Comparing bivalent and quadrivalent HPV vaccines

Modelling can help, but the tender price determines cost

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In September 2008, the Department of Health in the United Kingdom started a national vaccination programme of human papillomavirus (HPV) in 12-13 year old schoolgirls. A catch-up programme for girls up to the age of 18 was simultaneously started. At that time, Jit and colleagues reported cost comparisons of the two available vaccines.[1] Their cost threshold analysis showed that if the bivalent vaccine, Cervarix, which protects against HPV types 16 and 18, cost £13 (€15; $21) to £21 less per dose than the quadrivalent vaccine, Gardasil, both vaccines would be equally cost effective, although the bivalent vaccine would be less effective because it does not prevent anogenital warts. In an accompanying editorial, Kim concluded that policy decisions would continue to benefit from such model based analysis.[2]

Now, three years later, a political decision is again needed on the continuation of the vaccination programme, and Jit and colleagues have re-evaluated the two vaccines, taking into account more potential differences between the vaccines.[3] They conclude that at the same price level the quadrivalent vaccine is still more cost effective and that the price differential between both vaccines seems larger than stated in their previous analysis.

In 2008 it was unclear whether the target of 80% coverage would be reached. Now we know that coverage for all three doses ranges from 76.4% (England) to 86.9% (Scotland).[4] This excellent result was due to an efficient and well planned launch, and it secured the effectiveness of the vaccination programme at a population level. This coverage compares well with other countries—in the Netherlands coverage was 51.9% at first call and is still only 56.4% after recall.[5] The Dutch paid for ignoring the importance of modern communication through social media networks and the impact of negative, although unfounded, messages conveyed by them. The safety of both the bivalent vaccine, which was used in the UK national programme, and the quadrivalent vaccine were monitored weekly by the Medicines and Healthcare Product Regulatory Agency (MHRA) in more than four million doses distributed across the UK.[6] Only recognised and listed side effects were reported, and other adverse findings could not be related to the vaccines.

How should we decide which vaccine to use for a national vaccination programme? An evidence based approach should ideally rely on more than one comparative study. In one observer blinded head to head study the bivalent vaccine induced a higher, more sustained immune response than the quadrivalent vaccine.[7] However, a sustained rise in antibodies may not be needed to secure protection against a future infection.[8] Conversely, antibodies other than those tested for may have a protective role.

Another selection criterion could be the duration of protection. Although reports on sustained antibody titres have a different time range for both vaccines, Jit and colleagues justifiably use three scenarios for duration of protection that are similar for both vaccines.

Protection against multiple cancers would also be an attractive argument in favour of a vaccine. In one of Jit and colleagues' scenarios, "the pessimistic one," the authors assume that the bivalent vaccine protects against cervical cancer alone, whereas the quadrivalent vaccine also protects against other types of HPV-16 and HPV-18 related cancers. Just because clinical trials with the bivalent vaccine used only cervical cancer as an end point does not mean that it will not also be efficacious against other types of cancer. It is unlikely that the vaccines differ in this respect.

Jit and colleagues also made assumptions about protection against respiratory papillomatosis, a rare HPV-6 and HPV-11 related disease that is life threatening in young children. With no evidence, they assumed that a reduction in this disease, even in vertical infection, would follow the same pattern as for genital warts. If this were true, even protection against (respiratory) warts could save lives.

Finally, we should not forget that the vaccination programme aims to save lives from cervical cancer. This implies that politicians should trade deaths from cancer against morbidity from warts. The bivalent vaccine is more effective in preventing death as a result of cancer and for possibly longer than the quadrivalent vaccine, as acknowledged and assumed in the model used by Jit and colleagues. It has been estimated that the Italian programme, which uses the bivalent vaccine, would prevent 295 more deaths from cancer but 25 848 fewer cases of genital warts than if it used the quadrivalent vaccine.[9] Evaluation in terms of quality adjusted life years unfortunately does not reflect prevention of death, but it is necessary for the calculation of the incremental cost effectiveness ratio, which in turn defines the reasonable cost per dose.

Several models, mainly the Markow model and the transmission dynamic model, have been published to predict the cost effectiveness of various vaccination strategies. As Jit and colleagues also state, none of these economic evaluations has considered all the potential differences between the vaccines within the same model. In all models, assumptions are made on the basis of studies of the efficacy of the vaccines, measured by surrogate end points, and by immunological follow-up studies. And in every model evaluation, the bivalent vaccine would be cost effective only if it were a dozen or so pounds cheaper than the quadrivalent vaccine.

bmj.com
- News: Study shows HPV home testing could improve cervical screening uptake (*BMJ* 2011;342:d1734)
- Editorial: Monitoring HPV vaccination programmes (*BMJ* 2010;340:c1666)
- Editorial: Should HPV vaccine be given to men? (*BMJ* 2009;339:b4127)

Evidence of this type and level of difference should help decision makers. In this light it is essential to acknowledge that in all these models that have been meticulously validated and precisely calculated, the most decisive variable of all, the tender price, is confidential and thus unknown and not taken into account. In the end then, the key determinant of cost effectiveness is the only factor that cannot be evaluated, even though it will be important when deciding on the vaccine to be used in a national prevention scheme. Unfortunately, in most countries such decisions are also confidential, so we will never know whether the model or the money mattered.

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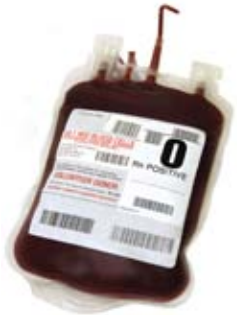
Blood donation in men who have sex with men

The UK's new policy of one year deferral needs a clear communication strategy



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- News: UK lifts lifetime ban on gay men giving blood (*BMJ* 2011;343:d5765)
- Head to Head: Should men who have ever had sex with men be allowed to give blood? (*BMJ* 2009;338:b311)
- Feature: Bad blood: gay men and blood donation (*BMJ* 2009;338:b779)
- Personal View: The blood service should ask donors about practice, not just partners (*BMJ* 2011;343:d5793)

In the linked study, Grenfell and colleagues present the views and experiences of men who have sex with men (MSM) regarding the blood donation ban and proposed alternatives.[1] The United Kingdom is changing the lifetime ban on men who have oral or anal penetrative sex with other men to a deferral period of one year from the last episode of penetrative sex. This change will take effect on 7 November 2011, which makes the implications of the study findings especially timely.

The first case of transfusion associated AIDS was reported in 1982. MSM had relatively high rates of infection, but blood collectors and regulators were slow to implement deferrals for fear of stigmatising gay men. This dilatory response has been characterised as a lamentable error of judgment.[2] In 1985 the UK and the United States both implemented a lifetime blood donation ban on men who have penetrative sex with men. With current deferrals and laboratory testing, HIV transmitted by transfusion is extremely rare. Because many believe that laboratory testing is infallible,[1] blood centres have been accused of being discriminatory in maintaining the ban.

Grenfell and colleagues found that MSM dislike the ban and that the compliance rate is 89%, which is lower than the 95-99% compliance rates reported elsewhere.[1 3 4] Reasons for non-compliance include infallibility of testing, confidence in HIV negativity, confusion about deferral criteria, and resentment over the discriminatory ban. Lack of understanding of deferral criteria was a major cause of non-compliance. Only 25% of men were aware that having penetrative sex with another man barred donation, and 33% believed that only penetrative sex without condoms excluded donation.[1] Another study showed that 23% of donors believe that deep kissing is sex and 45% believe that touching another man's genitals constitutes sex.[5] In the present study, men who had sexual contact with a man but not penetrative sex erroneously believed that they were ineligible to donate, when, in fact, non-penetrative activities such as genital touching and mutual masturbation do not disqualify donors.[1] The five year deferral was viewed as "tokenistic," but the one year deferral was thought to be acceptable and "a step in the right direction."[1]

So what are the next steps? Most MSM are sexually active and will continue to be barred from donating. Indeed, the number of newly eligible donors will be small.[6 7] The next step preferred by many MSM would be to institute detailed, non-biased, gender neutral questions that focus on activities such as condom use and number of sexual partners.[1 4] A weakness of this approach is that it ignores the epidemiological importance of the much greater prevalence of HIV in MSM. Such questions would need development and validation, and they may be impractical and cost prohibitive. In addition, many MSM who dislike the ban also find probing questions unacceptable.[8]

The UK authorities should heed the study's findings in communicating the change in the lifetime ban to a 12 month deferral. Those who have complied with the previous ban indicate that their behaviour will not change but are reluctant to speculate on the compliance of other MSM. The authors caution that they cannot accurately predict how donation behaviour may change under revised criteria.[1] Creative messages must emphasise that men who engage in penetrative sex with other men are still deferred for a year but that others are free to donate. Study participants advocated broad advertising strategies with targeted messages to MSM. Poorly crafted notifications could leave some with the misconception that the deferral has been completely lifted and all MSM may now donate.

The UK will monitor any new cases of HIV in the blood supply attributable to this change and must be ready to quickly revise the deferral. In 2010, the US government convened a two day conference examining the scientific and societal implications of changing the ban and came to a different conclusion, voting to continue the lifetime deferral. Countries maintaining the ban should carefully examine data from the UK and use them to frame future policies.

bmj.com/podcast
It's all in the blood
doc2doc
Should gay men be allowed to give blood? Discuss on BMJ Group's medical community, powered by doc2doc http://bit.ly/pkfX5n

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The temptations of chocolate

Observational evidence suggests a health benefit, but only randomised trials can give a definitive answer

RESEARCH, p 679

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Letter: Chocolate and blood pressure: Chocolate dose may be too much (*BMJ* 2010;341:c4176)
doc2doc
Chocolate appears to be heart healthy. Discuss on BMJ Group's clinical community, powered by doc2doc http://bit.ly/q6PlGy
bmj.com/podcasts
Oscar Franco talks about his linked meta-analysis

Epidemiologists only rarely bring good news—most messages about the health risks of our preferred consumption and behaviour patterns are unwelcome. It is therefore good to see a positive report on the health effects of chocolate, which people all over the world enjoy, in the linked study by Buitrago-Lopez and colleagues.[1]

The authors performed a systematic review and meta-analysis to assess the association of chocolate consumption with the risk of developing cardiometabolic disorders. The authors found no randomised trials, six cohort studies, and one cross sectional study. There was heterogeneity in terms of the measurement of chocolate consumption, methods, and outcomes evaluated. The highest levels of chocolate consumption were associated with a 37% reduction in cardiovascular disease (five studies: relative risk 0.63, 95% confidence interval 0.44 to 0.90) and a 29% reduction in stroke compared with lowest levels.

Chocolate consumption has a long and intriguing history. When the Spanish colonised America they found that the Aztecs used a psychoactive chocolate brew called "xocolātl" ("bitter drink") in their rituals. The Spanish did not like it, but after sugar was added to a drink made of ground and fermented cocoa beans, it became popular throughout Europe during the 17th and 18th centuries. The development of industrial production processes in the 19th century allowed the incorporation of cocoa into solid tablets and candies, which are the preferred means of consumption today.[2]

The potential health benefits of consuming chocolate have only recently been discovered. It was initially observed that indigenous Kuna Indians, living on isolated islands off the coast of Panama, had no age related increase in blood pressure or hypertension, unlike their acculturated tribe members on the mainland. Surveys showed that island dwelling Kuna adhered to a diet rich in chocolate, whereas city dwelling Kuna had lost this old habit.[3]

This stimulated research into the possible health effects of chocolate consumption and the specific compounds responsible for these effects. Laboratory studies and observational and small scale experimental studies on humans have found that chocolate consumption not only lowers blood pressure,[4] but that it may also have positive effects on serum cholesterol, platelet activity, endothelial function, and glucose tolerance.[5 6]

The chemical compounds responsible for these effects are likely to be flavonoids—naturally occurring plant pigments that are common in fruit, tea, red wine, and cocoa beans. The biological mechanisms of flavonoids are still unknown. They have been related to, among other things, their antioxidant properties and to the fact that they increase the bioavailability of nitric oxide, which has vasodilatory and other beneficial effects on the cardiovascular system, but no scientific consensus exists.[6-8]

Studies that link chocolate consumption with health outcomes (instead of intermediate outcomes like blood pressure) are less common, and reasonably good studies are all observational, as shown by Buitrago-Lopez and colleagues' review.[1] Their conclusion that a high level of chocolate consumption may reduce the risk of "cardiometabolic disorders" (cardiovascular disease plus diabetes and metabolic syndrome) by a third is remarkable. If this represents a causal effect it is substantial and comparable in magnitude to that of several other lifestyle related determinants of cardiovascular disease, such as serum lipids.[9 10]

As the authors note, the underlying studies do not allow a reliable assessment of the dose of chocolate (or its biologically active ingredients) needed to obtain a significant health effect. The observational nature of these studies also precludes a definitive conclusion about the causal nature of the association—as in all epidemiological studies of diet and health, residual confounding by other dietary factors than the one under study or by other aspects of a participant's lifestyle is always possible.[11]

Although it is tempting to jump to conclusions with practical relevance, it is therefore too early to make health claims on chocolate products, or for inclusion of chocolate consumption

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The benefits of chocolate were initially seen in indigenous Kuna Indians

in dietary guidelines for the general public or dietary advice to patients with cardiovascular disease.

A few well designed randomised controlled trials are now needed: adequately powered, with cardiovascular health outcomes, measured over a sufficiently long follow-up period, and looking at the effect of a realistic level of chocolate consumption (with the added energy intake balanced against a reduction in energy intake in other parts of the diet). For epidemiologists and the chocolate industry alike, this must be a temptation no one can resist.

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Putting research into primary care practice

The European initiative is a good start, but excludes too many patients and crucial aspects of primary care

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The European Medical Research Council and European Science Foundation recently published a strategic report in its series of "Current Forward Looks" entitled *Implementation of Medical Research in Clinical Practice*.[1] The collaboration has previously published two strategic reports on the ways forward for basic biological research and for investigator driven clinical trials.[1] By suggesting a strategy on the use of research in practice, it now intends to close the loop. The strategy holds much potential for improving the quality of clinical practice and clinically oriented health services research.

The report has three main strengths: firstly, it takes strategy and policy to the level of specific recommendations for improving the quality of clinical research; secondly, it presents a strong case for the implementation of good research; and, thirdly, it gives special attention to the particular problems encountered in general practice.

The report proposes that the quality of clinical research could be improved by closer national and European coordination of independent funding of larger projects, better understanding of the need for funding of high quality systematic reviews, more transparency in research, and better education and career opportunities for clinically oriented researchers. This is good research policy, which goes beyond simply recommending how research should be conducted and presented.[2]

For decades it has been clear that the weak point in research is the implementation of new findings.[2 3] The report gives updated and relevant suggestions for developing guidelines, but relies completely on such guidelines to close the gap between research and practice. However, guidelines are not enough.[2 4] Improvement requires health services research and evidence based leadership in healthcare, with a strong focus on the clinical management of the total disease trajectory.[2 5 6] This demands independent public funding of health services research that looks at how to implement and sustain change in clinical practice, and the training of doctors in evidence based leadership and decision making.[5] For more than 50 years, clinical research has been successful at developing good methods for answering the question of whether treatment A is better than treatment B. However, good health services research should answer the question, "is it better to organise (and pay) our total patient trajectory according to method A than method B"[7]? To answer such a question, more independent, academic, and good organisational research is needed.

With respect to the particular front line problems seen in general practice, the third part of the report offers several suggestions, but its recommendations are not enough to respond to the wide range of future problems in primary care.[3] The report correctly identifies the general practitioner's three main tasks. Firstly, the general practitioner should deal with healthy people seeking medical advice and counsel those who have risk factors for future disease. We need tools and methods that enable general practitioners, in a dialogue with the patient, to give appropriate advice,[8] which ideally should align evidence and policy with patients' preferences.[9] Secondly, the general practitioner must deal with patients in whom the final diagnosis is a symptom not a disease (about 25% of patients). Despite the lack of a specific diagnosis many of these patients experience great suffering and impairment. The report uses the stigmatising and outdated term "the imagined ill" for this group of patients, despite the expansion of more specific knowledge on the pathophysiology of these conditions (for example, chronic pain).[10-12] Thirdly, general practitioners encounter patients with classic acute and chronic diseases.

In terms of practical recommendations, this part of the report is insufficient. It does highlight the need for clinical primary care research, but it seems to argue that the relevance of this need is confined to the third of the three above mentioned patient groups. Evidence based research that is oriented towards all aspects of clinical

care in general practice and does not simply focus on the biomedical aspects of care is urgently needed. Methods also need to be developed to ensure that patients are appropriately involved in clinical decisions—for example, decisions about long term treatment, such as preventive treatment of hypertension or hypercholesterolaemia.[3 4 9] Research should include the whole spectrum of patients attending general practice and the diagnostic and treatment processes initiated by general practitioners, including how they communicate with the rest of the healthcare system. New clinical and health services research methods and the involvement of anthropologists, psychologists, and sociologists will be needed.[2 3 11]

Despite the best intentions of the European Science Foundation's report, a genuine leap forward would require a follow-up report on how to ensure that evidence based practice captures all aspects and functions of general practice. A research agenda is also needed on how best to coordinate care and involve patients in clinical decisions. Such a fourth report may then close the loop in strategic thinking across Europe about how to improve evidence based clinical practice.

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Personalised medicine for hypertension

Measuring plasma renin could refine the treatment of resistant hypertension

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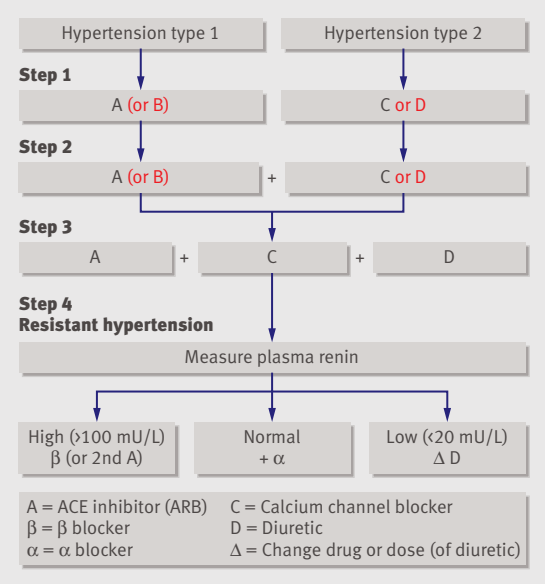
The two broad reasons for tailoring antihypertensive treatment are that susceptibility to complications from treatment varies between people and hypertension has a variety of causes. It is well known that people with asthma should avoid β blockers and that men should avoid higher doses of spironolactone (because of gynaecomastia); the National Institute for Health and Clinical Excellence (NICE) will soon be recommending diuretics over calcium blockade in the very elderly (>80 years) because of superior efficacy in preventing heart failure.[1]

More interesting but more challenging is whether treatment can be tailored to the pathogenesis of hypertension in individual patients. Hypertension has multiple causes, so treating all patients the same way is as illogical as it would be to treat all cases of anaemia with vitamin B_{12} or all cases of pneumonia with penicillin. Recent prospective randomised trials and post-hoc analyses of earlier trials and accompanying editorials provide the evidence and impetus needed to implement plasma renin measurement as the "bacteriology" of hypertension.[2-5]

Although the early promise of genetic studies in hypertension and the availability of multiple distinct classes of effective drugs first prompted the exploration of individual variation in response, practical pharmacogenetics in hypertension now seems far off. Of 29 common variants so far associated with blood pressure, only one explains even 1 mm Hg of variance in blood pressure.[6] The inference is that many hundreds, maybe thousands, of variants are needed to explain the inherited component of hypertension.

In contrast, the definition in physics of pressure as force divided by area suggests that there are only two physiological pathways to increased blood pressure. Either the cross sectional area of small resistance arteries is reduced, or the weight of the column of fluid comprising the circulation—effectively salt and water—is increased, or both. The complex molecular pathogenesis of essential hypertension causes most patients to lie on a spectrum between the two extremes of volume excess and vasoconstriction. The exceptional patients with single causes—so called secondary hypertension—congregate towards one or other extreme. These patients show greater falls of blood pressure than is seen in essential hypertension when they are treated with the appropriate single drug—for example, α blockade for the vasoconstriction of phaeochromocytoma or mineralocorticoid receptor blockade for the Na^+ excess of primary hyperaldosteronism (Conn's syndrome). Such patients therefore offer a proof of principle that tailored treatment works.

The drugs for which we have evidence of long term benefit fall into four main classes—A (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), B (β blockers and α blockers), C (calcium channel blockers), D (diuretics)—serendipitously, the initial letter of the drug class. The first two work by blocking the renin-angiotensin system, the second two by eliminating Na^+.[7] Crossover studies comparing each class in the same patients show that, as might have been predicted by the physics, there are broadly only two categories of antihypertensive drug. One comprises the "AB" drugs, which target the renin-angiotensin system at one point or another, so reversing the principal cause of vasoconstriction. The other comprises the "CD" drugs, which target Na^+ excess. The original AB/CD rule provided an easy mnemonic for determining the



The Cambridge "αβΔ" guideline for treatment of patients with hypertension but no comorbidities.[7] Steps 1-3 describe the AB/CD rule, as modified by the National Institute for Health and Clinical Excellence in 2006. Step 4 offers guidance for patients whose blood pressure is still above the target range despite triple therapy. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

right category in an individual patient, and it was based on observations that plasma renin declines with age and is lower in patients of African or Caribbean origin.[8] Effectively, AB/CD used age and ethnicity as surrogates for plasma renin. The AB/CD crossover trials were performed in younger people (<55 years) with hypertension, whose blood pressure responded better to AB drugs than to CD ones.[8 9] Subsequently, several large trials of people who were a minimum of 55 years old found that CD drugs reduced systolic blood pressure by about 5 mm Hg more than AB drugs.[10]

The rule proposed switching categories in those who did not respond to the appropriate drug for their age or ethnicity.[8] The switch enables about 20% of patients to avoid receiving unnecessary combination treatment and possibly prevents some patients from having a paradoxical pressor response to the "wrong" drug.[2] The NICE version of the AB/CD rule dropped this switch and therefore recommends less individualised treatment than the original version. NICE also relegated B drugs (in 2006) and D drugs (in 2011) to third or fourth line treatment of hypertension. Both moves are controversial, relative to other international guidelines, and the relegation of D drugs ignores the importance of Na^+ excess in the pathogenesis of hypertension. But reduced prescribing of B drugs after 2006 had the compensation of enabling renin to be measured without changing treatment. A low plasma renin occurs when the kidneys detect an excess of Na^+ in the circulation and is an invaluable diagnostic test for Na^+ excess. However, B drugs work by blocking renin secretion and so a suppressed plasma renin on β blockade is not a reliable measure of Na^+ excess in patients taking these drugs. Conversely, A, C, and D drugs normally increase renin secretion (by a different mechanism in each case), so a plasma renin that is low despite taking these drugs is even stronger evidence than in untreated patients of Na^+ retention. Indeed, the detection of a suppressed renin in patients on multiple therapy and the development of a specific scan for the aldosterone secreting adenomas of Conn's syndrome have greatly helped to identify an endocrine tumour as the most common curable cause of hypertension. This diagnostic application is sufficient reason alone to adopt renin testing in hypertension, and it validates the interpretation of a low plasma renin as a diagnostic measure of Na^+ excess. But we now also know that a low renin in patients receiving treatment predicts a better blood pressure response to D drugs than to AB drugs.[5 11]

Currently, only a few centres in the United Kingdom offer the newer, most accurate measure of renin activity, so a delay in implementation is inevitable. Meanwhile, the British Hypertension Society (BHS) is midway through a pair of BHF funded collaborative studies to establish the predictive value and cost effectiveness of renin measurement, both at initial diagnosis and in resistant hypertension (patients with uncontrolled hypertension despite treatment with A, C, and D drugs, where NICE considers the evidence insufficient to guide choice). Subject to confirmation in the BHF trials, the figure incorporates available theory and evidence into our α,β,Δ extension of AB/CD as a working mnemonic for resistant hypertension.

The renin assay is now cheaper (about £12; €14; $19) and better evidenced than many routine tests in medicine; there is something perverse about raising the barrier for a condition that is the most common cause of serious morbidity and most frequent indication for long term treatment. Current guidance varies between top-down prescription and trial and error experimentation in the patient. There is now a third way—a 30 minute laboratory test that measures plasma renin.

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