Drug therapy for prevention of cardiovascular disease – should surrogate measures be abandoned?

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ABSTRACT – It has been suggested that the most effective method of reducing cardiovascular disease (CVD) is to define overall CVD risk and apply fixed doses of anti-hypertensive, hypolipidaemic and anti-platelet therapies, using the evidence base from clinical outcome studies. Such studies have examined large numbers of patients with a wide representation of subgroups and demonstrated equivalent benefits in all subsets. In so doing, there may be over-interpretation of the data leading to large-scale applicability of the findings to individuals who were not genuinely represented in the study populations. Most lipid-lowering studies have been unable to consider the possibility that optimal correction of dyslipidaemia would have been more effective than the use of a fixed dose of statins. Studies of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockade have produced contradictory findings regarding unique non-hypotensive beneficial CVD effects, and suboptimal control of mild hypertension was a frequent finding in the study populations. Scrutiny of concomitant therapy in studies that focus on a particular issue such as LDL (low-density lipoprotein) cholesterol or blood pressure supports the notion that benefits from the agent may be attenuated by other drugs. Widespread application of fixed doses of all these agents to at-risk cases will increase the incidence of inappropriate use and side effects. Clinical experience with modulators of the renin-angiotensin

system in hypertensive diabetic renal disease confirms reduced efficacy, and more frequent deterioration of renal function than observed in clinical trials. Measurement of individual biomedical CVD risk factors along with overall risk estimation should continue to be the mainstay of clinical practice. This will allow appropriate case selection for different agents, optimisation of dosage or better assessment of compliance where treatment is less efficacious, and monitoring for adverse effects of therapy. Pragmatic individualisation of care should remain the basis for treating asymptomatic CVD risk factors.

KEY WORDS: anti-platelet therapy, cardiovascular disease, diabetes, dyslipidaemia, hypertension, statins

Defining and treating total cardiovascular disease (CVD) risk through assessment of several individual risk factors is more effective in reducing CVD than treating levels of single risk markers in isolation,¹ as they operate in a synergistic fashion.² There are conflicting approaches regarding drug therapy, as individuals can be selected on the basis of estimated risk and treated with fixed doses of therapies where there is an evidence base, or by dose titration to biomedical targets, based on individual levels of risk factors, co-morbidity and concurrent therapy. All patients with coronary heart disease (CHD) or an equivalent risk of future CVD events could potentially be treated with fixed doses of angiotensin-converting enzyme (ACE) inhibitors, β -blockers, statins and aspirin, assuming no contraindications.¹

Alternatively, risk prediction for primary prevention of CVD could utilise tables based on blood pressure, the ratio of total:HDL (high-density lipoprotein) cholesterol, and the presence or absence of smoking and diabetes. These tables are based on data from a limited population, are unsuitable for diabetes or ethnic minority populations, and remain untested in developing countries.² They make no allowance for gradation of risk with increasing hyperglycaemia or tobacco consumption, and take no account of serum triglycerides and microalbuminuria.² Selection for hypolipidaemic therapy based on estimated risk³ conflicts with

Key Points

Reduction of risk for cardiovascular disease (CVD) is achieved most effectively by considering and treating for multiple CVD risk factors, but this has led to the inappropriate suggestion that fixed dosage of several therapies should be initiated uniformly in routine clinical practice

The opportunities for, and limitations of, CVD risk reduction from clinical trials need to be more widely acknowledged

Application of clinical research findings may need to be tempered in individualised care

Monitoring of biomedical measures is essential in the treatment of asymptomatic CVD risk factors, in order to demonstrate both efficacy and safety

recommendations to treat to target lipid levels, and contrasts with the approach taken with blood pressure.⁴⁻⁶ Platelet dysfunction is currently treated based on defined risk, rather than on direct measurement of platelet reactivity.

This paper reinforces the case for individual care, integrating risk assessment and biomedical measurement, rather than uniform initiation of fixed doses of cardio-protective therapies based on estimated risk or a pre-defined risk category.

Randomised controlled studies and relevant articles were identified by Medline computer search and contemporary monthly journal searches.

Studies of fixed-dose statin hypolipidaemic therapy on the basis of CVD risk

The Heart Protection Study (HPS),^{7,8} the largest study to date, demonstrated that a fixed daily dose of 40 mg simvastatin in 20,000 individuals at high risk of CVD (65% with established CVD) reduced the composite fatal and non-fatal CVD endpoint by roughly 25%, with an average low-density lipoprotein (LDL) cholesterol reduction of 1 mmol/l. Over 4,000 subjects had total serum cholesterol levels less than 5 mmol/l, and roughly 6,000 had diabetes mellitus, of whom almost 4,000 had no CHD. Serum triglycerides fell by 0.3 mmol/l and HDL cholesterol levels were unaltered. Benefits were equivalent in men and women aged up to 80, regardless of the presence or absence of pre-existing documented macrovascular disease, diabetes, baseline lipid levels, or contemporary use of other therapies (Table 1). The cumulative annualised major vascular event rate was over 5% in the placebo group, whereas current recommendations for hypolipidaemic therapy range from a 1.5 to 3% annualised CVD risk.^{2,3}

One interpretation of the HPS could be to use simvastatin 40 mg in all men and women aged 40 to 80 years with atherosclerosis, diabetes or treated hypertension, whose serum cholesterol was greater than 3.5 mmol/l, without further lipid measurement. This seems counter-intuitive to more effective CVD prevention, as observational studies demonstrate continuous positive relationships between CHD risk and LDL chole-

Table 1. Clinical characteristics of subjects in lipid-lowering studies.

	Heart Protection Study*	4S Study†	VAHIT*	ASCOT*	ALLHAT†
Number of participants	20,536	4,444	2,531	10,305	10,355
Average time of study (years)	5	5.4	5.1	3.3	4.8
Primary end point (Fatal + non-fatal CHD)	24	30-42	22	34	9
(Relative risk reduction) (%)					
Baseline lipids (mmol/l)					
TC	5.9	6.8	4.5	5.5	5.8
LDLC	3.4	4.9	2.9	3.4	3.8
HDLC	1.06	1.19	0.83	1.3	1.2
Tg	2.1	1.5	1.8	1.7	1.7
Alteration in lipids (mmol/l)					
TC	-1.2	-1.7	-0.2	-1.3	'-0.49'
LDLC	-1	-1.7	0	-1.2	-0.49
HDLC	-0.03	0.10	0.10	0	?
Tg	-0.3	-0.15	-0.6	-0.37	?
Annualised (% pa) event rate					
Placebo	2.4	4.2	4.3	0.9	1.7
Active	1.7	2.9	3.3	0.6	1.6
Concurrent treatment (%)					
ASA	63	37	82	17	31
Beta blockers	26	57	43		?
ACEI	20	?	21	-	21
Baseline characteristics (%)					
Smokers	15	24-27	19-22	33	23
Diabetes mellitus	29	4.5	25	24.5	35
HBP	41	26	57	100	100
Women	25	19	None	18.8	49
Non-white	?	None	10	5.4	59
Blood pressure (mmHg)					
Baseline	144/81	139/83	132/77	164/95	146/84

Heart Protection Study: Refs 7,8; 4S Study: Refs 10,11; VAHIT: Ref 13; ASCOT: Ref 14; ALLHAT: Ref 15.

Studies: ALLHAT = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; 4S Study = Scandinavian Simvastatin Survival Study; VAHIT = Veterans Affairs High-density lipoprotein cholesterol Intervention Trial.

ACEI = angiotensin-converting enzyme inhibitors; ASA = aspirin; CHD = coronary heart disease;

HBP = hypertension; HDLC = HDL cholesterol; LDLC = LDL cholesterol; TC = total cholesterol; Tg = triglycerides.

*Fixed dosage of trial medication.

†Variable dosage of trial medication.

sterol,⁷ and earlier intervention studies demonstrated that the magnitude of benefit of statins depends on absolute baseline risk, partly reflected by levels of lipids, HDL and use of other CVD therapies.⁹⁻¹¹ More recently, the benefits of aggressive lowering of LDL cholesterol have been reaffirmed.¹²

The HPS study population had elevated mean triglycerides and reduced mean HDL cholesterol (Table 1). A previous study found that improvements in HDL cholesterol and triglycerides reduced CVD risk reduction as much as the HPS, without any alteration in LDL cholesterol.¹³ HPS suggested that relative benefits were irrespective of HDL cholesterol or triglyceride levels, but this does not negate the possibility that improvements in these parameters would have achieved greater absolute risk reduction, as 20% actively treated still sustained major CVD events.

There are limits to the concept of case selection for statins.² Annualised CVD event rates amongst placebo-treated patients with diabetes and CHD was 8% in one study, but over 50% did not sustain any CVD event over 5.4 years.^{2,11} The highest absolute risk and benefit with statins in HPS was amongst those with diabetes and established CVD.⁸ Few clinicians would currently recommend a wait-and-see approach in this situation.

Questions remain regarding the diabetic cohort in HPS as there were few with type 1 diabetes and/or aged less than 50.⁸ The albuminuric status of the subjects was not given, although this increases CVD risk,² and the efficacy of simvastatin in normoalbuminuric diabetes is unclear. There is a lingering doubt that the CVD benefit may have been overstated for all those with diabetes aged over 40 with total cholesterol over 3.5 mmol/l, including those with short duration of type 1 diabetes, and without complications.

The annualised CHD rate in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)¹⁴ of statins in a high-risk population was much lower than in HPS, despite equivalent reductions in total and LDL cholesterol, perhaps because established CHD was an exclusion factor, and use of other CVD protective drugs and HDL cholesterol levels were higher (Table 1). In addition, blood pressure was unaltered in HPS but fell considerably in ASCOT (Table 1). Low CVD event rates in another trial of combined blood pressure and lipid lowering (Table 1)¹⁵ support the notion that optimal blood pressure control attenuates absolute CVD risk and absolute benefit of statins. The suggestion that CVD may be abolished by treatment with a combination of CVD prevention therapies¹ could be undermined if the benefits of statins are not additive to other CVD agents. Moderation of absolute risk reduction by aspirin has been recorded in a high-risk population treated with ACE inhibitors.¹⁶

Furthermore, mean changes in lipids in research studies may be within the range of individual biological and analytical variation, requiring serial measures to confirm real improvements in clinical practice, where reduced efficacy and compliance are seen.^{2,17} A consistent reduction in LDL cholesterol of at least 1 mmol/l should be documented to conform to the average outcome of HPS.

The impact of statin use in women without low HDL cholesterol or established heart disease, or in Afro-

Caribbean and South Asian communities, requires clarification. The appropriate therapeutic strategy for individuals who sustain CVD events despite adherence to a fixed dose of statin is not established, but it seems prudent to carry out risk assessment and select hypolipidaemic agents to optimise the full lipid profile.

Studies of fixed doses of ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta-blockers on the basis of CVD risk

The use of fixed doses of ACE inhibitors (or ARBs) for CVD risk reduction is complex. Stroke incidence is more amenable than CHD to optimal blood pressure control. Clinical indications for these agents extend beyond hypertension to include renoprotection in diabetes, left ventricular dysfunction and cardiac failure.

The Heart Outcomes Prevention Evaluation (HOPE) study^{18,19} originally suggested that modification of the renin-angiotensin system reduced CVD with modest lowering of blood pressure, in a population where the majority had CHD and almost 50% had hypertension (Table 2).⁶ Benefits were considered independent

Table 2. Clinical characteristics of subjects in major anti-hypertensive studies involving ACE inhibitors and angiotensin receptor blockers.

	HOPE*	LIFE†	EUROPA*	ANBP2†
Number of participants	9,297	9,193	13,655	6,083
Average duration of study (years)	5	4	4.2	4.1
Primary endpoint (MI, CVA CHD death) risk reduction (%)	22	13	20	11
Baseline blood pressure (mmHg)	139/79	174/98	128/78	168/98
Achieved blood pressure	136/76	144/81	122/76	142/86
Annualised event rate (% pa)				
Placebo/comparator drug	3.6	3.2	2.4	5.9
Active treatment	2.8	2.8	1.9	5.6
Concurrent treatment (%)				
ASA	76	27→74	92	12
Beta blockers	40	—	62	—
Other anti-HBP drugs	47	98	—	—
Lipid-lowering drugs	29	31–36	58	13
Baseline characteristics (%)				
Smokers	14	16	?	7
Diabetes mellitus	39	13	12	7
Women	27	54	15	51
Non-white	?	8	?	?
Lipid status				
Total cholesterol	65% >5.2	6.1†	63% >6.5	37% >6.5
HDL cholesterol	18.5% <1.0	1.5†	?	?
(mean levels † or % above/below threshold (mmol/l))				

HOPE: Refs 18,19; LIFE: Ref 21; EUROPA: Ref 25; ANP2: Ref 20.

Studies: HOPE = Heart Outcome Prevention Evaluation; LIFE = Losartan Intervention For Endpoint reduction in hypertension study; EUROPA = EUROpean trial On reduction of cardiac events with Peridopril in stable coronary Artery disease; ANBP2 = Australian National Blood Pressure Study 2.

ASA = aspirin; CHD = coronary heart disease; CVA = cerebrovascular accident; HBP = hypertension;

MI = myocardial infarction.

*Fixed dosage of trial medication.

†Variable dosage of trial medication.

of blood pressure lowering, but there was a dropout rate of over 30%, poor case matching, and 24-hour ambulatory blood pressure recordings demonstrated substantially lower overnight blood pressure readings than was apparent from single day-time readings.^{17,18}

More recent studies have reported CVD benefits with ACEIs/ARBs in treat-to-target blood pressure studies, apparently additional to the impact of blood pressure lowering.^{20,21} However, reduced incidence of both stroke and CHD was inconsistent.¹⁴ Other studies where blood pressure control was the primary objective recorded equivalent outcomes among those treated with ACE inhibitors and beta-blockers,^{22,23} and it would seem that the extent of blood pressure reduction is more important than class effects.²⁴ A recent study of add-on ACEI therapy in stable CHD²⁵ recorded a 20% relative risk reduction in major CVD with modest blood pressure lowering, but over 50% had hypertension as currently defined (Table 2).⁶

ACEIs/ARBs may prevent nephropathy progression in diabetes, and are recommended for diabetic hypertension^{4,6} although the majority require additional anti-hypertensive agents. However, hypertension in type 2 diabetes may be associated with renal vascular disease in 17% of cases,²⁶ which may explain the reported 16% discontinuation rate of these agents due to progressive renal dysfunction in a treat-to-target clinical study.²⁷

Effective CVD reduction will follow efforts to lower both systolic and diastolic blood pressure by a tailored individual approach, including use of ACEIs/ARBs. Their routine addition may yield only modest CVD benefits when blood pressure targets have been attained, and there is active management of other CVD risk markers. High dosage may be unsuitable in over 15% with type 2 diabetes, hypertension and nephropathy.

Optimising anti-platelet therapy

Platelet activity is not currently measured to determine the likely benefit from aspirin, clopidogrel or dipyridamole. As platelet responsiveness to aspirin is reduced in diabetes and hyperlipidaemia,^{28,29} its assessment could be the basis for dosage selection, or maximum dosage routinely used. A strategy is required for those who sustain CVD events despite being on aspirin in suitable dosage. There is support for addition of dipyridamole or clopidogrel following stroke or coronary angioplasty, and evidence that clopidogrel is more efficacious in diabetes.^{30,31}

The cardiovascular polypill – the end of individualised care?

Wald and Law¹ suggested that CVD might be reduced by more than 80% using a polypill containing fixed doses of a statin, beta blocker, diuretic, ACE inhibitor, aspirin and folate. This provocative concept did not fully acknowledge that many published studies in stable CHD are in effect polypill studies. In the European trial on reduction of cardiac events with perindopril in stable coronary heart disease (EUROPA) study, all had CHD with hypercholesterolaemia, 50% had hypertension, use of aspirin was ubiquitous, and the majority took beta-blockers and

statins (Table 2).²⁵ The annualised event rate was 2% per annum, which compares favourably with the 5% per annum event rate in the placebo group of previous secondary prevention studies,^{7–11} and supports active treatment of total CVD risk. At first sight, this supports the polypill concept,¹ but attenuation of benefit with polypharmacy appears to be the clinical reality.^{13–15,25} Given the widespread use of other CVD therapies, the additional relative rate reduction by addition of an ACEI in EUROPA was only 0.5% per annum (Table 2).

Conclusions

In the future we should consider pragmatic tailored strategies. Where polypharmacy and iatrogenic disease pose a major challenge, we should be ready to investigate in greater detail an individual's therapeutic needs and responsiveness to treatment. Individualising care whereby full appraisal of the factors that contribute to CHD can be measured and used as a basis for selecting therapies and their dosage still seems to be the most appropriate method for clinical care. Fixed dosage of several agents based on risk formulation will relegate clinical medicine to a thoughtless process with inherent limitations and dangers.

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Conflict of interest

I have served on professional advisory boards for Astra Zeneca, Glaxo Smith Kline and Takeda Pharmaceuticals, and received support for presentations and attendance at scientific meetings from these and other pharmaceutical companies.

I am the sole author and guarantor of the views expressed in this article.

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