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Contents

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Graphical work 'Havenloods' by Marjoke Schulten. For details about the artist, her work, and how to order see elsewhere in this journal.

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On 30 January 2003, *Benecke N.I.* organised a meeting for internists and cardiologists, focussing on new developments in the fields of cardiology and vascular medicine. The symposium was chaired by the undersigned author, and was sponsored by an educational grant from Merck Sharp and Dome.

Six opinion leaders (three internists, two cardiologists and one molecular biologist) were asked to review the literature of 2002 and to select the most important publications within their fields of interest. The meeting was titled 'The Big Picture', symbolising the aim to make a sharp selection of important and relevant breakthroughs within the enormous amount of publications on cardiovascular medicine in 2002.

In the present era of evidence-based medicine, several important clinical trials with hard endpoints were extensively and critically discussed. These trials concerned classical risk factors for atherosclerosis such as hypertension (ALLHAT, LIFE, ANBP-2) and hypercholesterolaemia (HPS, PROSPER, ALLHAT-LLT), but also important issues as the management of haemostasis and thrombosis (ASPECT-2, CREDO), heart failure (COPERNICUS, Val-HeFT) and arrhythmias (AFFIRM, RACE, MADIT-II, MIRACLE). Fortunately, the programme was not restricted to the issue of evidence-based medicine, as all six opinion leaders also covered future perspectives by reviewing important publications on innovative new drugs and drug targets. Moreover, as an expert in molecular biology, one of the speakers was able to identify promising new molecular techniques within the field of cardiovascular medicine. In the forthcoming decades, these techniques may be introduced in the diagnostic and therapeutic approach to the patient with cardiovascular disease.

All contributions were of high interest and triggered fruitful discussions. The audience, the speakers and the organisers agreed that a symposium like this deserves a yearly update for several reasons. First, because new important publications on the discussed issues will arise every year. The second reason was that this first 'The Big Picture' symposium did not address the whole field of cardiovascular medicine. A yearly update would enable the organisers to focus on other risk factors next time, such as diabetes mellitus, insulin resistance, obesity or hyperhomocysteinaemia. And last but not least, a yearly update would contribute to an optimal communication between internists and cardiologists on the intriguing field of cardiovascular medicine.

The Netherlands Journal of Medicine, the journal of the Dutch Society of Internal Medicine, offers the opportunity to publish proceedings of high-quality meetings within the broad field of internal medicine. In this supplement, 'The Big Picture' symposium of 30 January 2003 is summarised by six interesting and independent contributions by opinion leaders in the field of cardiology and vascular medicine, covering topics from molecular aspects to evidence-based medicine. With this approach, the highlights discussed will reach a large proportion of the internists in the Netherlands. Further, the issue will be available on request to all medical doctors and scientists who are interested in the aforementioned fields.

Professor Paul Smits, internist-pharmacologist
Associate editor *the Netherlands Journal of Medicine*

Implantable defibrillator therapy

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ABSTRACT

Sudden cardiac death (SCD) is the most important cause of death in the industrialised world. Treatment with antiarrhythmic drugs (AAD), however, proved disappointing in preventing SCD. From drugs with electrophysiological properties, only treatment with β-blockers has been shown to improve clinical outcome. This lack of efficiency of AADs heralded a new era of secondary and primary prevention trials, comparing implantable cardioverterdefibrillator (ICD) with drug therapy. Three large randomised secondary prevention trials were conducted in patients with prior myocardial infarction wo where resuscitated from VT or VF. Meta-analysis of these three studies show consistent ICD benefit. This ICD benefit is also observed in three large randomised primary prevention trials in patients with a prior myocardial infarction and left ventricular dysfunction. The beneficial effect of ICD therapy proves to be significantly more pronounced in patients with the lowest left ventricular ejection fraction (26-30%). In patients with nonischaemic dilated cardiomyopathy and low ejection fractions, however, currently the only evidence-based indication for ICD implantation is secondary prevention.

INTRODUCTION

Sudden cardiac death (SCD) is the most important cause of death in the industrialised world. It is defined as '... unexpected death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of onset of symptoms...'[1] As tachyarrhythmias are the recorded rhythm in over 80% of victims presenting with SCD,[2] in the context of this paper arrhythmic death will be considered to be synonymous to SCD. In Western Europe and the USA, the incidence of SCD rate reaches up to 1‰ of the general population, accounting for about 350,000 SCDs a year in Europe. In the 20 to 75 age group of the general population in the Maastricht area in the Netherlands, an overall incidence of 1:1000 SCD was recorded as well.[3] The incidence of SCD, however, markedly increases in the presence of coronary artery disease, a history of previous coronary events, impaired left ventricular function or the combination of a previous myocardial infarction with low ejection fraction.[4] From these risk factors, reduced left ventricular ejection fraction appears to be the single most important risk factor for mortality and SCD.[5] In patients with a history of myocardial infarction, low ejection fraction and nonsustained ventricular tachycardias (VTs), the five-year incidence of SCD is even >20%.[6]

Despite increasing knowledge on basic life support in the general population, survival to hospital discharge after an out-of-hospital SCD is as low as 9%,[7] emphasising the importance of both primary and secondary prevention strategies. Use of antiarrhythmic drugs (AAD) and implantable cardioverter-defibrillators (ICD) have been considered the mainstay of therapy. However, from the drugs with electrophysiological properties, only treatment with the β-adrenergic receptor antagonists has been shown to improve clinical outcome.[5] Therefore, these β-blockers should be regarded as mandatory in high-risk patients.

Table 1
Antiarrhythmic drug prevention trials

STUDY	PATIENTS (N)	DESIGN	RESULT
CAST[8]	1498	Flecainide/encainide versus placebo post-MI and PVC	Excessive death
SWORD[9]	3121	D-sotalol versus placebo post-MI and EF <0.40	Excessive death
EMIAT[10]	1486	Amiodarone versus placebo post-MI and EF <0.40	No change
CAMIAT[11]	1202	Amiodarone versus placebo post-MI and NSVT >10 PVC/h	No change

Primary prevention trials demonstrated neutral (amiodarone) or deleterious (class Ic and class III antiarrhythmic drugs) effects on total mortality. MI = myocardial infarction, PVC = premature ventricular contractions, EF = ejectim fraction, NSVT = nonsustained ventricular tachycardia.

Treatment with all other AADs, however, proved to be either harmful or at best have a neutral effect on all-cause mortality (*table 1*). The lack of efficiency of AADs in preventing SCD heralded a new era of secondary and primary prevention trials, comparing ICD with drug therapy.

Three large randomised secondary prevention trials of ICD versus AADs have been conducted in patients resuscitated from ventricular fibrillation (VF) or VT.

The AVID (Antiarrhythmic drug Versus Implantable Defibrillator) trial and the CIDS (Canadian Implantable Defibrillator Study) enrolled patients with previous VF or VT for randomisation of ICD therapy versus mainly amiodarone. In the AVID trial only a minority of patients received sotalol.[12,13] The CASH (Cardiac Arrest Survival in Hamburg) trial randomised cardiac arrest survivors to ICD versus amiodarone or metoprolol.[14] A meta-analysis of these three studies showed a consistent ICD benefit, with a significant reduction in death from any cause with the ICD (hazard ratio 0.72), which is almost entirely due to a 50% reduction in arrhythmic death.[15] This beneficial effect of ICD therapy is significantly more pronounced in patients with a left ventricular ejection fraction <35%.

However, as SCD is often the initial symptom of ischaemic heart disease, primary prevention strategies have been studied extensively as well. MADIT (Multicentre Automatic Defibrillator Implantation Trial) demonstrated a 54% reduction in total mortality within two years with ICD therapy in patients with prior myocardial infarction, reduced left ventricular ejection fraction (<0.35), spontaneous asymptomatic nonsustained VT and inducible, nonsuppressible sustained VT during programmed electrical stimulation.[16]

MUSTT (Multicentre Unsustained Tachycardia Trial) tested the hypothesis that AAD therapy guided by electrophysiological testing would reduce the risk of sudden death among patients with coronary artery disease, a left ventricular ejection fraction of <40% and asymptomatic, nonsustained VT. Patients were randomised to no therapy or to electrophysiologically guided AAD or ICD therapy .[17]

In MUSTT, antiarrhythmic therapy caused a 28% reduction in cardiac arrest or death from arrhythmia, which was almost entirely due to ICD therapy, and not to AAD therapy. Electrophysiological testing proved of poor prognostic value to identify patients at risk for SCD. Finally, underscoring the lack of efficiency of AADs in preventing SCD, no difference in outcome was seen between patients receiving no therapy or AAD therapy.

Further analyses of the aforementioned ICD prevention trials demonstrate that patients with the lowest left ventricular ejection fractions benefit most from ICD therapy. AVID data showed no ICD survival benefit in patients with a left ventricular ejection fraction >0.35, whereas for patients with a left ventricular ejection fraction of 0.20 to 0.34, there was a significantly improved survival.[18] In CIDS, patients with the highest mortality risk, as based on age, left ventricular ejection fraction <0.35 and NYHA class III or IV, demonstrated a 50% relative risk reduction of death in the ICD group, whereas in the three lower risk-quartiles, there was no benefit.[19] In MADIT, patients were included with an ejection fraction ≤0.35. However, benefit from ICD therapy was concentrated almost exclusively in those patients with a left ventricular ejection fraction <0.26.[20]

MADIT II

MADIT II tested the survival benefit of primary prevention with ICD implantation in patients with a prior myocardial infarction and a left ventricular ejection fraction <0.30.[21] Ventricular arrhythmias were not required for inclusion. And given its poor prognostic value to determine the risk for SCD in patients with coronary heart disease, no additional invasive electrophysiological testing was performed. Patients were randomly assigned to receive an ICD (742 patients) or conventional medical therapy (490 patients). Mean left ventricular ejection fraction was 0.23 in both treatment groups. Concomitant drug use did not differ between groups: in particularly, use of β-blockers and of ACE inhibitors was 70% in both treatment groups. After an average follow-up of 20 months, the trial was stopped when mortality differences between the two groups reached the prespecified efficacy boundary. Mortality rates were 19.8% in the conventional therapy group and 14.2% in the ICD group, a relative risk reduction of 31%.

Given the impact of this landmark trial on medical logistics and expenditure, further risk stratification within the MADIT II population seems warranted. The authors state

that subgroup analyses showed no significant differences in the beneficial effect of ICD therapy on survival in subgroups stratified according to, amongst others, ejection fraction and QRS interval. However, in accordance with observations in previous ICD trials, hazard ratios with 95% confidence intervals do suggest a trend towards increased beneficial effect of ICD therapy in patients with the highest risk for SCD, i.e., patients with QRS intervals >0.15 sec and left ventricular ejection fractions <0.25.

ICD THERAPY IN NONISCHAEMIC DILATED CARDIOMYOPATHY

Thus, so far ICD trials have convincingly shown that implantation of an ICD in patients with a prior myocardial infarction and advanced left ventricular dysfunction improves survival. Although over 60% of the populations of ICD trials are in New York Heart Association functional class (NYHA) II-III heart failure, it is uncertain if the data can be extrapolated to patients with nonischaemic dilated cardiomyopathy and low left ventricular ejection fractions. Undoubtedly, these patients do have an increased risk of dying suddenly as well. Depending on the functional class, one-year mortality rates range between 14 to 44% in NYHA III to IV. Up to 50% of these deaths is supposedly due to ventricular tachyarrhythmias. Nevertheless, risk stratification for primary prevention in these patients is difficult. A small primary prevention trial (CAT) with 104 patients with recent onset nonischaemic cardiomyopathy and a left ventricular ejection fraction <0.30 did not provide evidence in favour of prophylactic ICD implantation in these patients, and was stopped prematurely.[22] Another small primary prevention trial (AMIOVERT) compared amiodarone treatment with ICD therapy in 103 patients with nonischaemic dilated cardiomyopathy and an ejection fraction <0.35, and asymptomatic nonsustained VT defined as >3 beats, less than 30 seconds, >100 bpm. The study lasted four years without a demonstrated survival benefit from either treatment. The study, however, may not be conclusive. It combined data from the randomised and registry groups, which seems a methodological flaw.[23]
Ongoing trials such as DEFINITE (Defibrillators In Non-Ischaemic Cardiomyopathy Treatment Evaluation) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) will have to provide useful data on the role of ICD and amiodarone in patients with nonischaemic cardiomyopathy. DEFINITE is a primary prevention study comparing ICD therapy versus optimal medical therapy, including β-blockers and ACE inhibitors, in nonischaemic cardiomyopathy patients with a left ventricular ejection fraction <0.35 and spontaneous ventricular arrhythmia (nonsustained VT or >10 PVCs/h) on Holter monitoring. After including 458 patients, the enrolment phase was completed in August 2002. Results are to be expected this year. SCD-HeFT is an ongoing prospective, clinical trial enrolling 2500 patients with nonischaemic cardiomyopathy and a left ventricular ejection fraction <0.35. On top of standard medical care, patients will be allocated to placebo, amiodarone or ICD therapy.

CONCLUSION

For primary prevention of SCD, ICD implantation seems warranted in patients with ischaemic cardiomyopathy with a low left ventricular ejection fraction. In patients with nonischaemic dilated cardiomyopathy and low left ventricular ejection fractions, however, currently the only evidence-based indication for ICD implantation is secondary prevention.

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ABOUT THE COVER

'Havenloods'

Marjoke Schulten

Marjoke Schulten (1970) attended the Academy of Art in Rotterdam where she graduated in 'Free Graphics'. At the same time she studied Art and Culture Sciences at the Erasmus University, she completed this study in 2001. Since 1995 she teaches history of art at the Grafisch Lyceum Rotterdam. Besides her studies, Marjoke has always been developing her own professional practice as pictorial artist.
In her recent work she translates her home base Rotterdam to the mythical upper- and underworld. She sees the Rotterdam harbour as a meeting place between water and land; two worlds with each its own dynamic in which you can travel. Returning elements in her etches are ships, cranes, sailors and fish. In addition to several individual expositions she has exhibited her work at many group expositions in the Netherlands and in France.
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Haemostasis and thrombosis: new developments in treatment strategies

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ABSTRACT

The pivotal studies from 2002 in the field of clinical haemostasis and thrombosis were all about the evaluation of existing or novel antiplatelet and anticoagulant strategies. Most of the new agents are specifically targeted to haemostatic pathways, which have recently been shown to be of importance *in vivo* and usually have a higher efficacy in comparison with currently available treatment strategies. In some cases this also results in a (relatively modest) increase in the risk of bleeding. The clinical use of the new compounds is often much more convenient than that of the currently available antithrombotic modalities.

INTRODUCTION

The most important published clinical studies in the field of haemostasis and thrombosis in 2002 all concern anticoagulant treatment of arterial or venous thromboembolism. One of these studies once again compares the currently widely used aspirin and vitamin K antagonists (coumarin derivatives) as secondary prevention after myocardial infarction, whereas the others relate to new antiplatelet and anticoagulant agents. The need for new anticoagulant agents is quite obvious. Firstly, the current agents are insufficiently effective. For example 10 to 15% of patients undergoing major orthopaedic surgery develop venous thromboembolism, despite prophylaxis with low-molecular-weight (LMW) heparin.[1] Furthermore, the available anticoagulants are relatively unsafe. Serious bleeding in patients treated with coumarin derivatives occurs in 1 to 2% per year, whereas in 5 to 10% per year less serious bleeding complicates this treatment.[2,3] Lastly, current anticoagulant agents are often cumbersome with regards to their clinical use, requiring repeated laboratory control and frequent dose adjustments. Increasing knowledge on the function of the haemostatic system *in vivo* has resulted in a new generation of anticoagulant agents, both directed at platelet aggregation and at inhibition of fibrin formation. Some of these new agents are now being tested in clinical phase II and III studies.

THE ASPECT STUDY

In the ASPECT (Anticoagulation in Secondary Prevention of Coronary Thrombosis Trial) study aspirin was compared with vitamin K antagonists after myocardial infarction. Both aspirin and oral anticoagulation with vitamin K antagonists are effective as secondary prophylaxis in patients after myocardial infarction or unstable angina. A head-to-head comparison of these two agents with adequate dosing and a sufficiently large sample size has so far not been performed.[4] The ASPECT-2 study addressed the issue as to which anticoagulant regimen was most effective in preventing recurrent atherothrombotic complications after an acute coronary syndrome.[2] This study included 999 patients with a previous episode of acute myocardial infarction or unstable angina. Patients were randomised to receive aspirin, high-intensity coumarin (INR 3.0-4.0),

or aspirin in combination with moderately dosed coumarin (INR 2.5-3.0). Mean follow-up was 26 months and the main outcome parameter was death, acute myocardial infarction or stroke. The incidence of this composite endpoint was significantly lower in the high-dose coumarin and moderate-dose coumarin plus aspirin group compared with the aspirin-alone group (5, 5, and 9%, respectively), resulting in a hazard ratio of about 50% (95% confidence interval (CI) 0.3-1.0) of coumarin-containing regimens versus aspirin alone. There was a nonsignificant trend towards a lower mortality in the coumarin group (1%), compared with the coumarin plus aspirin group (3%) and the aspirin-alone group (4%). The incidence of major bleeding was 2% in the group receiving aspirin plus coumarin and 1% in the two other groups. Haemorrhagic stroke only occurred in 1 of 332 patients (0.3%) in the aspirin plus coumarin group. Another salient result in this trial was again the demonstration of the poor regulation of vitamin K antagonist therapy, resulting in only about 50% of patients being in the therapeutic range for only 50% of the time, as had been shown by previous trials as well.

LONG-TERM CLOPIDOGREL AND ASPIRIN AFTER PERCUTANEOUS CORONARY INTERVENTIONS

Clopidogrel belongs to the class of thienopyridine derivatives which act by blocking the adenosine 5'-diphosphate (ADP) receptor on the platelet. A previous study comparing clopidogrel with aspirin as secondary prophylaxis in patients with a myocardial infarction, stroke or peripheral arterial disease demonstrated an equivalent efficacy of these two antiplatelet agents.[5] The combination of clopidogrel and aspirin was shown to be superior to aspirin alone in another study of patients after an acute coronary event (defined as acute myocardial infarction or unstable angina).[6] In this study of over 12,000 patients, the incidence of the combined endpoint of cardiovascular mortality, myocardial infarction or stroke was 9.3% in the clopidogrel plus aspirin group compared with 11.5% in the aspirin-alone group (relative risk 0.8, 95% CI 0.72-0.89). Earlier studies had already shown the superiority of the combination aspirin and clopidogrel in the protection against acute thrombotic occlusion of coronary stents in the first six weeks after placement in comparison with various combinations of anticoagulant agents at relatively high doses.[7] The CREDO (Clopidogrel for Reduction of Events During Observation) trial was designed to answer the question whether the combination clopidogrel plus aspirin would also offer longer-term protection against cardiovascular mortality, myocardial infarction or the need for revascularisation in patients who had been treated with intracoronary stents.[8] More than 2000 patients in 99 different centres participated in the trial. During a 12-month follow-up the incidence of the composite endpoint was 8.5% in the clopidogrel plus aspirin group and 11.5% in the aspirin-alone group, a relative risk reduction of 27% (95% CI 3.9-44.4). Major bleeding was somewhat more frequent in the aspirin plus clopidogrel group (8.8%) compared with the aspirin group (6.7%). In previous studies the incidence of major bleeding with the combination aspirin and clopidogrel was comparable with bleeding induced by aspirin alone.[5,6] Based on these results, it can be concluded that the combination aspirin and clopidogrel is a promising strategy for secondary prophylaxis of atherothrombotic events. Future studies should determine whether the additional protection offered by this combination will also be present at even longer follow-up.

DISAPPOINTING RESULTS OF ORAL GLYCOPROTEIN IIB/IIIA INHIBITION

The platelet glycoprotein (GP) IIb/IIIa receptor can bind to fibrinogen, which is the pivotal event in platelet aggregation. Competitive inhibition of this receptor is therefore theoretically the most potent antiplatelet therapy available. The prototype of GP IIb/IIIa inhibitors is the humanised monoclonal antibody abciximab. In four large trials with this compound the efficacy of abciximab in patients undergoing (complex) percutaneous intracoronary interventions, with and without stent placement, was confirmed.[9-12] Based on this success and in view of the potential disadvantages of murine monoclonal antibody therapy, and the relatively high price, a large array of alternative GP IIb/IIIa receptors have been developed. These agents are synthetic peptides, containing the sequence 'arginine-glycine-aspartamic acid (RGD)', which is essential for the interaction with the GP IIb/IIIa receptor, or peptidomimetics, which mimic this RGD sequence. Clinical trials again show a superior efficacy in patients with complex coronary revascularisation.[13,14] Subsequent studies with these agents in patients with acute coronary syndromes (acute myocardial infarction or unstable angina) were more difficult to interpret. It seems that GP IIb/IIIa inhibition is specifically successful in patients who undergo coronary interventions and is less effective, compared with standard therapy, in less complicated situations.[15] Recently, oral formulations of GP IIb/IIIa have become available, which allow long-term treatment. A number of studies have been performed with these compounds, mostly comparing oral GP IIb/IIIa inhibition with aspirin. Disappointingly, most of the studies did not show any benefit of the oral GP IIb/IIIa inhibitors and were prematurely stopped.[16-18] The reason for this

outcome is not clear but it could be that a too low systemic bioavailability after oral ingestion or a too low dose (in view of an otherwise unacceptable bleeding risk) might be a factor.[19] Also, insufficient knowledge on consequences of long-term blockade of the GP IIb/IIIa receptor might explain the unexpected result. Post-hoc analyses of the various studies even suggest a detrimental effect of GP IIb/IIIa receptor antagonists, which has led to speculation on paradoxical induction of platelet aggregation by these inhibitors.

EFFICACY AND SAFETY OF NEW THROMBIN INHIBITORS

Thrombin is the central enzyme in the coagulation process, not only mediating the conversion of fibrinogen to fibrin, but also the most important physiological activator of platelets and various other coagulation factors. Inhibition of thrombin can be achieved by administration of heparin, which potentiates the physiological inhibition of thrombin by endogenous antithrombin. In view of the limited capability of the heparin antithrombin complex to inhibit surface-bound thrombin, new antithrombin-independent anticoagulants have been developed.[20] In experimental studies the higher anticoagulant efficacy of these agents has indeed been confirmed. The prototype of these thrombin inhibitors is hirudin, originally derived from the saliva of leeches (*hirudo medicinalis*) and as such already familiar to 12th century physicians as an effective anticoagulant. Nowadays, hirudin is produced by recombinant technology. Recombinant hirudin and its derivatives have been studied extensively in a number of clinical studies, mostly in patients with acute coronary syndromes. From these studies it was concluded that these agents have a somewhat higher efficacy compared with heparin, but that major bleeding is a serious limiting factor.[21] Other practical disadvantages of hirudin and hirudin derivatives are the exclusive parenteral mode of administration and the need to regularly monitor the intensity of anticoagulation.

Recently, a new direct thrombin inhibitor has become available that has no such limitations. Melagatran is a synthetic thrombin inhibitor, which has predictable pharmacokinetic properties and can thus be used in a fixed dose.[22] Moreover, the pro-drug ximelagatran is relatively quickly absorbed after oral ingestion and results in sufficient systemic availability, rendering this agent suitable for long-term use as an oral anticoagulant. The first large clinical studies with (xi)melagatran were performed in patients undergoing prosthetic hip or knee surgery.[23,24] In several dose-finding studies the efficacy of melagatran in comparison with current antithrombotic prophylaxis (mostly low-molecular-weight (LMW) heparin) was evaluated. These studies showed an incidence of venographic thrombosis in patients who received the highest dose of (xi)melagatran at 15.1% compared with 28.2% in the LMW heparin group. This benefit was, however, only achieved at the expense of a twofold higher risk of serious bleeding (2.4% in the LMW heparin group versus 5.0% in the (xi)melagatran group). In a subsequent study in comparable patients the perioperative dose of (xi)melagatran was slightly reduced, which resulted in an equal efficacy but a lower bleeding rate (3.3%).[25] Another study demonstrated that in patients who were initially treated with the current antithrombotic agents (heparin followed by vitamin K antagonists) for six months, long-term treatment with ximelagatran resulted in a sharp decline in recurrent venous thromboembolism compared with placebo.[26] Remarkably, there was no increase in the incidence of serious bleeding during the 18-month follow-up (incidence 1% and no fatal or intracerebral bleeding). Currently, ximelagatran is being studied in the acute phase of patients with venous thromboembolism, for the prevention of cerebral infarcts in patients with atrial fibrillation, and in patients with acute coronary syndromes.

SPECIFIC FACTOR XA INHIBITION

Pentasaccharides are synthetic compounds that specifically inhibit factor Xa by selective binding to antithrombin.[27] Pentasaccharides lack the string of sulphated chains, present in about 50% of heparin molecules, which is required for inhibition of thrombin. Therefore, pentasaccharides have only specificity towards factor Xa. The agents have a good systemic bioavailability after subcutaneous administration and predictable pharmacokinetics, which makes control of the intensity of anticoagulation unnecessary. There are two pentasaccharides currently under study, fondaparinux and idraparinux. The main difference between these two agents is the elimination half-life, which is 15 to 20 hours for fondaparinux and five and a half days for idraparinux. This means that idraparinux can be administered once weekly, which renders the subcutaneous route of administration less cumbersome. After initial dose-finding studies the efficacy of fondaparinux was evaluated in two studies in patients who underwent hip replacement surgery.[28,29] In both studies the administration of fondaparinux, started postoperatively, was compared with the LMW heparin enoxaparin. The only difference between the two studies was that in one study a relatively high dose of enoxaparin was started postoperatively and in the other study a lower dose of enoxaparin was started preoperatively. The incidence of (venographic) venous thrombosis was 4.1 to 6.1% in the fondaparinux-treated patients compared with 8.3 to 9.2% in the enoxaparin group. A similar result was achieved in

subsequent studies in patients with fractured hips and in major knee surgery.[30] A pooled estimate of these studies leads to the conclusion that fondaparinux treatment results in a 55% reduction of the risk to develop postoperative thrombosis after major orthopaedic surgery compared with LMW heparin.[31] It should be mentioned, however, that these results concern venographic thrombosis, which is mostly asymptomatic and of which the clinical relevance is not clear. The risk of serious bleeding with pentasaccharides in these studies was about 1.5-fold higher. A dose-finding study of pentasaccharides for the treatment of venous thromboembolism showed the efficacy of fondaparinux and this agent is now being investigated in a phase III trial, comparing fondaparinux with LMW heparin in patients with venous thrombosis and comparing fondaparinux with unfractionated heparin in patients with pulmonary embolism. Pentasaccharides also appear to be effective in arterial thrombosis, as indicated in a study in which fondaparinux was compared with unfractionated heparin as adjunctive therapy after thrombolysis for acute myocardial infarction and in a study of unstable angina (with LMW heparin as the comparator). The long-acting idraparinux was investigated in dose-finding studies for the long-term treatment of venous thrombosis, demonstrating that a low dose of idraparinux was as effective as vitamin K antagonists in the prevention of recurrent thrombosis but was associated with less bleeding.[32] If treatment with pentasaccharides is complicated by bleeding, results from a trial in healthy subjects indicate that administration of recombinant factor VIIa is effective to reverse the anticoagulant effect.[33]

CONCLUSION

A better insight in the function of the haemostatic system *in vivo* has resulted in the development of new antiplatelet agents and anticoagulants. Initial clinical studies show that these agents often have a higher efficacy in the prevention and treatment of arterial and venous thromboembolism. The clinical applicability of most of the new agents is less demanding than with the currently available agents, for example due to more predictable pharmacokinetics, a long half-life, or an oral formulation. Results of ongoing and planned clinical trials will determine the definite position of the new generation of anticoagulants in clinical practice.

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New developments in the treatment of hypertension: are some antihypertensives more equal than others?

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ABSTRACT

In 2002, a major topic of discussion in the field of clinical hypertension was the efficacy of the various types of antihypertensive agents. The results of three large endpoint studies have recently been published and it was hoped that these would provide some answers. What could be concluded from their findings is that angiotensin II receptor (A II) antagonists can now also be allowed as initial treatment for uncomplicated essential hypertension. Thiazide diuretics remain the treatment of choice in patients with uncomplicated essential hypertension because of low costs. Recent trials suggest however, that agents that interfere in the renin-angiotensin system, such as ACE inhibitors and A II antagonists, may be superior in preventing end-organ damage. We therefore propose that subgroups of patients should be defined, in which specific agents should be preferentially used because of proven efficacy.

INTRODUCTION

In 2002, the main development in the field of clinical hypertension was the issue whether some blood pressure lowering agents are superior to others in the initial treatment of hypertension for the prevention of end-organ damage. The history underlying this question started with the well-known meta-analyses by Collins and MacMahon. These authors showed that there is a log-linear association between untreated blood pressure and the incidence of end-organ damage.[1] That this association implies a cause-effect relationship was suggested by their subsequent finding that when blood pressure is reduced with antihypertensive treatment, the incidence of cerebrovascular disease is diminished in comparison with placebo, with exactly the same proportion as might be expected from the induced change in blood pressure.[2] In remarkable contrast to the evidence for stroke, the reduction in coronary heart disease seen with active treatment versus placebo fell significantly short of the difference expected from the observational epidemiological evidence (14 instead of 24% risk reduction). Many hypotheses have been put forward to explain this discrepancy. One of the most cited has been that these early placebo-controlled trials were performed with diuretics and β-blockers. These drug classes are known to induce adverse metabolic effects, such as a rise in serum glucose and blood lipids. These negative metabolic events were supposed to offset the beneficial effects of blood pressure lowering on the incidence of especially cardiovascular events.

A number of trials have since been published that compared the effects on cardiovascular morbidity and mortality of conventional (i.e. diuretics and β-blockers) versus newer antihypertensives (i.e. calcium channel antagonists and ACE inhibitors). The latter groups of agents are known to have a more favourable metabolic profile. In general, these trials found no relevant differences in prevention of hypertension-related endpoints. Because of these findings national and international guidelines state that agents from all four drug classes may be chosen as initial treatment of uncomplicated essential hypertension. On the basis of costs, however, the preference is given to diuretics and β-blockers.[3]

STAESSEN'S META-REGRESSION ANALYSIS

Since the publication of these guidelines at least two studies have been published that question whether all antihypertensives are equally efficacious.[4,5] This led Staessen *et al.* to perform a meta-analysis in 2001, in which they systematically analysed all available randomised controlled hypertension trials.[6] Compared with conventional drugs, calcium channel antagonists and ACE inhibitors offered similar overall cardiovascular protection, but calcium channel blockers provided more reduction in the risk of stroke (13.5%, p=0.03), whereas the risk of myocardial infarction was increased (19.2%, p=0.01). Significant heterogeneity was observed among the included studies, especially with regard to differences in achieved blood pressure. This may have influenced the results obtained. Therefore, the authors decided to investigate further the relation between odds ratios expressing benefit and achieved blood pressure difference. This meta-regression analysis across 27 trials (136,124 patients) showed that odds ratios could be fully explained by achieved differences in systolic pressure (*figure 1*). The authors, therefore, emphasise the importance of adequate blood pressure control, and they conclude that, on average, all antihypertensive drugs have similar long-term efficacy.

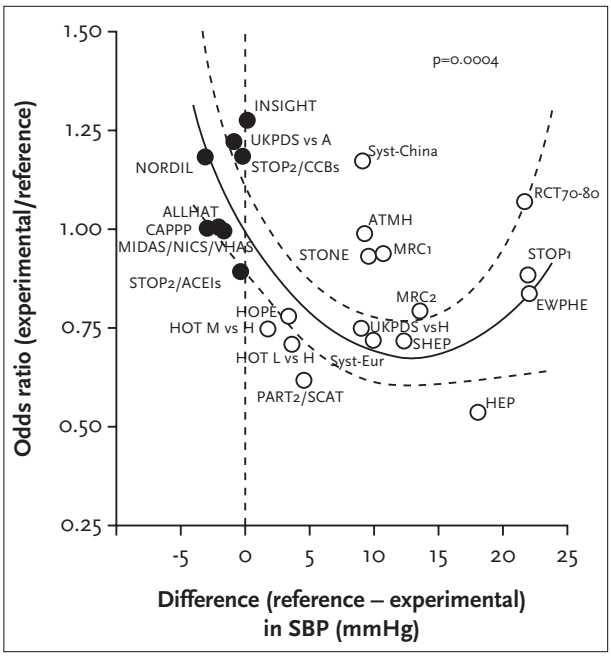

Figure 1

Relation between odds ratios for fatal and nonfatal stroke and corresponding differences in systolic blood pressure[6]

Regression lines were plotted with 95% CI and were weighted for the inverse of the variance of individual odds ratios. SBP = systolic blood pressure.

Interpretation

This meta-analysis pools data from trials that included rather different populations (e.g. diabetics versus non-diabetics, isolated systolic hypertensives versus diastolic hypertensives) and different interventions (e.g. primary versus secondary prevention, placebo versus active control treatment). It is questionable whether such heterogeneous studies can be pooled into one meta-analysis. Schunkert *et al.* point out that, by using the same dataset but plotting it in a different way, results diametrical to the conclusion of Staessen *et al.* can be reached.[7] These authors therefore argue that meta-regression analysis, although tempting, is not justifiable according to the principles of biomedical statistics. It is furthermore remarkable that the obtained 95% confidence interval (CI) of the aggregate dataset is wider than that of many of the individual trials whereas by increasing power by pooling a great number of datasets, a narrower 95% CI was to be expected. Even so, a large proportion of the included trials lie outside the 95% CI, thus questioning the statistical methods used (*figure 1*). We conclude therefore that, although a valuable effort, this meta-regression analysis cannot provide the definite answer to the question whether some antihypertensives may be superior to others in preventing end-organ damage. This answer can perhaps be obtained from three large endpoint studies that were recently published, the ALLHAT, LIFE and ANBP-2 studies.

THE ALLHAT STUDY

The trial that was supposed to end all discussion on the aforementioned question is the Antihypertensive and Lipid-Lowering treatment to prevent Heart ATtack (ALLHAT) study.[8] This study was designed to determine whether treatment with a calcium channel blocker or an ACE inhibitor lowers the incidence of coronary heart disease events versus treatment with a diuretic. It is the largest prospective randomised controlled trial thus far in medicine. A total number of 33,357 subjects, aged 55 years or older with essential hypertension and at least one other coronary heart disease risk factor, were randomly assigned to receive chlorthalidone, amlodipine or lisinopril. Mean follow-up was 4.9 years. Systolic blood pressures were significantly higher in the amlodipine and lisinopril groups compared with the chlorthalidone-treated group (*figure 2*). As expected the thiazide diuretic induced unfavourable metabolic effects, such as an increase in serum glucose and cholesterol, and a decrease in serum potassium. No difference, however, was observed between the three treatments in the incidence of the primary outcome parameter of fatal or nonfatal myocardial infarction (*figure 3*). For amlodipine versus chlorthalidone, all four secondary outcomes were similar (all-cause mortality, combined coronary heart disease,

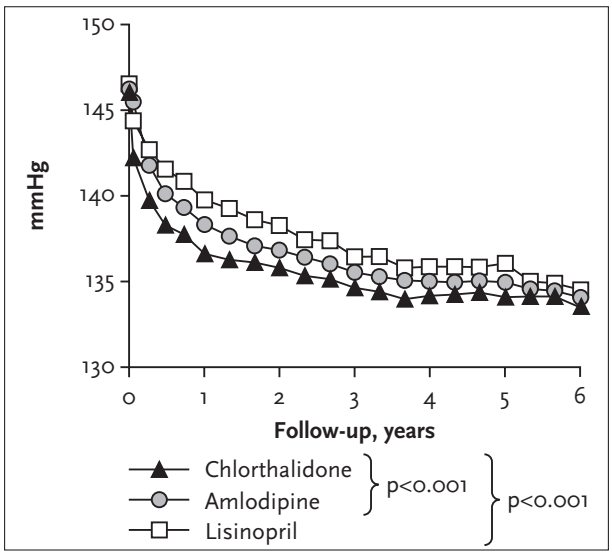

Figure 2
Mean systolic blood pressure during follow-up in ALLHAT in chlortalidone (n=15,255), amlodipine (n=9048) and lisinopril (n=9054) treated patients[8]

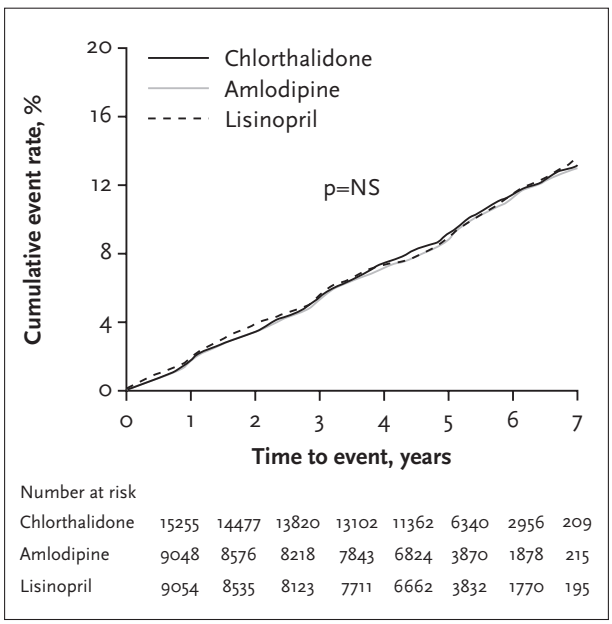

Figure 3
Cumulative event rates in ALLHAT for the primary composite outcome (fatal coronary heart disease or nonfatal myocardial infarction)[8]

stroke and combined cardiovascular disease). Only one out of a number of tertiary outcome parameters was observed more frequently with amlodipine, namely heart failure (*figure 4*). For lisinopril versus chlorthalidone, from the four secondary outcome parameters both stroke and cardiovascular disease (especially the component heart failure) occurred more often with lisinopril (*figure 4*).

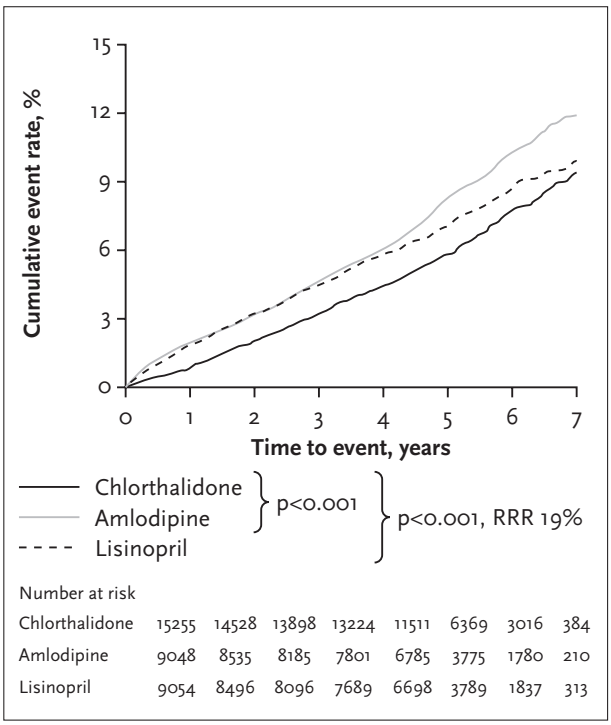

Figure 4
Cumulative event rates in ALLHAT for heart failure in patients treated with chlorthalidone (n=15,255), amlodipine (n=9,048) and lisinopril (n=9,054)[8]

Interpretation

The ALLHAT study is unique in that it is the largest prospective randomised controlled trial ever performed, and that it has been government coordinated and not industry driven. Its design was rather ambitious; a so-called 2 by 4 factorial design. Participants were randomised either to receive placebo or an HMG-CoA reductase inhibitor, and to one of four different antihypertensive treatment groups. The results with regard to lipid control are discussed elsewhere in this supplement. With regard to the present publication on the effects of blood pressure control it appears that the internal validity of the hypertension arm of the ALLHAT study is limited by the fact that blood pressure control was not similar in the three treatment groups (*figure 2*). It is now difficult, if not impossible, to decide whether one or more of the investigated drugs has a blood pressure independent effect, which after all was the primary objective of the ALLHAT study. The difference in incidence of stroke for instance between the chlorthalidone- and lisinopril-treated patients can at least partly be explained by the difference in blood pressure control. The external validity of this trial is limited for several reasons. First, unlike the West-European situation, less then half of the patients were of Caucasian descent. It is generally agreed that in Afro-Americans ACE inhibitors are of limited value, especially in cases when a diuretic is not used concomitantly.[9] In the ALLHAT study prescription

of a diuretic in the ACE inhibitor group was precluded per protocol. This flaw in study design is expected to influence the results that will be obtained if many blacks are included. Subgroup analysis of the ALLHAT confirms this assumption. The beneficial effects of chlorthalidone were purely limited to black patients, whereas in non-blacks no differences were found. Second, mean baseline blood pressure in the population under study was 146/84 mmHg. This is lower than in any of the previously published antihypertensive treatment trials. According to present guidelines many of these patients should not have been treated with blood pressure lowering agents. Furthermore, during the study blood pressure was far lower than in any other hypertension trial, even significantly lower than in the intensive treatment arm of the HOT (Hypertension Optimal Treatment) study. Third, chlorthalidone was chosen as the representative of thiazide diuretics. This agent, however, is not commonly used. Whether results obtained with chlorthalidone can be extrapolated to hydrochlorothiazide, the thiazide diuretic that is used by most clinicians, is questionable. Hydrochlorothiazide has a markedly shorter half-life. Fourth, in case of insufficient blood pressure control open-label agents could be added. By protocol the choice was restricted to clonidine, reserpine, atenolol or hydralazine. Three of these agents are now obsolete. In clinical practice physicians tend to co-prescribe hydrochlorothiazide if an ACE inhibitor provides insufficient blood pressure control. These two drug classes are known to potentiate each other's antihypertensive efficacy. The fact that the combination of an ACE inhibitor and a diuretic was excluded by protocol flaws the results obtained, especially in blacks, as discussed above. Fifth, surprisingly heart failure was more common with the ACE inhibitor than the diuretic. The explanation probably lies in the fact that during the prerandomisation phase many of the patients were on diuretics. When patients were randomised to the ACE inhibitor or the calcium channel antagonist group, their diuretics were withdrawn. Heart failure, already present in some patients before start of the study but compensated for by the use of diuretics, becomes clinically apparent at the moment the diuretic is withdrawn. *Figure 4* shows that the difference between the diuretic and the two other antihypertensives was already near maximal in the first months of the study. This observation clearly pleads for the aforementioned explanation. Of note, at the end of follow-up the line of the ACE inhibitor tends to cross the line of the diuretic (*figure 4*). This probably indicates the specific cardioprotective effect of the ACE inhibitor.

THE LIFE STUDY

In ALLHAT two drug classes were not investigated, β-blockers and angiotensin II receptor (A II) antagonists. This limitation was overcome in the 'Losartan Intervention For Endpoint reduction in hypertension' (LIFE) study.[10] In this study 9193 patients aged 55 to 80 years with essential hypertension and left ventricular hypertrophy (LVH) ascertained by ECG were randomly assigned to the A II antagonist losartan or the β-blocker atenolol. If blood pressure control was inadequate, first hydrochlorothiazide and then other antihypertensives could be added (the choice for which specific agent being left to the discretion of the treating physician). Mean follow-up was 4.7 years. Of the participants, 92% were of Caucasian descent. Mean baseline blood pressure was 174/98 mmHg and similar in the losartan versus atenolol group. Blood pressure control during follow-up was also similar in the two treatment groups. The relative risk for the incidence of the primary composite endpoint, namely death or nonfatal stroke or myocardial infarction, was with 0.87 statistically significant in favour of the A II antagonist. This difference in the incidence of the primary composite endpoint could be fully explained by the lower incidence of stroke with the A II antagonist, since the incidence of myocardial infarction was similar to slightly higher. In this trial 57 patients had to be treated to prevent one event. Patients on losartan had fewer adverse effects and discontinued study medication significantly less. Diabetes mellitus developed in statistically significantly fewer patients on the A II antagonist than on the β-blocker. The results in the subgroup of patients with diabetes mellitus at baseline were shown in a separate publication.[11]
In these high-risk patients the results obtained were more outspoken, both with regard to relative as well as to absolute risk reduction. Only 17 patients had to be treated to prevent one death or nonfatal stroke or myocardial infarction.

Interpretation

The LIFE study is the first hypertension trial to show that one antihypertensive is superior to another with regard to the prevention of the combined primary outcome parameter of cardiovascular mortality, stroke and myocardial infarction. In this respect it can be called a landmark study. The internal validity of this study appears quite solid. No differences, for instance, were observed between the two treatment groups in baseline characteristics or in blood pressure control. External validity is limited by the fact that only subjects with LVH were included. In only a quarter of patients with hypertension is LVH present. Furthermore, in daily practice it is quite uncommon to assess whether a patient has LVH before antihypertensive treatment is started. Interestingly, subgroup analysis suggests that the beneficial effect of the A II antagonist is not dependent on left ventricular mass. Such subgroup analyses should, however, be interpreted with caution.

THE ANBP-2 STUDY

In the second 'Australian National Blood Pressure' (ANBP-2) study 6083 elderly subjects with essential hypertension, who were 65 to 84 years of age, were randomised to receive either an ACE inhibitor (predominantly enalapril) or a diuretic (predominantly hydrochorothiazide).[12] Subjects were followed for 4.1 years in this prospective, randomised, open-label study with blinded endpoints. At baseline, the treatment groups were well matched in terms of age, sex and blood pressure (167/91 versus 168/91 mmHg, respectively). By the end of the study, blood pressure had decreased to a similar extent in both groups (a decrease of 26/12 mmHg). The hazard ratio for the primary composite endpoint (death or cardiovascular event) was significantly in favour of the ACE inhibitor (0.89 with 95% CI 0.71 to 0.97; p=0.02). Among male subjects the hazard ratio was 0.83, whereas among female subjects the hazard ratio was 1.00. The rates of nonfatal cardiovascular events and myocardial infarctions decreased with ACE inhibitor treatment, albeit not statistically significantly. A similar number of strokes occurred in each group, although there were more fatal strokes in the ACE inhibitor group.

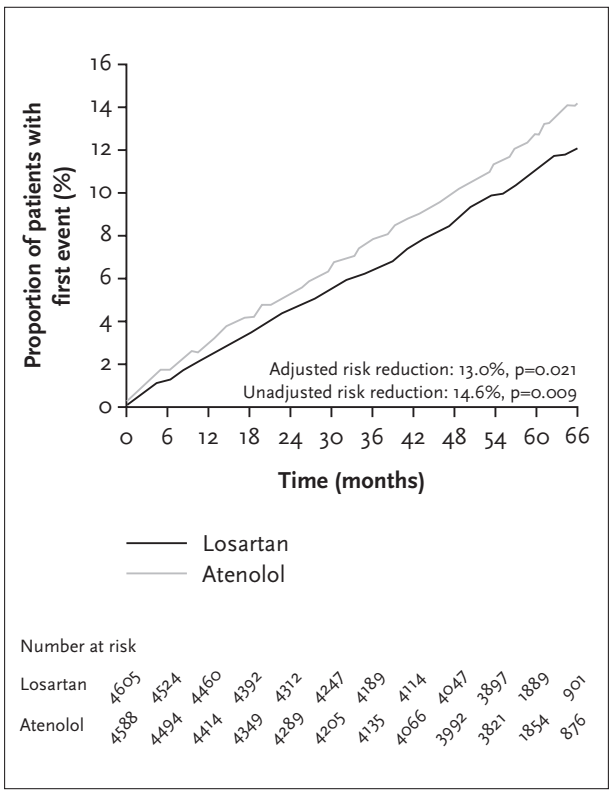

Figure 5
Cumulative event rates in LIFE for the primary outcome (cardiovascular mortality, stroke and myocardial infarction) in patients treated with atenolol (n=4,588) and lisinopril (n=4,605)[10]

Interpretation

The ANBP-2 study is, after the LIFE study, the second outcome trial that shows that one antihypertensive is superior to another, with regard to the prevention of the combined primary outcome parameter. Interestingly, in both studies agents interfere with the renin-angiotensin system, which proves to be advantageous. Concerning the internal validity of this study there are no major problems. External validity is limited by the fact that only elderly subjects aged 65 to 84 years were included. In daily practice, however, the vast majority of the patients with essential hypertension belong to this age category. Although the primary and most of the composite endpoints were in favour of the ACE inhibitor, fatal stroke occurred significantly more often in patients using this drug. This finding was also observed with ACE inhibitors in the CAPPP (Captopril Prevention Project)[5] and the ALLHAT[8] study. In these two trials this may have been caused by the blood pressure difference between the two treatment groups, in both to the detriment of the ACE inhibitor. No such difference in blood pressure control was, however, present in the ANBP-2 study. This brings forward the question whether ACE inhibitors may be disadvantageous with respect to cerebroprotection. This is in contrast to the findings with the other class of agents that interfere with the renin-angiotensin system. With A II antagonists it has been found that there is a significant reduction in cerebrovascular endpoints.[11,13] A possible difference between ACE inhibitors and A II antagonists in cerebropotection is an interesting issue that needs further study. We want to emphasise that the main message of the ANBP-2 study is that use of ACE inhibitors in older subjects leads to better overall outcome than treatment with diuretic agents, despite similar reductions in blood pressure.

DO ALLHAT, LIFE AND ANBP-2 CONTRADICT EACH OTHER?

The above-mentioned limitations of the ALLHAT study seriously hamper the relevance of the results obtained. Its over-ambitious design and lack of surveillance with regard to the blood pressure control during the trial resulted in findings that are difficult to interpret and extrapolate. In our opinion the results obtained do not support the conclusion of the authors that 'thiazide diuretics are superior in preventing cardiovascular disease'. What can be concluded from this study in our view is that calcium channel blockers (dihydropyridine) appear safe, despite the recent turmoil on this point. Furthermore, thiazide diuretics are efficacious in lowering blood pressure and preventing cerebrovascular and cardiovascular endpoints. The statistically significant and clinically relevant difference in blood pressure control to the disadvantage

of the ACE inhibitor, together with the large percentage of Afro-Americans, preclude firm conclusions with regard to this latter class of drugs for the Dutch situation.
The LIFE study suggests that in hypertensive patients with LVH, an A II antagonist is superior to a β-blocker in preventing hypertension-related end-organ damage. One could reason that since the findings of the LIFE study are so surprising, one should await a second study. During the meeting of the International Society of Hypertension in 2002 the results of the 'Study on Cognition and Prognosis in the Elderly' (SCOPE) were presented.[12] In this study the A II antagonist candesartan was compared with open treatment in elderly patients with predominantly isolated systolic hypertension. Although the results obtained were not statistically significant because of lack of power, the relative risk reduction in the incidence of the primary composite endpoint, stroke and new-onset diabetes was remarkably similar to the figures obtained in the LIFE study. These studies, different in patient selection (essential hypertension and LVH versus elderly patients with predominantly isolated systolic hypertension) and design (A II antagonist compared with β-blocker versus A II antagonist compared with open treatment), thus show similar results. The ANBP-2 study emphasises once again the role that angiotensin II may have in the pathophysiology of cardiovascular disease.

CONCLUSIONS

With the above data in mind, we conclude that after the recent publications the present guidelines for the initial treatment of hypertension do not have to be changed drastically. The differences that we propose are that after the publication of the LIFE study, A II antagonists can now also be allowed as initial treatment for uncomplicated essential hypertension. Thiazide diuretics were and will remain the treatment of choice in patients with uncomplicated essential hypertension because of low costs. The recent LIFE, ANBP-2 and SCOPE studies suggest, however, that agents that interfere in the renin-angiotensin system, such as ACE inhibitors and A II antagonists, may be superior in preventing end-organ damage. However, as long as these agents are under patent, and thus more expensive, their initial use instead of diuretics in the population at large does not seem cost-effective. The crux of the story lies in our opinion in the definition of subgroups in which specific agents should be preferentially used because of proven efficacy. For instance, in diabetic nephropathy ACE inhibitors or A II antagonists are the treatment of choice, whereas in angina β-blockers should be preferred. We should consider adding left ventricular hypertrophy to this list. In such patients A II antagonists can be started as primary treatment, especially in patients with diabetes where cost-effectiveness seems adequate. Needless to say that the discussion as to who decides what is cost-effective in saving lives, and on which grounds, resembles a Gordian knot and is beyond the scope of this commentary.

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New developments in the management of heart failure: a review of the literature in 2002

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ABSTRACT

In 2002, several studies were directed at new developments in the management of heart failure. In the COPERNICUS study, the previously reported benefits of the β-adrenoreceptor blocker carvedilol regarding morbidity and mortality in patients with mild-to-moderate heart failure were also found in patients with severe heart failure. Carvedilol not only improves survival but when given in addition to conventional therapy, ameliorates the severity of heart failure and reduces the risk of clinical deterioration, hospitalisation and other serious adverse events.
The diagnostic value of B-type natriuretic peptide (BNP) in patients with congestive heart failure has been a topic of study for the past five years. Many questions still need to be answered but the results of a study by Maisel *et al*. show that BNP is not only of diagnostic value but is also important for prognosis and evaluation of therapy.
A substudy of the Val-HeFT study focussed on the effects of the angiotensin receptor blocker valsartan on BPN and noradrenaline levels. Valsartan significantly reduced the combined endpoint of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure, if added to prescribed therapy. However, in a post-hoc observation an adverse effect on mortality and morbidity was seen in the subgroup receiving valsartan, an ACE inhibitor and a β-blocker, which raised concern about the potential safety of this specific combination.
And finally, interesting work by Abraham *et al*. on cardiac resynchronisation through atrial-synchronised biventricular pacing clearly shows that this therapy can produce a significant clinical improvement in patients with moderate-to-severe congestive heart failure and intraventricular conduction delay.

INTRODUCTION

This review aims to highlight the most relevant publications on congestive heart failure published in 2002. Unfortunately, there were no real landmark studies in this particular year. Nonetheless, some substudies of previously published large trials have raised important issues. Furthermore, other publications are also of interest.

BETA-ADRENORECEPTOR ANTAGONIST AND HEART FAILURE

The first study concerns the effect of carvedilol on the morbidity of patients with severe chronic heart failure. The results of COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival Study) were published by Packer *et al.*[1]

Background

In the past few years, knowledge on the value of β-adrenoreceptor-blocking agents in patients with mild to moderately severe congestive heart failure has considerably increased (*table 1*). However, the effect of β-adrenoreceptor-blocking agents in patients with severe congestive heart failure is less obvious. In May 2001, Packer *et al.* published the effects of carvedilol on survival in severe chronic heart failure in the *New England Journal of Medicine*.[1] They reported the results in 2289 patients with symptoms of heart failure at rest or on minimal exertion. The patients were clinically euvolaemic and had ejection fractions of less than 25%. In a double-blind fashion the patients were randomly assigned to placebo or to treatment with carvedilol for a mean period of 10.4 months, during which standard therapy for heart failure was continued. A total of 1133 patients received the placebo regimen, while 1156 patients were treated with carvedilol. Patients who required intensive care, had marked fluid retention or were receiving intravenous vasodilators or positive inotropic drugs were excluded from the study. In the placebo group there were 190 deaths, while in the carvedilol group there were 130 deaths. This meant a difference of 35% in the decrease in mortality in favour of the carvedilol-treated patients (p=0.0014). For the combined endpoint death or hospitalisation there was a difference of 24% in favour of the patients treated with carvedilol. The favourable effects on both endpoints were seen consistently in all subgroups. This made the authors come to the following conclusion: the previously reported benefits of carvedilol with regard to morbidity and mortality in patients with mild-to-moderate heart failure were also found in patients with severe heart failure.

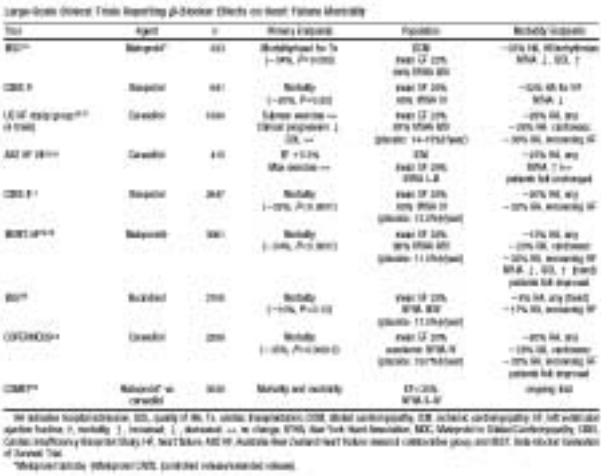
These results warranted the publication of the secondary endpoints, especially looking at differences in morbidity.[2] The secondary endpoints in the same patient population were:

- combined risk of death or hospitalisation for any reason;
- combined risk of death or hospitalisation for a cardiovascular reason;
- combined risk of death or hospitalisation for heart failure;
- the patient global quality-of-life assessment.

Carvedilol reduced the combined risk of death or hospitalisation for a cardiovascular reason by 27% (p=0.00002) (*figure 1*) and the combined risk of death or hospitalisation for heart failure by 31% (p=0.000004) (*figure 2*). Patients in the carvedilol group also spent 27% fewer days in the hospital for any reason (p=0.0005) and 40% fewer days in the hospital for heart failure (p<0.0001) (*figure 3*). These differences were the result of both decreases in the number of hospitalisations and a shorter duration of each admission. In the carvedilol group more patients felt

Table 1

Large-scale clinical trials reporting β-blocker effect on heart failure morbidity[7]



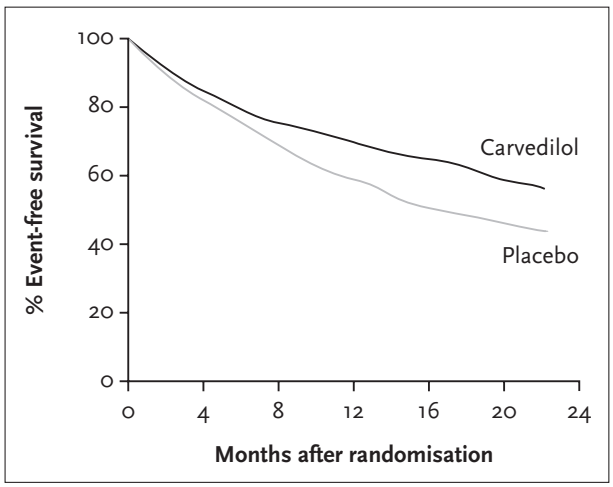


Figure 1

Kaplan-Meier analysis of time to death of hospitalisation for a protocol-specified cardiovascular reason in all patients randomised to placebo or carvedilol[1]

The 27% lower risk in the carvedilol group was highly significant (p=0.00002).

some improvement and fewer patients felt worse than in the placebo group after six months of treatment. Carvedilol-treated patients also experienced less serious adverse events (p=0.002). Serious adverse events were worsening of heart failure, sudden death, cardiogenic shock or ventricular tachycardia. With these data the investigators show that not only in mild to moderately severe congestive heart failure but also in severe heart failure carvedilol not only improves survival but also, when given in addition to conventional therapy, ameliorates the severity of heart failure and reduces the risk of clinical deterioration, hospitalisation and other serious adverse

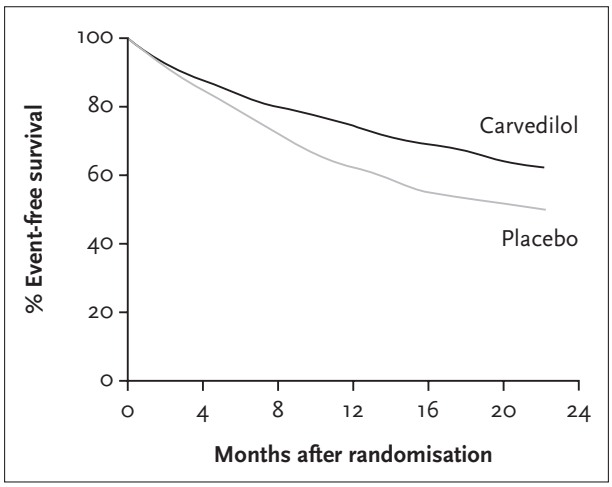


Figure 2

Kaplan-Meier analysis of time to death of hospitalisation for heart failure in all patients randomised to placebo or carvedilol[1]

The 31% lower risk in the carvedilol group was highly significant (p=0.000004).

events (*figure 4*). Whether the use of carvedilol, being a combined β1-, β2- and α-adrenoreceptor antagonists, should be advocated above the use of β1-selective compounds (bisoprolol and metropolol) is at this moment uncertain.

Table 1 gives a rough comparison of the data from different trials on β-adrenoreceptor antagonists and heart failure. Only head-to-head comparison of these drugs in a double-blind prospective study can answer this question.

B-TYPE NATRIURETIC PEPTIDE AND THE DIAGNOSIS OF HEART FAILURE

The next important article published in 2002, entitled Rapid Measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure, was by Maisel *et al.*[3]

Background

The prevalence of symptomatic heart failure in the general population in Europe varies from 0.4 to 2%. So in many patients with complaints of dyspnoea, congestive heart failure is the main cause of the symtoms. The sensitivity of diagnostic tools based on symptoms and findings during physical examination is low. It is known that B-type natriuretic peptide (BNP) is released from the cardiac ventricles in response to increased wall tension. Taking this fact into account the investigators conducted a prospective study in 1586 patients, who came to the emergency department with acute dyspnoea and whose BNP was measured with a bedside assay. The purpose of this study was to investigate whether the determination of

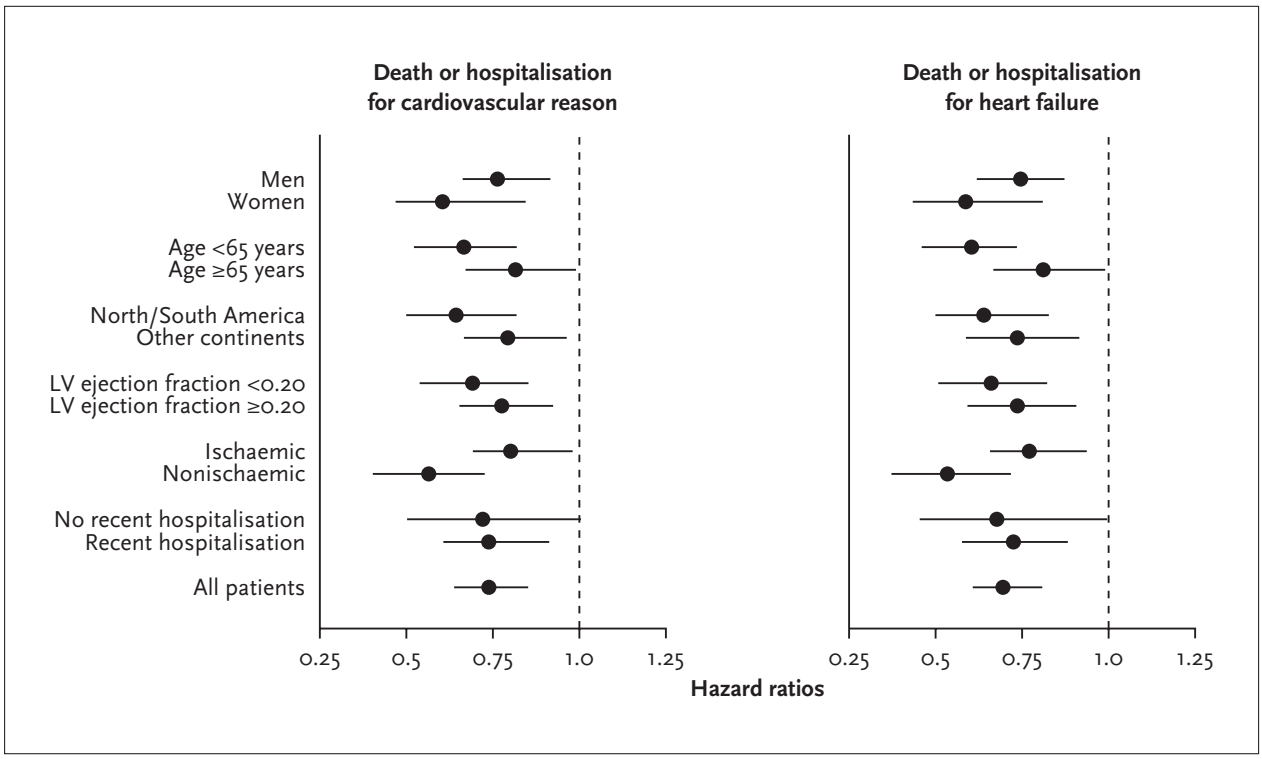


Figure 3

Hazard ratios (and 95% CI) for death from any cause in subgroups defined according to baseline characteristics[1]

LVEF = left ventricular ejection fraction. Recent hospitalisation refers to hospitalisation for heart failure within the year before enrollment.

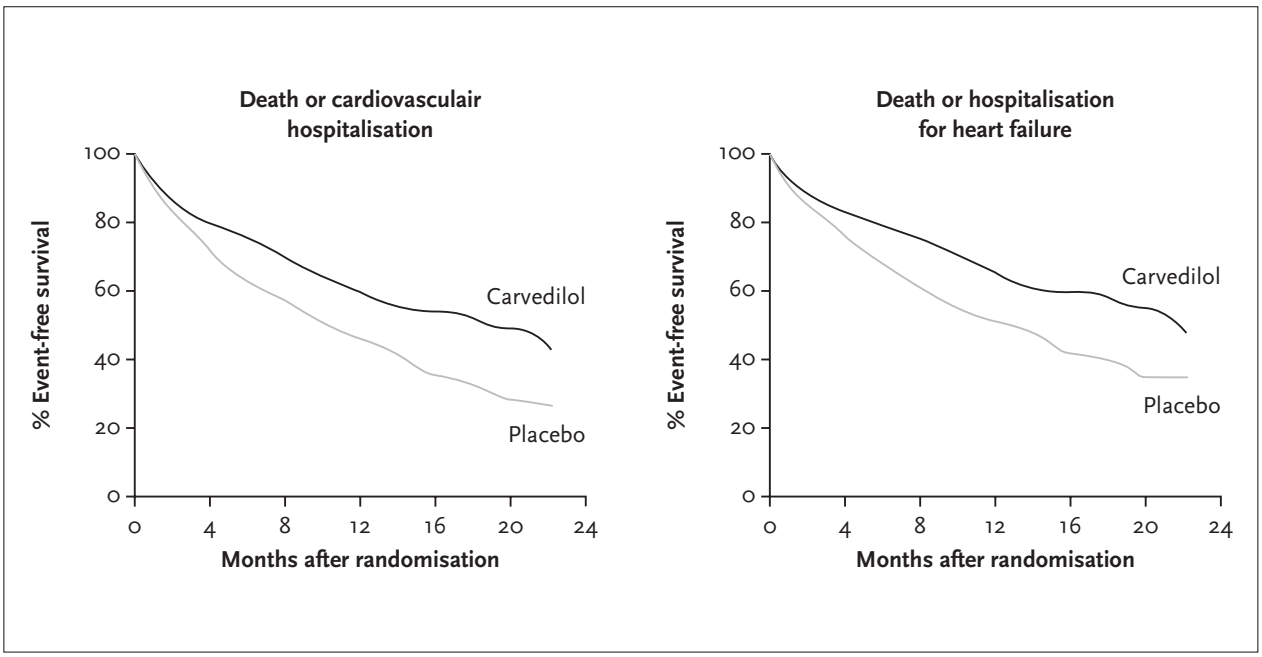


Figure 4

Kaplan-Meier analysis of time to death or cardiovascular hospitalisation (left panel) or death or hospitalisation for heart failure (right panel) in the 624 patients randomised to placebo or carvedilol who had recent or recurrent decompensation or a very depressed ejection fraction (≤15%)[2]

In both analyses, carvedilol reduced the risk of a major clinical event by 33% (both p=0.002).

BNP could improve the accuracy of the diagnosis in patients with acute dyspnoea. Furthermore, they tried to determine reliable cut-off values of BNP for the diagnosis congestive heart failure. The clinical diagnosis of congestive heart failure was made by two independent cardiologists who were blinded for the results of the BNP assay.

Results

The final diagnosis of this study was dyspnoea due to congestive heart failure in 744 patients (47%), dyspnoea due to noncardiac causes in 72 patients with a history of left ventricular dysfunction (5%) and no finding of congestive heart failure in 770 patients (49%) (*figure 5*). BNP levels in themselves were more accurate than any historical or physical finding or other laboratory values in identifying congestive heart failure as the cause of dyspnoea in this type of patient. The diagnostic accuracy of BNP at the cut-off point of 100 pg/ml was 83.4%. The negative predictive value of BNP at levels of less than 50 pg/ml was 69% (*figure 6*). In a multiple logistic regression analysis, measurements of BNP added significant independent predictive power to other clinical variables in models predicting whether patients had congestive heart failure or not. In the past five years, important progress has been made on the value of BNP in patients with congestive heart failure, but many questions still need to be elucidated. In this respect this study is of special importance. It is

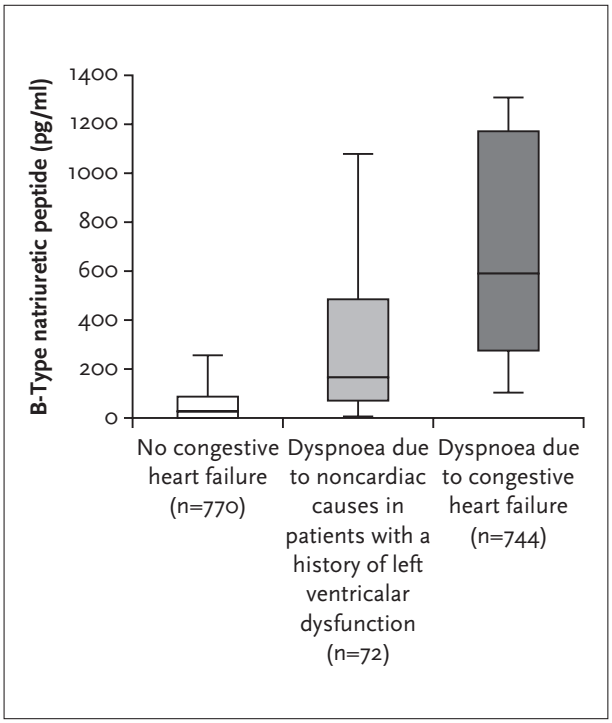
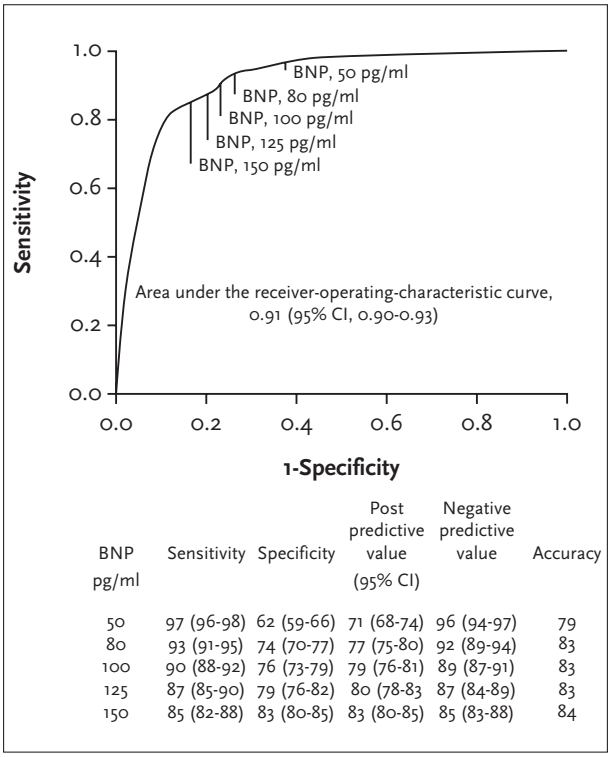


Figure 5

Box plots showing median levels of B-type natriuretic peptide measured in the emergency department in three groups of patients[3]

Boxes show interquartile ranges and I bars represent highest and lowest values.



BNP pg/ml	Sensitivity	Specificity	Post predictive value (95% CI)	Negative predictive value	Accuracy
50	97 (96-98)	62 (59-66)	71 (68-74)	96 (94-97)	79
80	93 (91-95)	74 (70-77)	77 (75-80)	92 (89-94)	83
100	90 (88-92)	76 (73-79)	79 (76-81)	89 (87-91)	83
125	87 (85-90)	79 (76-82)	80 (78-83	87 (84-89)	83
150	85 (82-88)	83 (80-85)	83 (80-85)	85 (83-88)	84

Figure 6
Receiver operating characteristic curve for various cut-off levels of B-type natriuretic peptide (BNP) in differentiating between dyspnoea due to congestive heart failure and dyspnoea due to other causes[3]

becoming more and more evident that the determination of BNP levels in patients with complaints of dyspnoea is not only of diagnostic value but is also important with regard to prognosis and evaluation of therapy.

ANGIOTENSIN II RECEPTOR ANTAGONIST, HEART FAILURE AND NEUROHUMORAL PARAMETERS

Background

In 2002, Cohn *et al.* published the results of the Valsartan Heart Failure Trial (Val-HeFT).[4]
A further analysis of these results, focussed on the effects of valsartan on BNP and noradrenaline level, was published in *Circulation*.
Val-HeFT was a randomised trial of the angiotensin receptor-blocker valsartan in chronic heart failure. The rationale of this study was based on the important role of angiotensin II in the progression of congestive heart failure and on the recent insight that angiotensin II is still produced in patients on ACE inhibitors. Up to now, it was not known whether addition of an angiotensin II receptor blocker is useful in patients with congestive heart failure treated with currently recommended drugs,

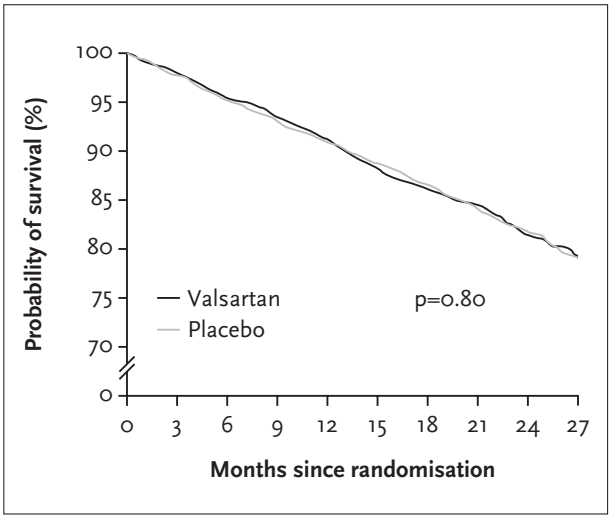


Figure 7
Kaplan-Meier analysis of the probability of survival[4]

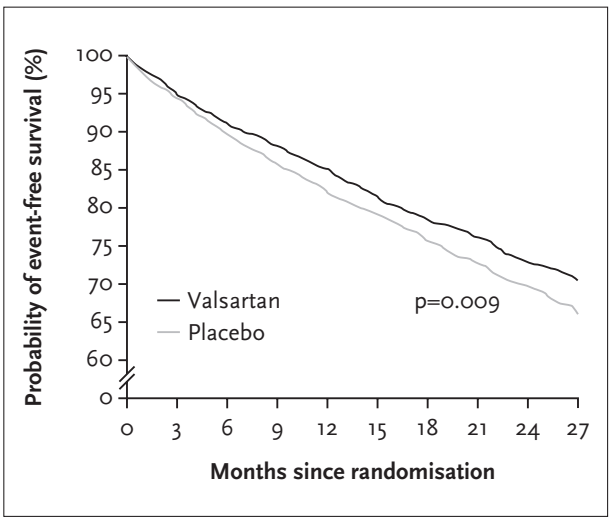


Figure 8
Kaplan-Meier analysis of the probability of freedom from the combined endpoint (death any cause, cardiac arrest with resuscitation, hospitalisation for worsening heart failure or therapy with intravenous inotropes or vasodilators)[4]

especially ACE inhibitors. In the Val-HeFT a total of 5010 patients with heart failure of New York Heart Association (NYHA) class II, III or IV were randomly assigned to receive 160 mg of valsartan or placebo twice daily on top of their normal medication (diuretic, digoxin, β-blockers, ACE inhibitors). The primary outcomes were mortality and the combined endpoint of mortality and morbidity defined as the incidence of cardiac arrest with resuscitation, hospitalisation for heart failure and receipt of intravenous inotropics or vasodilator therapy for at least four hours. The main results showed an overall mortality that was similar in the two groups (*figure 7*).

The incidence of the combined endpoint, however, was 13.2% lower with valsartan than with placebo, (*figure 8*) predominantly because of a lower number of patients hospitalised for heart failure: 455 (18.2%) in the placebo group and 346 (13.8%) in the valsartan group (p<0.001). Treatment with valsartan resulted in a significant improvement in NYHA class, ejection fraction and signs and symptoms of heart failure as well as in quality of life as compared with placebo (p<0.001). The authors concluded that valsartan significantly reduced the combined endpoint of mortality and morbidity, and improved clinical signs and symptoms in patients with heart failure if added to prescribed therapy. However, in the post-hoc observation an adverse effect on mortality and morbidity was seen in the subgroup receiving valsartan, an ACE inhibitor and a β-blocker, which raised concern about the potential safety of this specific combination (three is a crowd!) (*figure 9*).
In a substudy of Val-HeFT, changes in circulating BNP and norepinephrine (NE) were studied, knowing that the levels of these neurohormones are strongly related to the severity and the prognosis of heart failure.[5] The long-term effects of an angiotensin receptor blocker on BNP and NE in heart failure patients were not known.

Methods and results

Both BNP and NE were measured in 4284 patients, randomised to valsartan or placebo at baseline and at 4, 12 and 24 months after randomisation. BNP and NE concentrations were similar at baseline in the two groups and were decreased by valsartan, starting at four months, and remained decreased for up to 24 months (*figure 10*). BNP increased over time in the placebo group. Concomitant therapy with both ACE inhibitors and β-blockers significantly reduced the effect of valsartan on BNP but not on NE (*figures 11* and *12*).
This study shows for the first time that an angiotensin receptor blocker decreases two major markers of the severity of heart failure. The effects on BNP and NE can be seen within four months and last for at least 24 months. As such, the benefit of valsartan in heart failure, which was consistent across all variables analysed with the exception of mortality (combined endpoint of morbidity and mortality, quality of life, clinical signs, NYHA class, left ventricular ejection fraction, and left ventricular diameter) can now be extended to BNP and NE levels. However, the exact clinical meaning of these findings still has to be elucidated.

CARDIAC RESYNCHRONISATION IN CHRONIC HEART FAILURE

In June of 2002, Abraham *et al.* published an interesting study on the results of cardiac resynchronisation in chronic heart failure.[6]
The rationale of this study was that previous studies have suggested that cardiac resynchronisation achieved through

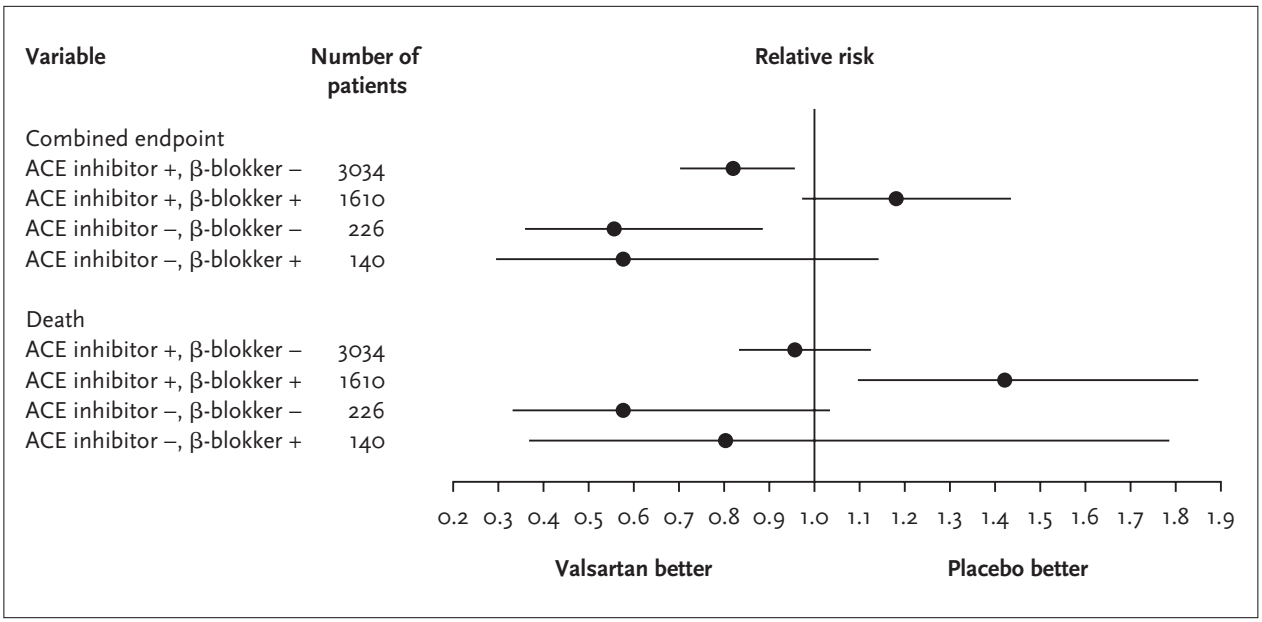


Figure 9

Relative risks and 95% CI for the combined endpoint (death any cause, cardiac arrest with resuscitation, hospitalisation for worsening heart failure or therapy with intravenous inotropes or vasodilators), according to the background therapy at baseline, as calculated by means of a Cox regression model[4]

ACE = angiotensin-converting enzyme + the use of the drug and non-use.

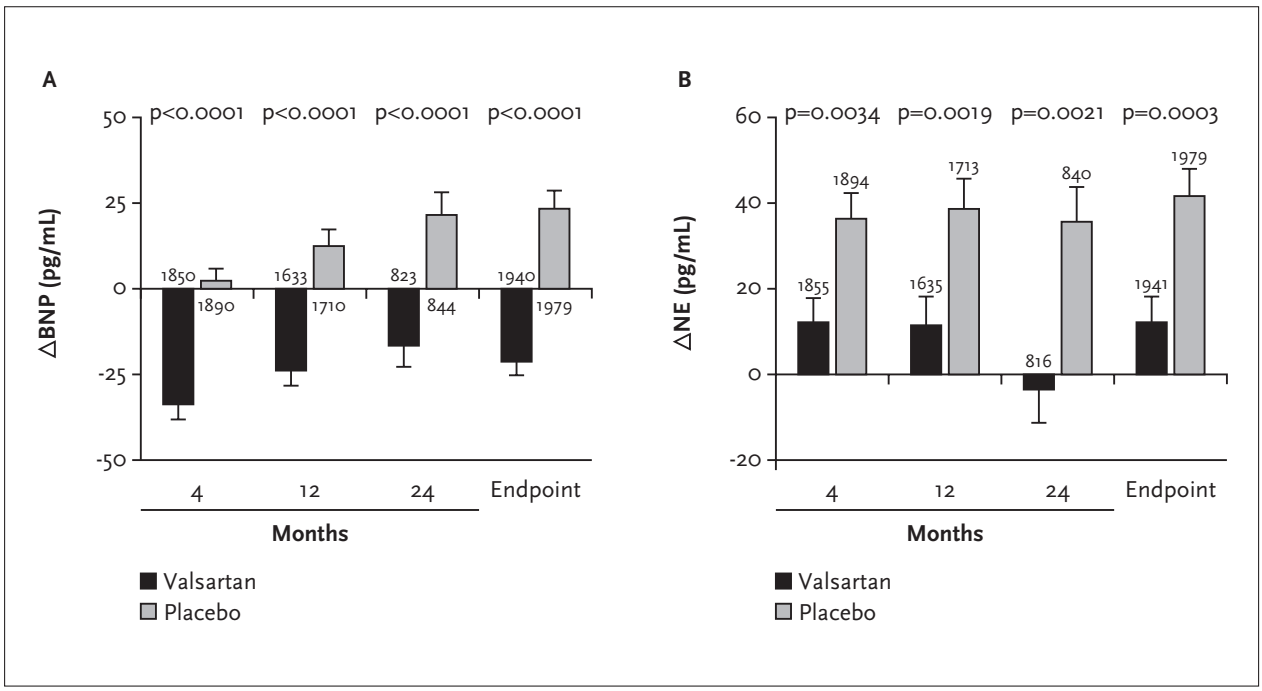


Figure 10

Change from randomisation in plasma concentrations of (a) BNP and (b) NE at 4, 12 and 24 months and at endpoint[5]

Data are presented as least-squares mean ± SEM, with probability values for between-treatment comparison of means. Number of patients in group are shown in bar.

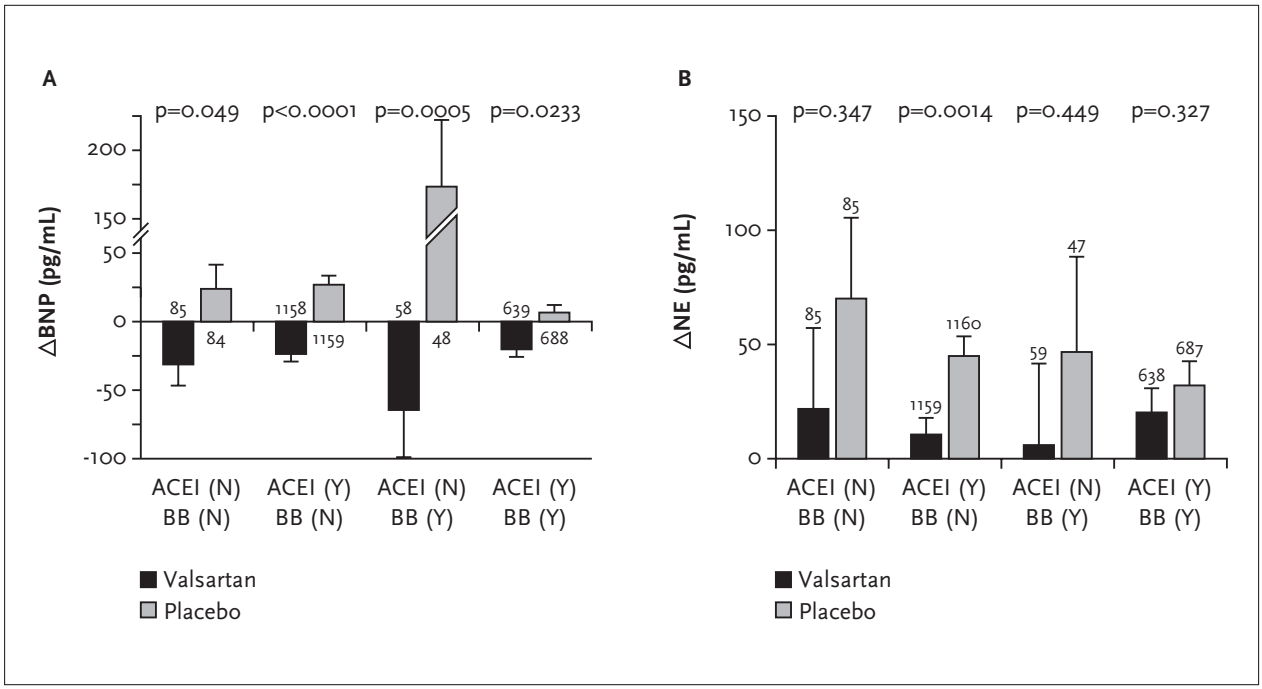


Figure 11

Effects of valsartan on changes from randomisation in plasma concentrations of (a) BNP and (b) NE at endpoint in four subgroups defined by concomitant therapy[5]

Combinations were ACEI (Y/N) and BB (Y/N). Data are presented as least-squares mean ± SEM, with probability values for between-treatment comparison of means. Treatment x 4 subgroup interaction: BNP p=0.109, NE p=0.2413.

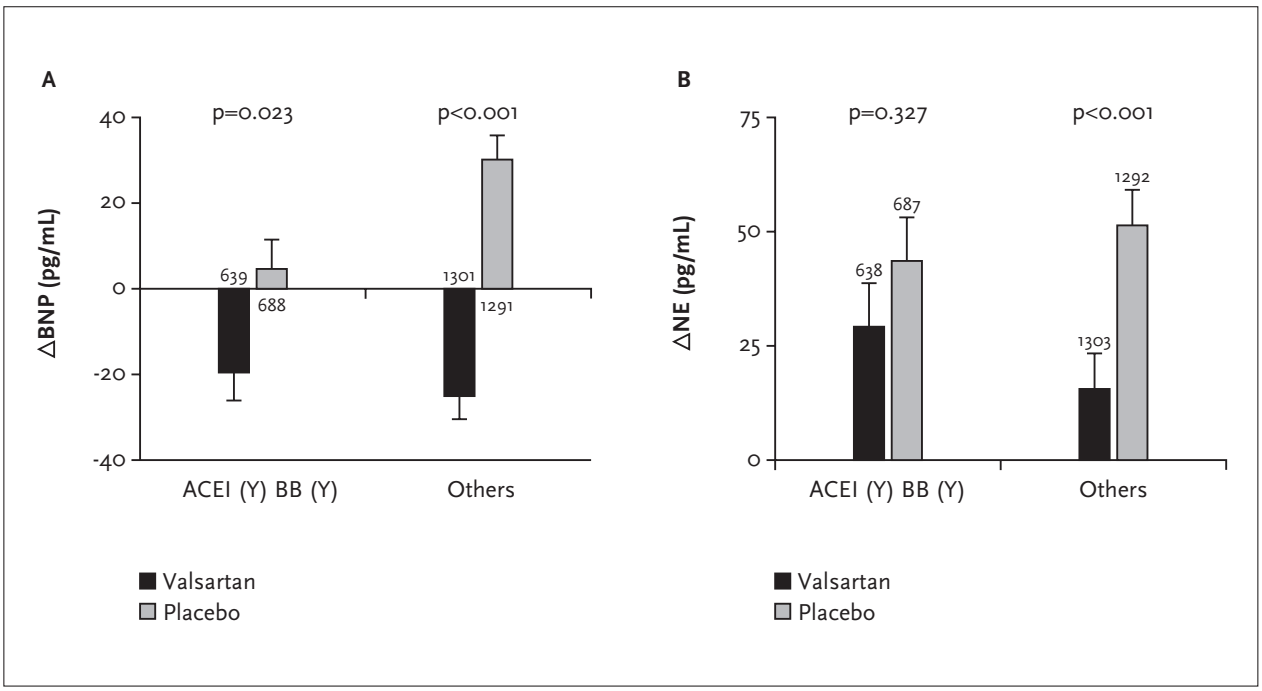


Figure 12

Effects of valsartan on changes from baseline to endpoint in (a) BNP and (b) NE by subgroups on ACE1 (Y/N) and/or BB (Y/N) at randomisation[5]

Two-group ANOVA test for interaction: ACEi (y)/BB (Y) versus others. BNP: treatment x ACEi/BB, p=0.0228; NE: treatment x ACEi/BB, p=0.2289. Data are presented as least-squares mean ± SEM. Probability values are for between-treatment comparison of means. Number of patients in group are shown in bar. BNP at baseline: ACEi (Y)/BB (Y): placebo 164 ± 8, valsartan 169 ± 8 pg/ml; others: placebo 169 ± 6, valsartsan 181 ± 6 pg/ml. NE at baseline: ACEi (Y)/BB (Y): placebo 449 ACEi (Y)/BB (Y):10, valsartan 456 ± 10 pg/ml; others placebo 461 ± 8, valsartan 449 ± 8 pg/ml. No significant differences ACEi (Y)/BB (Y) versus others or placebo versus valsartan.

atrial-synchronised biventricular pacing produces clinical benefits in patients with heart failure and an intraventricular conduction delay. In the present study, 453 patients from 45 different medical centres with moderate-to-severe congestive heart failure were investigated in a double-blind fashion. They all had an ejection fraction of 35% or less and a QRS interval on the ECG of 130 msec or more. They were randomly assigned to a cardiac-resynchronisation group (228 patients) or to a control group (225 patients). The conventional medical treatment was continued. Follow-up lasted for six months and all patients received a device. The primary endpoints were the NYHA classification, quality-of-life assessment and the distance walked in six minutes. Secondary endpoints were maximal exercise performance, left ventricular ejection fraction and left ventricular end-diastolic diameter, severity of mitral valve insufficiency and QRS interval. During the study 571 patients appeared to be eligible. Of these, 47 patients had to be excluded because implantation was not successful (43 patients), pacing appeared to be necessary (2 patients) or they developed unstable congestive heart failure (2 patients). A total of 71 patients only joined the pilot period of the study (three months). Of the remaining group of 453 patients, 225 patients were randomised to the control group and 228 patients to the paced group. The result of the study was very promising (*table 2*). In the paced group there was a significant improvement in six-minute walking distance compared with the non-paced group (p=0.005). There was also a significant improvement in functional NYHA class (p<0.001). The quality of life as well as the ejection fraction improved significantly in the paced group: p=0.001 and p<0.001 respectively. In the paced group there were also less hospitalisations. Probably the most important reason for the better results in the paced group was a reduction in the severity of the mitral valve insufficiency. This study clearly shows that cardiac resynchronisation in moderate-to-severe congestive heart failure with intraventricular conduction delay results in a significant clinical improvement. Implantation of the pacemaker was unsuccessful in only 8% of the patients, and as such this treatment modality can help the majority of this specific group of patients.

Table 2
Effect of cardiac resynchronisation on efficacy endpoints[6]

TABLE 2. EFFECT OF CARDIAC RESYNCHRONIZATION ON EFFICACY END POINTS.

END POINT*	CONTROL GROUP	CARDIAC-RESYNCHRONIZATION GROUP	P VALUE
Change in the distance walked in six minutes — m			
Median	+18	+39	0.005
95 percent confidence interval	8 to +25	+26 to +54	
No. of patients	198	214	
Change in the Minnesota Living with Heart Failure score			
Median	−9	−18	0.001
95 percent confidence interval	−12 to −5	−22 to −12	
No. of patients	192	213	
Change in the New York Heart Association functional class — no. (%)			<0.001
Improved by two or more classes	12 (6)	34 (16)	
Improved by one class	62 (32)	109 (52)	
No change	115 (59)	64 (30)	
Worsened	7 (4)	4 (2)	
Change in peak oxygen consumption — ml/kg/min			
Median	+0.2	+1.1	0.009
95 percent confidence interval	−0.2 to +0.8	+0.6 to +1.7	
No. of patients	145	158	
Change in total exercise time — sec			
Median	+19	+81	0.001
95 percent confidence interval	−1 to +47	+62 to +119	
No. of patients	146	159	
Change in patient's view of progress — no. (%)			<0.001
Markedly improved	24 (12)	80 (38)	
Moderately improved	42 (22)	46 (22)	
Slightly improved	44 (23)	40 (19)	
No change	51 (26)	26 (12)	
Slightly worse	20 (10)	11 (5)	
Moderately worse	10 (5)	5 (2)	
Markedly worse	4 (2)	1 (1)	
Absolute change in left ventricular ejection fraction — %			
Median	−0.2	+4.6	<0.001
95 percent confidence interval	−1.0 to +1.1	+3.2 to +6.4	
No. of patients	146	155	
Change in left ventricular end-diastolic dimension — mm			
Median	0.0	−2.5	<0.001
95 percent confidence interval	−1 to +2	−6 to −1	
No. of patients	98	90	
Change in area of the mitral regurgitant jet — cm^2			
Median	−0.5	−2.7	<0.001
95 percent confidence interval	−1.1 to 0.0	−4.0 to −2.1	
No. of patients	118	116	
Change in QRS duration — msec			
Median	0	−29	<0.001
95 percent confidence interval	−10 to 0	−38 to −12	
No. of patients	192	206	

*The numbers of patients with data available for each variable are listed.

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Molecular biology and genetics in cardiovascular research: highlights of 2002

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ABSTRACT

In the future treatment of haemophilia B, a real breakthrough may be a strategy that uses site-specific genomic integration of a gene therapy vector to produce therapeutic levels of human clotting factor IX (FIX). A clinically relevant expression of plasma levels of FIX was noted for over 12 months. The strategy will be applicable for a broad range of therapeutic genes and tissues.
Following the concept that angiogenic growth factors could stimulate revascularisation, a highly interesting novel approach to the 'bio-bypass' has been presented that appears to have some unexpected advantages. It was demonstrated that specifically designed transcription factors can regulate gene expression *in vivo*.
Another important finding was that myocardial stress signals all appear to converge to a common downstream target, the class II histone deacetylases. In mice, hypertrophic stimuli proved to lead to the activation of a novel and so far unique cardiac HDAC kinase that phosphorylates the signal-responsive sites in class II HDACs. A major implication is that the cardiomyocytic HDAC kinase could well be a novel therapeutic target for the treatment of hypertrophy and heart failure.
And finally, Catherine Verfaillie and her group published a landmark paper demonstrating that pluripotent stem cells that have the potency to differentiate into most, if not all, somatic tissues can also be isolated from adult bone marrow.

INTRODUCTION

Nowadays, molecular biology and genetics are as much part of cardiovascular research as biochemistry or clinical epidemiology. Hence, selecting the top papers from the cardiovascular literature published in the year 2002 that involve 'a molecular biological or genetic approach' can only be done using subjective selection criteria which are, above all, based on personal perspective and taste. The four papers discussed have in common that they all describe a scientific breakthrough that was facilitated by the innovative use of molecular biology and that may well affect the design of experimental clinical protocols of the near future. Moreover, the concepts and implications put forward by these studies will be very likely applicable to molecular medicine in general.

SITE-SPECIFIC GENOMIC INTEGRATION PRODUCES THERAPEUTIC FACTOR IX LEVELS IN MICE

Olivares EC, Hollis RP, Chalberg TW, Meuse L, Kay MA, Calos MP. Nat Biotechnol 2002;20(11):1124-8
In October 2002 the gene therapy world was shocked by the news that leukaemia had developed in a three-year-old patient participating in a clinical trial for retroviral correction of severe combined immunodeficiency disease (SCID). This trial, led by Dr. Alain Fisher from the Necker Children's Hospital in Paris, had so far been one of the few real successes in gene therapy. SCID patients are deficient for the γc subunit of interleukin receptors and therefore lack T and NK lymphocyte function. In a land-

mark publication in *Nature* in 2000, the French group reported full correction of the immunodeficiency in two young SCID patients through stable transduction of bone marrow derived CD34-positive haematopoietic stem cells with a retroviral vector carrying an intact copy of the γc subunit gene.[1] Ten patients had been successfully treated with this vector[2] when the serious adverse event happened that had been identified as a potential risk associated with retroviral vectors. For a permanent correction of a genetic deficiency, the gene therapy vector has to integrate into the genomic DNA of the host cell. With the retroviral vector used, integration takes place in a random fashion and the risk of this method is that the strong constitutive viral promoter is accidentally positioned directly upstream of a potential oncogene. Analysis of the SCID patient's leukaemic T-cell clone showed that this was exactly what had happened as the retroviral vector had been inserted in the known T-cell leukaemia gene LMO-2 on chromosome 11.

A second gene therapy trial published in the year 2000 was reported in *Nature Genetics* by researchers from Pennsylvania.[3] Intramuscular injection of B type haemophilia patients with an integrating adeno-associated vector (AAV) coding for the human clotting factor IX (FIX) resulted into a clinically relevant expression of 5 to 7% of normal plasma levels of FIX for over 12 months. Gene therapy of haemophilia holds a lot of promise as only 1 to 5% of normal clotting factor levels are needed for a significant correction of the clotting deficiencies. Not withstanding this initial success, chromosomal integration of the used AAV virus remains a relatively random process with the associated risk of unwanted (in)activation of endogenous genes. Hence, the report by Olivares *et al.* in the November issue of *Nature Biotechnology* in 2002 may well represent a true breakthrough in the future treatment of haemophilia B as a strategy was presented that uses site-specific genomic integration of a gene therapy vector to produce therapeutic levels of FIX.[4] To obtain 'controlled' integration of the gene therapy vector the authors used a molecular biological trick that was learned from the *streptomyces* bacteriophage ϕC31. After injection into the host bacterium the phage DNA integrates into the host genome by recombination of a 40 base pairs long phage attP sequence with a specific complementary host sequence called the attB site (*figure 1*). The only factor needed for this recombination is the so-called integrase enzyme that is encoded for by the ϕC31 phage genome. Surprisingly, the integrase also works perfectly in eukaryotic cells such as mouse and human cells. In vitro studies showed that the chromosomes of these species contain a limited number of pseudo attB sites that are sufficiently homologous to the authentic streptomyces attB site to allow efficient integration of attP-site containing vectors, provided the ϕC31 integrase is present.[5] Olivares and co-

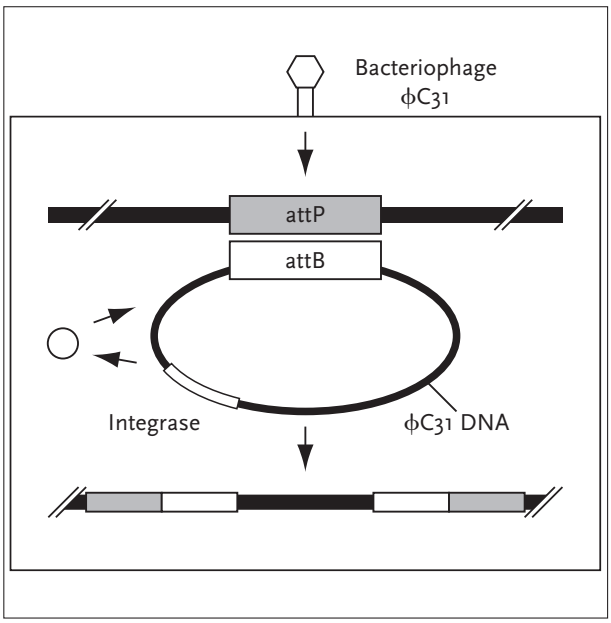

Figure 1

Schematic representation of the integration of bacteriophage ϕC31 DNA into the bacterial host genome

After injection of the ϕC31 DNA into the *Streptomyces* bacterium site-specific integration of the phage DNA into the host chromosome takes place through a ϕC31 integrase-dependent recombination between the attP sequence of the bacteriophage genome and the homologous attB sequence of the bacterial chromosome.

workers showed that simply adding an attP site to a FIX expression plasmid in combination with an expression vector for the ϕC31 integrase can lead to site-specific integration of the FIX vector into the mouse genome.

A simple high pressure/high volume injection of the naked plasmid DNAs into the mouse tail vein resulted in therapeutic levels of human FIX in the serum that were maintained for at least 250 days (*figure 2*). Surprisingly, as has been previously demonstrated, these hydrodynamic-based injections predominantly lead to transfection of the liver, the natural site of FIX expression. Control experiments confirmed that the FIX expression was derived from integrase-dependent vector insertion in two dominant pseudo attB sites present on mouse chromosome 2 and 11. As no genes have been shown to be present in these two loci and the same holds true for the human pseudo attB sites, these integration sites are expected to be relatively safe. Although one cannot exclude a certain degree of random integration of the used vectors, it is likely that the number of random integrations are greatly reduced. The authors note that the strategy used holds a strong potential for the treatment of haemophilia B and will also be applicable for a broad range of therapeutic genes and tissues. If the cellular expression of the non-self ϕC31 integrase is not associated with limiting immunological complications they may well be correct.

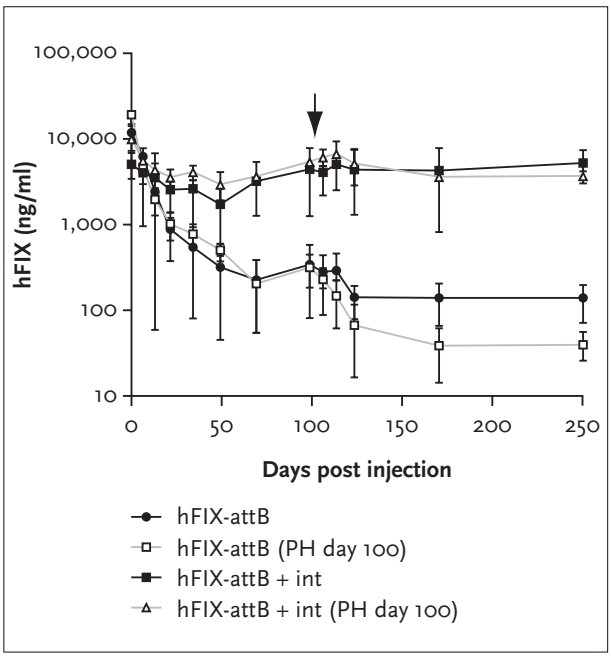

Figure 2

Therapeutic levels of human FIX persist after partial hepatectomy[4]

Mice received a large-volume tail vein injection of 25 g of hFIX-*attB* plasmid alone (circles) or with 25 g of integrase expression plasmid (squares). Two-thirds partial hepatectomies were performed on the indicated groups 100 days after injection (indicated by the vertical arrow). Persistence of expression after partial hepatectomy indicates stable integration of the FIX vector into the mouse genome.

INDUCTION OF ANGIOGENESIS IN A MOUSE MODEL USING ENGINEERED TRANSCRIPTION FACTORS

Rebar EJ, Huang Y, Hickey R, Nath AK, Meoli D, Nath S, Chen B, Xu L, Liang Y, Jamieson AC, Zhang L, Spratt SK, Case CC, Wolffe A, Giordano FJ. Nat Med 2002;8(12):1427-32

Gene therapy aimed at increasing tissue perfusion by stimulating the formation of neovascularisation or collateral formation is slowly but steadily developing from the experimental stage to a serious option for treatment of peripheral and cardiac ischaemic vascular disease.[6] The concept that angiogenic growth factors could stimulate revascularisation in patients (therapeutic angiogenesis) was first explored by Dr. Jeffrey Isner's group from St. Elizabeth's Medical Centre in Boston, USA. Direct injection of a purified DNA vector coding for vascular endothelial cell growth factor (VEGF) in the leg of patients with critical peripheral ischaemic vascular disease led in several cases to an improvement in rest pain, healing of ischaemic ulcera and increased vascularisation of the treated leg to an extent that was beyond expectations.[7] These seminal observations led to a true 'gold rush' for the identification of the optimal angiogenic factor and delivery strategy for the clinical application of this, both clinically and commercially, highly significant therapy. In the *Nature Medicine* of November 2002 a highly interesting novel approach to the 'bio-bypass' was presented that appeared to have some unexpected advantages.[8] To increase local levels of VEGF, not DNA or a viral vector coding for VEGF but a 'designer transcription factor' highly specific for endogenous 'natural' VEGF gene was infected. Transcription factors can turn on genes by binding to the gene promoter sequence that lies upstream of the coding sequences of the gene. They typically have two domains, one to bind the promoter of the target gene in a sequence-specific fashion and a second 'effector' domain that activates the transcription of the gene by RNA polymerases. One of the most common DNA binding motifs is the so-called zinc finger domain that is present in over 700 different human genes. A zinc finger domain spans about 30 amino acids and typically binds three base pairs of a double-strand DNA sequence. As these zinc fingers are often modular (e.g. three consecutive zinc fingers bind a sequence of nine base pairs) DNA-binding factors are evolved that selectively bind promoter sequences. The combined use of techniques for mutagenesis and selection, such as 'bacteriophage display', has facilitated the generation of collections of zinc finger motifs that can bind nearly all possible three base-pair sequences. Statistically, a specificity of 16 base pairs is more then sufficient to target a single site in the entire human genome. Based on this concept 'polydactyl zinc finger proteins' have been designed and developed that indeed were shown to be selective and effective activators of gene transcription.[9]

The study by Rebar *et al.* discussed here was intended to test whether these engineered transcription factors are effective *in vivo* using a polydactyl zinc finger designed to regulate the VEGF gene. Injections of an adenoviral vector encoding the novel transcription factor into mouse tissues induced the expression of the zinc finger protein and stimulated angiogenesis and markedly accelerated the healing of experimental wounds. Moreover, the neovasculature resulting from the zinc finger protein was functional and not hyperpermeable in contrast to novel vessels produced in the same model after expressing VEGF from an endogenous cDNA vector (*figure 3*). The VEGF gene codes a number of splice variants and recent data suggest that only the natural combination of these splice forms elicit the formation of physically mature neovasculature.[10] The hypermeability could thus be explained as being the result of the expression only on a single VEGF splice form. This study demonstrated that specifically designed transcription factors can regulate gene expression *in vivo* and, moreover, emphasises the importance of proteomics in that there is more involved than just the sequence of a gene, it is how that sequence is used to generate the protein(s) encoded by that gene.

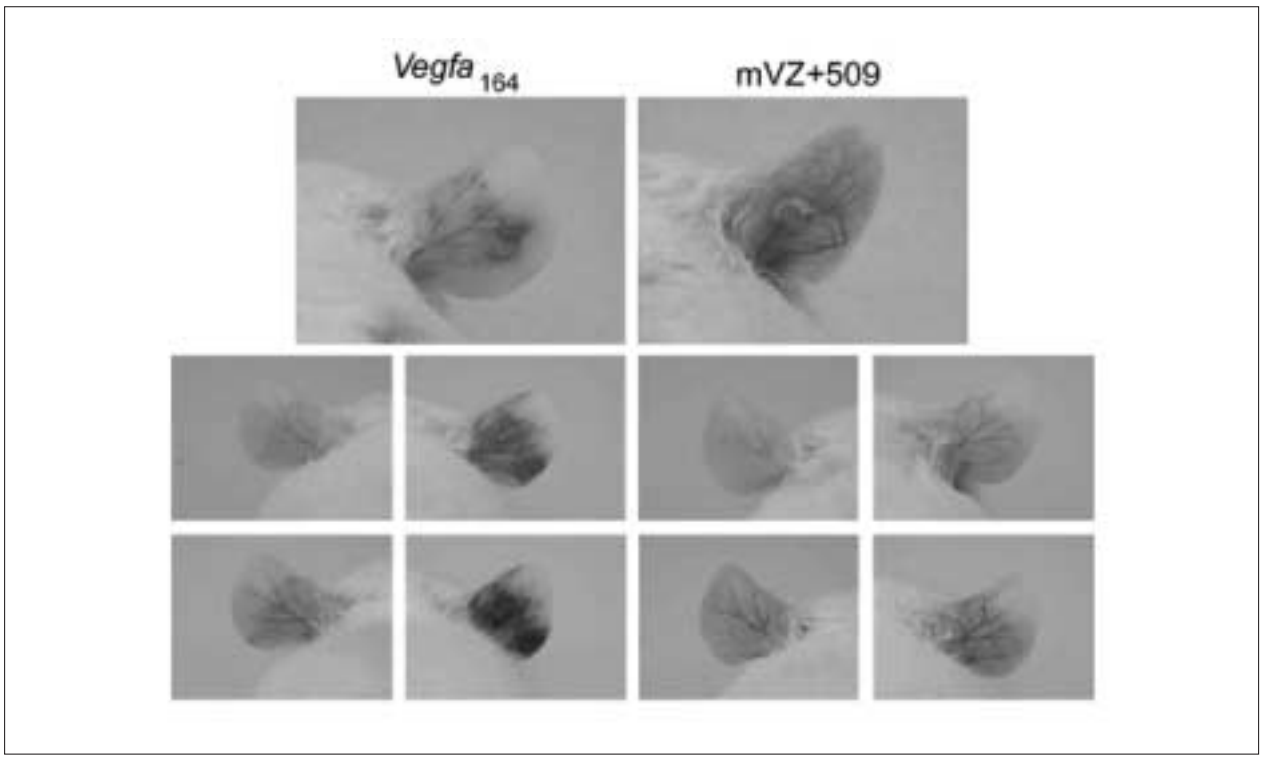

Figure 3

VEGF-activating ZFP expression induces angiogenesis in the mouse ear[8]

Subcutaneous injection of adenovirus encoding the polydactyl zinc-finger mVZ+509 that activates the endogenous VEGF gene results in visible neovascularisation after three days. Angiogenesis stimulated by mVZ+509 (top and middle right) does not produce a hyperpermeable neovasculature as determined by Evans blue dye extravasation (bottom right). The neovasculature induced by *Vegfa*$_{164}$ adenovirus transduction (left) shows spontaneous haemorrhage (middle) and Evans blue extravasation (bottom).

CLASS II HISTONE DEACETYLASES ACT AS SIGNAL RESPONSIVE REPRESSORS OF CARDIAC HYPERTROPHY

Zhang CL, McKinsey TA, Chang S, Antos CL, Hill JA, Olson EN. Northwestern Medical Centre Texas. Cell 2002;110:479-88

The adult myocardium responds to stress signals by hypertrophic growth, a process central to the development of heart failure. The nature of this stress signal can be quite diverse and include cardiac pressure overload, hypertension, myocardial infarction and autocrine and paracrine signalling pathways involving angiotensin II, endothelin and adrenergic signalling. Despite the diversity of these stress signals they all lead to the same outcome, the development of myocyte hypertrophy as a result of activation of a foetal cardiac gene programme.[11] In August 2002 a paper was published in the journal *Cell* by Dr. Eric Olsen's group from Texas Southwestern Medical Centre who for the first time showed that myocardial stress signals all appear to converge to a common down-stream target, the class II histone deacetylases.[12] Histone acetyl transferases (HATs) and histone deacetylases (HDACs) control gene expression through association with gene specific transcription factors. When HATs are recruited to genes by transcriptional activators they promote gene activation by acetylating nucleosomal histones. This results in a relaxed chromatin structure that facilitates transcription. In contrast, HDACs deacetylate histones leading to condensed chromatin and gene repression. The Olsen group showed that, in mice, hypertrophic stimuli such as thoracic aortic banding lead to the activation of a novel and so far unique cardiac HDAC kinase that phosphorylates the signal-responsive sites in class II HDACs like *HDAC9*. Mutants of the latter that can not be phosphorylated act as dominant negative repressors of cardiomyocyte hypertrophy and foetal cardiac gene expression *in vitro*.

Hence, the common pathway to hypertrophy laid out by this paper is the following. In the mature, differentiated cardiomyocytes the foetal cardiac gene programme is suppressed by gene repressor mediated recruitment of HDACs that keep the chromatin condensed and not accessible for the transcriptional machinery. However,

cardiac stress signals activate a kinase that leads to HDACs phosphorylation and inactivation. Subsequently, chromatin acetylation by HATs open up the chromatin associated with the foetal cardiac gene programme facilitating the expression of these genes and the progression of hypertrophy (*figure 4*). The importance of this pathway is dramatically demonstrated using *HDAC9* knock-out mice that indeed turn out to be hypersensitive to cardiac stress and, in three weeks, develop hypertrophic hearts with a 105% increase in left ventricular mass (*figure 5*).
A major implication of this study is that the cardiomyocytic HDAC kinase could well be a novel therapeutic target for the treatment of hypertrophy and heart failure. As the authors point out, current therapies target the early steps in hypertrophic signalling pathways such as cell surface receptors, calcium channels or the β-adrenergic receptors system. Although not yet characterised, the HDAC kinase appears to be a common denominator of these pathways and therefore a drug target of high potential.

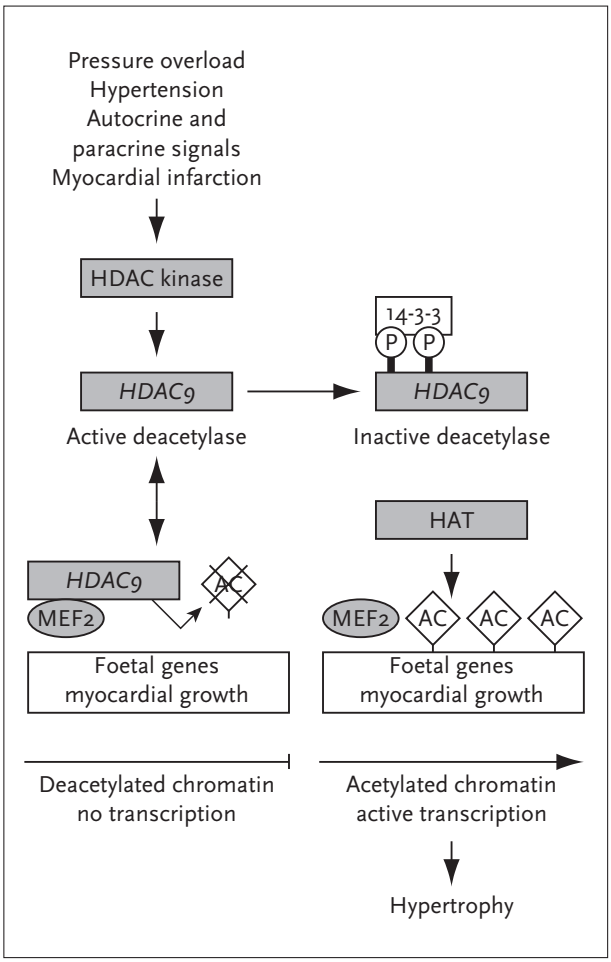

Figure 4
Repression of cardiac hypertrophy by class II HDACs
Class II HDACs associate with MEF2 and inhibit hypertrophy and the foetal gene programme. Stress signals stimulate an HDAC kinase that phosphorylates (P) HDACs at two conserved serine residues. When phosphorylated, HDACs bind 14-3-3, dissociate from MEF2, and are exported from the nucleus. Upon release of HDACs, MEF2 is free to associate with histone acetyltransferases (HATs) and to activate downstream target genes that drive a hypertrophic response.

PLURIPOTENCY OF MESENCHYMAL STEM CELLS DERIVED FROM ADULT MARROW

Jiang, et al. Nature 2002;418:41-9
In 2002 stem cells were one of the themes on central stage. Animal studies showing the potential of stem cells to grow new insulin-producing cells to treat diabetes[13] or dopamine-producing nerve cells to reverse the symptoms of Parkinson's disease[14] have delivered the proof of principle for future stem cell therapies. Nevertheless most studies were performed with embryonic stem cells. These cells, which can be obtained from the inner cell mass of the blastocyst, are pluripotent and can be cultured in high numbers. Although embryonic stem cells have been isolated from humans[15] ethical considerations and, more practically, the immunological incompatibility of the stem cells with the genetic makeup of the potential patients may limit their use. In the July 2002 issue of *Nature* Catherine Verfaillie and co-workers published a landmark paper demonstrating that pluripotent stem cells that have the potency to differentiate into most, if not all, somatic tissues can also be isolated from adult bone marrow.[16] This cell, termed the multipotent adult progenitor cell or MAPC, maintains its stem cell properties for over 80 population doublings and can be obtained from mesenchymal bone marrow cultures from different species including humans irrespective of the age of the donor. Previous studies had shown that, *in vitro*, MAPC can differentiate into multiple cells from the mesenchymal lineage[17] to endothelial cells[18] and even hepatocytes.[19] If the MAPC were truly pluripotent cells *in vivo*, these cells could be an ideal source for stem cell based therapies as these cells could be derived from the patient's own bone marrow, thereby avoiding tissue rejection. In the July paper the group demonstrated that when injected into an early blastocyst, single MAPCs contribute to virtually all somatic cell types. As the injected MAPC were obtained from a mouse donor carrying the traceable genetic marker *LacZ*, in the mice generated from injected blastocysts, MAPC derived tissues can be identified by a blue colour that develops after X-gal staining (*figure 6*).
This paper has inspired a large number of researchers all over the world to also try to isolate the MAPC or similar pluripotent adult cells as they may be an ideal source for therapy of inherited or degenerative disease.

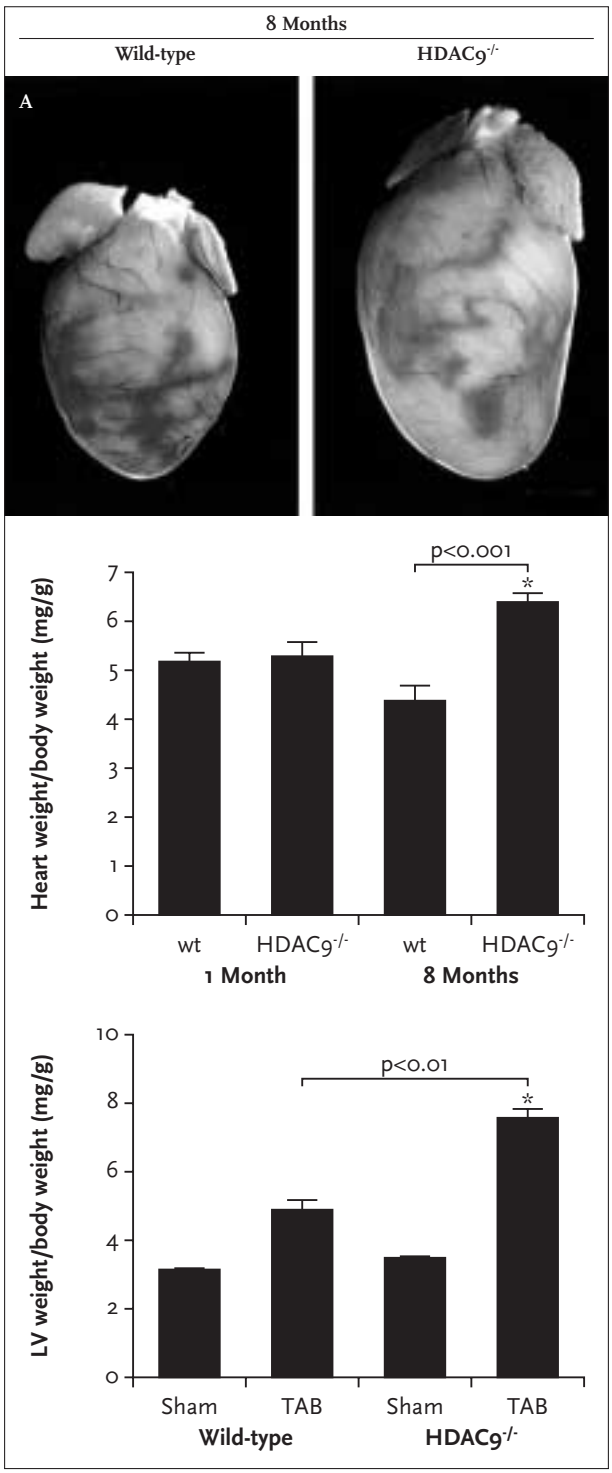

Figure 5

Cardiac hypertrophy in HDAC9 mutant mice[12]

(A and B) *HDAC9* mutant mice and wild-type littermates were sacrificed at one and eight months of age and heart weight-to-body weight ratios were determined. Values represent the mean ± standard deviation (SD). N=5. Scale bar equals 2 mm. (C) Hypersensitivity to TAB. Six-to-eight-week-old mice were subjected to thoracic aortic banding (TAB) or to sham operation. Twenty-one days later, animals were sacrificed and the ratios of left ventricular (LV) mass-to-body weight were determined. At least five mice of each genotype were analysed. Values represent the mean ± SD.

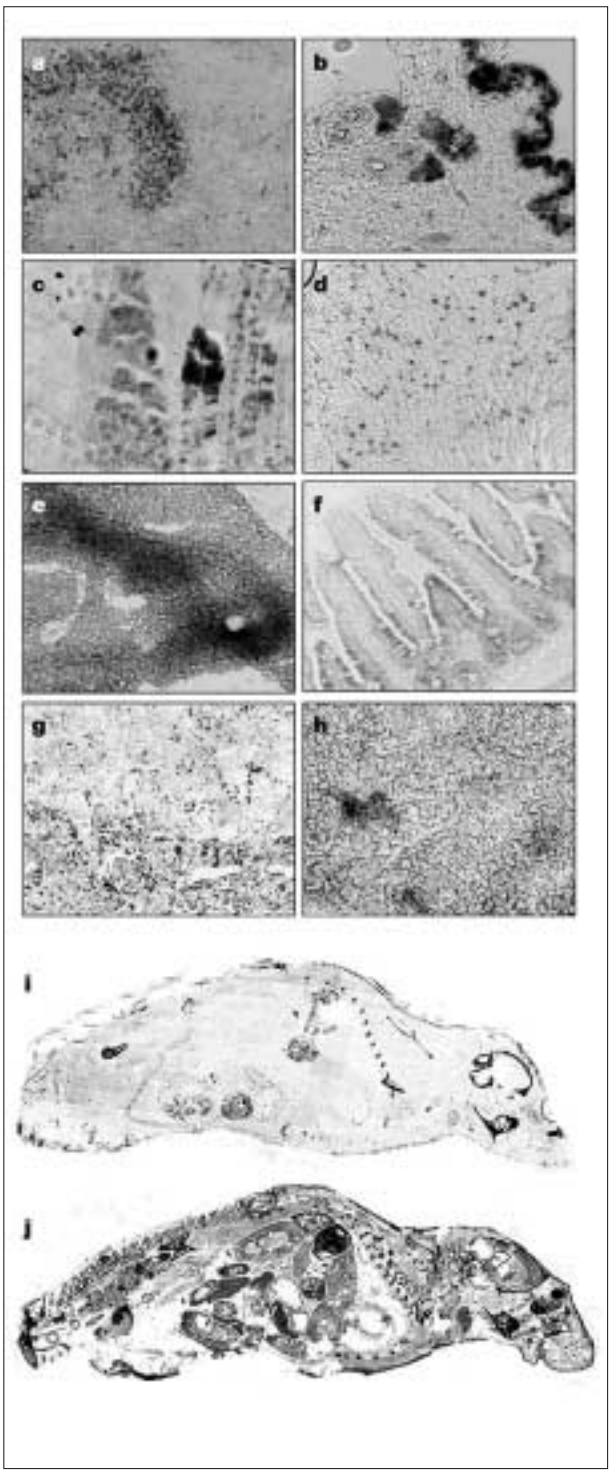

Figure 6

Chimaerism detection by X-gal staining and anti-gal staining in animals generated from blastocysts micro-injected with a single ROSA26 MAPC[16]

a-h: Images from X-gal-stained individual organs from a 45% chimeric mouse, determined by Q-PCR for Neo on tail clip. Tissue sections were from: brain (a), skin (b), skeletal muscle (c), myocardium (d), liver (e), small intestine (f), kidney (g) and spleen (h). i + j: Images from an X-gal-stained section through a mouse that was not chimeric (i) or was 45% chimeric (j). Magnification 20x.

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The future of lipid-lowering therapy: the big picture

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ABSTRACT

Several lipid-lowering intervention studies published in 2002 shed light on the current status and the future of cardiovascular risk reduction by drug therapy. The Heart Protection Study has demonstrated that simvastatin reduces heart attack, stroke and revascularisation risk by about one-third irrespective of total cholesterol, LDL cholesterol, patient's age or sex, or the nature of pre-existing cardiovascular disease. Coronary heart disease death and myocardial infarction risk reduction in elderly patients by pravastatin in the PROSPER study was similar to the benefit of statins in middle-aged populations in other studies. The ALLHAT-LLT study has failed to demonstrate a benefit of pravastatin on all-cause mortality, CHD death or nonfatal myocardial infarction, illustrating that too modest cholesterol lowering does not result in clinical benefit under all circumstances.
The cholesterol absorption inhibitor ezetimibe has demonstrated significant LDL and total cholesterol lowering, and induced an additional 21% LDL cholesterol lowering when added to ongoing statin therapy. The cholesteryl ester transfer protein inhibitor JJT-705 produced a dose-dependent increase in HDL cholesterol concentrations of up to 34% and improved the total cholesterol/HDL cholesterol ratio in healthy individuals while having very mild side effects. Cholesterol absorption inhibitors and HDL cholesterol enhancers may become useful tools to achieve further improvements in cardiovascular risk reduction in the future.

INTRODUCTION

Over the past decades, the significance of hypercholesterolaemia for the pathogenesis of coronary heart disease (CHD) and the benefits of cholesterol lowering for CHD risk reduction have been convincingly demonstrated in a range of clinical and epidemiological studies. Many well-controlled, randomised clinical trials with lipid-lowering agents, alone or in combination with other risk-reducing interventions, have demonstrated significant CHD risk reduction in various high-risk populations.

Today, no one questions the value of cholesterol-lowering interventions with respect to cardiovascular risk reduction in high-risk populations, such as those with manifest coronary heart disease or patients with hypercholesterolaemia and other risk factors without clinical evidence of cardiovascular disease. The question arises, however, whether the current achievements represent an end stage or just a point along the line of evolving cardiovascular risk management. In other words, have we achieved most if not all of the benefits of cholesterol lowering, or is the best still to come? Against the background of this question, five original papers, all published in the course of 2002, have been reviewed in search of clues.

HEART PROTECTION STUDY

The Heart Protection Study (HPS), the largest secondary prevention study in cardiovascular medicine conducted to date, has investigated a number of the remaining questions concerning the value of cholesterol lowering by statin therapy, including cardiovascular risk reduction at different baseline LDL concentrations and in specific subgroups such as older patients, women, and patients with various cardiovascular symptomatology at entry.[1] The HPS randomised 20,536 patients, aged 40 to 80 years, with baseline total cholesterol over 3.5 mmol/l and an increased risk of coronary heart disease (CHD) death due to pre-existing disease, notably myocardial infarction or other coronary artery disease, occlusive disease of noncoronary arteries, diabetes mellitus or treated hypertension. Patients were randomised to receive either 40 mg of simvastatin daily or placebo. The use of a statin was not considered specifically indicated or contraindicated by the patients' own general practitioners. Average follow-up was five years and compliance to simvastatin was 85%. In the placebo group 17% of patients were on a statin, as the use of statins other than simvastatin by these patients was not excluded.

At baseline, 52% of HPS participants were at least 65 years of age, and 28% were 70 years or more. Women constituted one quarter of the study population. Baseline total cholesterol concentrations were below 5.0 mmol/l in 20% of participants and between 5.0 and 6.0 mmol/l in 38%. LDL cholesterol concentrations were below 3.0 mmol/l in 33% of participants and between 3.0 and 3.5 mmol/l in another 25%.

The absolute difference in average LDL concentration during follow-up between simvastatin- and placebo-allocated patients was 1.0 mmol/l, without any relationship to pre-existing total cholesterol or LDL cholesterol level. Also age, sex, or prior disease were not determinants of the LDL cholesterol response to simvastatin. Treatment with simvastatin was associated with a significant 17% overall reduction (p<0.0001) in the risk of any vascular mortality. The risk of death due to coronary vascular causes was 5.7% in the simvastatin group and 6.9% in the placebo group. For death due to other vascular causes, these percentages were 1.9 and 2.2 % respectively. Overall mortality risk was reduced by 13% (p<0.0003) by simvastatin compared with placebo. Among nonvascular causes, neoplastic disease was the most prominent cause of death without any relation to treatment (3.5 and 3.4% on simvastatin and placebo, respectively).

Major vascular events, including coronary events (nonfatal myocardial infarction, coronary death), fatal and nonfatal stroke, and coronary and noncoronary revascularisation occurred less frequently in patients allocated to simvastatin than in patients receiving a placebo (relative risk: -24%; p<0.0001).

Analyses of the outcomes of the HPS in specific categories of patients have yielded a number of interesting conclusions. The proportional risk reduction by simvastatin in terms of the first major event appeared to be relatively independent of a number of factors, including but not limited to:

- Prior disease: myocardial infarction, other CHD or no prior CHD
- Sex
- Age: <65, 65-70, or ≥70 years
- Total cholesterol: <5.0, 5.0-6.0, or ≥6.0 mmol/l
- LDL cholesterol: <3.0, 3.0-3.5, or ≥3.5 mmol/l
- HDL cholesterol: <0.9, 0.9-1.1, or ≥1.1 mmol/l
- Triglycerides: <2.0, 2.0-4.0, or ≥4.0 mmol/l

The results of these subanalyses for the factors 'age' and 'sex' are shown in *table 1* and for the factors 'LDL cholesterol' and 'total cholesterol' in *table 2*. The results for the other factors were largely comparable with those for the factors shown in these figures, i.e. no notable effect of any factor on the degree of risk reduction by statin therapy.

Table 1
Rate ratio of major vascular events by age and by sex in the Heart Protection Study[1]

BASELINE FEATURE		NUMBER	PERCENTAGE
Age (years)	<65	9839	48%
	65-69	4891	24%
	70-74	4543	22%
	>74	1263	6%
Sex	Male	15454	75%
	Female	5082	25%

Table 2
Rate ratio of major vascular events by LDL and total cholesterol in the Heart Protection Study[1]

BASELINE LIPIDS		NUMBER	PERCENTAGE
LDL cholesterol (mmol/l)	<3.0 (116 mg/dl)	6793	33%
	≥3.0-<3.5	5063	25%
	≥3.5 (135 mg/dl)	8680	42%
Total cholesterol (mmol/l)	<5.0 (193 mg/dl)	4072	20%
	≥5.0-<6,0	7883	38%
	≥6.0 (232 mg/dl)	8581	42%

The main conclusion that can be drawn from the HPS is that simvastatin, after allowance for noncompliance, reduces the risk of heart attack, stroke and revascularisation by one-third. Furthermore, this risk reduction occurs irrespective of total cholesterol or LDL cholesterol levels at entry, the patient's age or sex, or the nature of pre-existing cardiovascular disease. There was no evidence of an increased cancer risk, or any other safety concerns in association with simvastatin treatment. Therefore, the HPS has finally resolved a number of issues that were under debate prior to this study, such as the efficacy of statins in patients with average or below-average cholesterol levels, women and elderly patients. The HPS has also confirmed the safety of statins in a large and demographically diverse population.

However, despite these positive outcomes, it should be kept in mind that the majority of deaths on statin therapy (781/1328 deaths) are still attributable to vascular disease, in particular coronary disease. Also, the risk reduction observed in this study is still far below the effect that should be expected from a long-term difference of 1.0 mmol/l in LDL cholesterol on the basis of epidemiological evidence in people without diagnosed vascular disease.

PROSPER

There have been many debates about the value of cholesterol lowering by statins in truly elderly patients. The HPS has already demonstrated that the benefits of statin therapy extend to patients aged 70 years or more. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) has specifically investigated the potential benefits and safety of statin therapy in even older patients.[2,3] The double-blind PROSPER study, conducted in Scotland, Ireland and the Netherlands, enrolled 5804 patients, men and women aged 70 to 82 years (mean: 75 years) with a history of, or risk factors for, vascular disease. Total cholesterol at entry was between 4.0 and 9.0 mmol/l. Patients were randomised to treatment with either pravastatin 40 mg a day or placebo. Average follow-up was 3.2 years. Major cardiovascular events were recorded, as well as general safety, cognitive function and disability.

Pravastatin lowered LDL cholesterol levels by 34% to an average of about 2.5 mmol/l, and total cholesterol levels by 23%. The risk of CHD death, nonfatal myocardial infarction, or fatal or nonfatal stroke (primary endpoint) was reduced by 15% (p=0.014) in patients receiving pravastatin. The risk of CHD death or nonfatal myocardial infarction (one of the secondary endpoints) was also significantly reduced by pravastatin (-19%; p=0.006), but the risk of fatal or non-fatal stroke was not significantly altered (+3%; p=0.81). CHD mortality was reduced by 24% (p=0.043). There were no significant treatment effects on heart failure requiring hospitalisation, revascularisation procedures, cognitive function, disability or all-cause mortality. Pravastatin was safe and well tolerated.

The relative risk reduction of the primary endpoint in the PROSPER study was slightly less than that seen in other statin trials in middle-aged patient populations. It may therefore be concluded that older age is no longer a reason to withhold statin therapy from patients at increased risk of major cardiovascular events. However, the degree of risk reduction on a number of endpoints, including the primary endpoint, was relatively limited just as in the HPS study.

ALLHAT-LLT

The third recently published trial shedding new light on the usefulness of cholesterol lowering by statins is the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT) in 10,355 patients.[4,5] This trial was part of the large-scale ALLHAT study in high-risk hypertensive patients in the primary care setting. Eligibility for ALLHAT-LLT was based on LDL cholesterol levels in patients aged over 55 years already enrolled in the main ALLHAT study. ALLHAT-LLT participants were older (average age 66 years), hypertensive, moderately hypercholesterolaemic patients with at least one additional CHD risk factor. Eligible patients were randomised to either pravastatin (40 mg a day) or usual care consisting of measures, at the discretion of the primary care physician, aimed at reducing LDL cholesterol. These measures could include statins or other lipid-lowering drugs. Patients were followed up for an average of 4.8 years.

In the course of the study, the percentage of patients in the pravastatin group who were on a statin decreased from 88% at two years to 83% at six years, while the percentage of statin users in the usual care group increased from 8% at two years to 26% at six years. Total cholesterol and LDL cholesterol levels dropped in both groups in the course of the study. Although the largest drop in cholesterol levels occurred in the pravastatin group, differences between the pravastatin and the usual care group were modest. LDL cholesterol levels in the pravastatin group were reduced by 28% from baseline, whereas the reduction in the usual care group was 11%. Accordingly, differences in cardiovascular endpoints were small and failed to reach statistical significance. The relative risk of all-cause mortality was 0.99 (95% CI: 0.89-1.11). The relative risk of CHD death and nonfatal myocardial infarction was 0.91 (95% CI: 0.79-1.04). Also all-cause mortality risk was not significantly

reduced in any of the subgroups of patients analysed, such as younger patients, older patients, men, women, diabetics, nondiabetics or patients with or without CHD at baseline.

Thus, the ALLHAT-LLT study has failed to demonstrate a benefit on the primary endpoint of all-cause mortality or the key secondary endpoint of CHD death or nonfatal myocardial infarction. Several explanations have been proposed for the lack of benefit from statin treatment, such as the relatively low adherence to pravastatin in the statin group and cross-over to statin therapy in the usual care group. The ALLHAT-LLT study has demonstrated that cholesterol lowering by statins does not result in clinical benefit when LDL cholesterol reduction is too modest. Taken in conjunction with the outcomes of the HSP and PROSPER studies discussed above, the ALLHAT-LLT results make it clear that there is still room for considerable improvement. Several strategies to improve cardiovascular risk reduction by lipid-altering strategies are being pursued and important emerging results will be reviewed briefly below.

EMERGING LIPID-ALTERING STRATEGIES

From the lipid-lowering trials and epidemiological studies conducted thus far, it can be concluded that cardiovascular risk is reduced more as LDL cholesterol levels are reduced further. One possible strategy to achieve further reductions in cardiovascular morbidity and mortality is therefore to apply more aggressive lipid lowering. Another possible strategy, which is reviving, is to increase the concentration of the 'protective' HDL cholesterol.

Several ongoing trials are investigating aggressive lipid lowering using currently approved statins. These trials are anticipated to provide valuable insights into the usefulness of aggressive lipid lowering in the next few years.

The development of more potent statins is exemplified by the recent approval and introduction of rosuvastatin, which is reported to reduce LDL cholesterol levels by 52 to 63% in the approved dose range of 10 to 40 mg daily.[6] Rosuvastatin has not yet been investigated in long-term clinical endpoint studies, but this will most likely occur in the years to come.

Novel drugs affecting lipid levels by mechanisms other than HMG-CoA reductase inhibition are cholesterol absorption inhibitors, such as ezetimibe, and cholesteryl ester transfer protein (CETP) inhibitors, such as the experimental agent JJT-705. Human data on ezetimibe and JJT-705 supporting their potential for cardiovascular risk reduction have recently been reported.

Ezetimibe

Ezetimibe is an orally active 2-azetidinone derivative which is rapidly absorbed and extensively conjugated to form a glucuronide.[7] Ezetimibe-glucuronide acts at the brush border of the small intestine and inhibits the uptake of dietary and biliary cholesterol into enterocytes, but not the absorption of triglycerides or lipid-soluble vitamins. In animals, ezetimibe inhibited intestinal cholesterol absorption by up to 96%. It has a long terminal half-life allowing once-daily dosing.

The effect of ezetimibe on cholesterol absorption and plasma lipids has recently been investigated in a randomised, double-blind, placebo-controlled cross-over study in 18 male patients with mild to moderate hypercholesterolaemia. During ezetimibe treatment for two weeks, cholesterol absorption was significantly reduced by 54% compared with placebo treatment ($p<0.001$). Endogenous cholesterol synthesis increased, but the overall effects of ezetimibe on plasma lipids were favourable (*figure 1*), showing significant reductions in total and LDL cholesterol concentrations. The addition of ezetimibe to ongoing statin therapy significantly reduced LDL cholesterol (-21%; $p<0.001$)) and triglyceride levels (-11%; $p<0.01$) compared with placebo.[8] The incremental lowering of LDL cholesterol concentrations when statins and ezetimibe are combined may be due to the ability of statins to reduce the compensatory increase in hepatic cholesterol synthesis induced by ezetimibe.

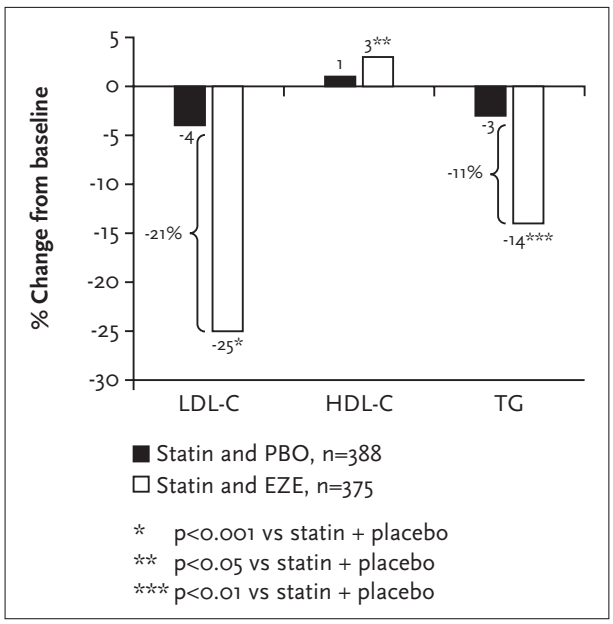

Figure 1
Changes in plasma lipids (baseline versus endpoint) induced by ezetimibe or placebo in male patients with mild to moderate hypercholesterolaemia[7]

Cholesteryl ester transfer protein inhibition

A low HDL cholesterol level has been identified as a risk factor for CHD. A potential strategy to improve the CHD risk profile would be to increase plasma HDL cholesterol concentration. Cholesteryl ester transfer protein (CETP) represents a possible drug target by which this may be achieved. In human lipoprotein metabolism, CETP mediates the transfer of cholesteryl esters from HDL to apolipoprotein-B containing particles in exchange for triglycerides. CETP inhibition may thus be expected to lead to higher HDL concentrations.

JJT-705 is an experimental agent, which has been shown to inhibit CETP, to increase HDL cholesterol and to inhibit the progression of atherosclerosis in cholesterol-fed rabbits. JJT-705 has now been investigated in healthy individuals to assess its effects on HDL and LDL cholesterol levels and its safety.[9] This study was a multicentre, randomised, placebo-controlled, dose-response study in 198 healthy individuals, aged 18 to 65 years, with mildly elevated LDL cholesterol levels (mean 3.9 mmol/l), HDL cholesterol ≤1.6 mmol/l and triglycerides ≤4.5 mmol/l. After a four-week run-in period, subjects were treated with JJT-705 at dose levels of 300, 600 or 900 mg a day, or placebo for four weeks.

At the end of the four-week treatment period, HDL cholesterol levels showed a dose-dependent increase of up to 34% at the highest dose (*table 3*). This was accompanied by a slight but significant 7% decrease in LDL cholesterol concentration at the highest dose. The ratio total cholesterol/HDL cholesterol was dose-dependently decreased, indicating reduced atherogenicity of the lipid profile under treatment with JJT-705. Measurements of CETP activity and CETP mass were altered in the direction expected for a drug known to inhibit CETP.

The side effect profile of JJT-705 was remarkably clean and the drug was well tolerated. There were no signs of toxicity according to physical examination and routine laboratory tests during and after treatments (there was a four-week post-treatment observation period). JJT-705 may have mild gastrointestinal side effects: diarrhoea, flatulence and nausea tended to be associated more frequently with JJT-705 treatment than with placebo, although this association failed to reach statistical significance for any of the doses of JJT-705 tested.

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Table 3

Absolute changes in CETP activity, CTP mass and plasma lipids and lipoproteins in healthy individuals treated with JJT-705 for four weeks[9]

	PLACEBO	JJT-705		
	(n=50)	300 mg (n=48)	600 mg (n=47)	900 mg (n=52)
CETP activity (% control)	0.9 ± 13.2	-15.4 ± 11.9§	-29.6 ± 19.5§	-37.2 ± 17.6§
CETP mass (μg/ml)	0.0 ± 0.3	0.9 ± 0.6§	1.3 ± 0.5§	1.6 ± 0.8§
TC (mmol/l)	0.0 ± 0.5	-0.1 ± 0.5	0.0 ± 0.6	0.0 ± 0.6
HDL (mmol/l)	0.04 ± 0.15	0.18 ± 0.15#	0.32 ± 0.22§	0.40 ± 0.29§
LDL (mmol/l)	-0.1 ± 0.5	-0.2 ± 0.5	-0.2 ± 0.6	-0.3 ± 0.6*
Triglycerides (mmol/l)	0.0 ± 0.4	0.0 ± 0.6	-0.1 ± 0.5	-0.2 ± 0.6
TC/HDL (ratio)	-0.2 ± 0.6	0.7 ± 0.8#	0.9 ± 0.8§	-1.2 ± 0.7§

*Values are means ± SD. TC = total cholesterol, * p≤0.01, # p≤0.001, § p≤0.0001 (versus placebo).*

NOTES