the use of antibacterial prophylaxis should be tightened; patients should be reminded of the importance of compliance; and hospital hygiene must receive the attention that it used to have when the protective power of antibiotics was not available.

Antimicrobials must be used only when absolutely indicated, for the appropriate length of time, and at the optimum dose. We are far from this target the world over, and action is needed now.

We declare that we have no conflicts of interest.

*Sandro Vento, Francesca Cainelli
ventosandro@yahoo.it

Department of Internal Medicine, School of Medicine, Faculty of Health Sciences, University of Botswana, Gaborone, Botswana

1 The Lancet. Urgently needed: new antibiotics. *Lancet* 2009; **374:** 1868.
2 van de Sande-Bruinsma N, Grundmann H, Verloo D, et al. Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis* 2008; **14:** 1722–30.
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4 Belmonte O, Drouet D, Alba J, et al. Evolution of enterobacteriaceae resistance to antibiotics in Reunion island: emergence of extended spectrum betalactamases. *Pathol Biol* 2009; published online Oct 26. DOI:10.1016/j.patbio.2009.07.021.
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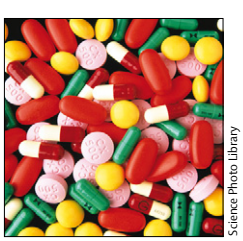
Your Editorial[1] on the urgent need for more antibiotics comes at an opportune time. Except in the case of South Africa, very little data exist on the burden of antibiotic resistance in sub-Saharan Africa, where presumptive treatment of febrile illness with an antimalarial drug is common. This practice has contributed to resistance to all common antimalarials.[2]

WHO is about to publish revised guidelines recommending prescription of antimalarial drugs only to patients of any age with confirmed malaria (in situations where confirmation is possible). The availability of rapid diagnostic tests (RDTs) for malaria is the driving force for the new guidelines. However, the lack of a rapid point-of-care test to diagnose other infections could become a barrier to the effective implementation of the guidelines. Many health-care providers ignore the malaria RDT results and continue to prescribe antimalarial drugs for patients who test negative or substitute antibiotics for antimalarials.[3] Sub-Saharan Africa may soon be faced with a substantial increase in the blind use of antibiotics. In Zanzibar, the introduction of RDTs led to a substantial increase in the prescription of antibiotics.[4] And in a randomised controlled trial setting, the use of RDTs led to a striking increase in the unconfirmed diagnosis of urinary-tract infection and overprescription of antibiotics.[5]


Science Photo Library

Efforts to address the problem of antibiotic resistance must be global and should incorporate strategies for monitoring antibiotic use in the era of confirmation-based management of malaria in sub-Saharan Africa.

We declare that we have no conflicts of interest.

*Frank Baiden, Seth Owusu-Agyei, Jayne Webster, Daniel Chandramohan
baidenf@yahoo.co.uk

Kintampo Health Research Centre, PO Box 200, Kintampo, Ghana (FB, SOA); and London School of Hygiene and Tropical Medicine, London, UK (JW, DC)

1 The Lancet. Urgently needed: new antibiotics. *Lancet* 2009; **374:** 1868.