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Original Scientific Paper

Use of secondary preventive medications after the first attack of acute coronary syndrome

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Background **It is not well-known to what extent evidence-based medications, such as β-blockers, hypolipidemic medications, and angiotensin-converting enzyme inhibitors, are prescribed after an attack of acute coronary syndrome in the general healthcare setting and what is the compliance of patients with these prescriptions.**

Design **We conducted a countrywide record linkage study.**

Methods **We used record linkage of the National Hospital Discharge Register, Causes of Death Register, and Social Insurance Institution's drug reimbursement records to identify drug purchases of patients aged 35–74 years hospitalized for the first nonfatal acute coronary syndrome in Finland during 1995–2003 ($n = 53\,353$).**

Results **In 2003 about 28 and 15% of the patients did not receive hypolipidemic medications or β-blockers, respectively, after their acute coronary syndrome and a further 6 and 10% discontinued the use about 3 months later. Patients aged 65–74 years were less likely to receive hypolipidemic medications [odds ratio (OR) 0.55; 95% confidence interval (CI), 0.53–0.58] and β-blockers (OR 0.77; 95% CI, 0.74–0.81) than younger patients. Diabetic patients received less hypolipidemic medications (OR 0.82; 95% CI, 0.78–0.86) and were more likely to discontinue the medication (OR 1.15; 95% CI, 1.05–1.26) than nondiabetic patients. In proportional hazards regression analyses the regular use of hypolipidemic medication or β-blockers was associated with lower risk of cardiovascular death: adjusted hazard ratios 0.47 (95% CI, 0.41–0.53) and 0.54 (95% CI, 0.49–0.60), respectively.**

Conclusions **Our study showed that the evidence-based use of medications after acute coronary syndrome was suboptimal in Finland, particularly in elderly and diabetic patients. Consistent use of these medications, however, was associated with a better prognosis.** ***Eur J Cardiovasc Prev Rehabil*** **14:386–391 © 2007 The European Society of Cardiology**

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Introduction

Clinical trials have shown that certain cardiac medications, such as β-blockers, hypolipidemic medications and angiotensin-converting enzyme (ACE) inhibitors, are effective in the secondary prevention of coronary heart disease (CHD) events [1–3]. Evidence-based guidelines recommend the use of these medications to most patients with CHD unless there are specific contraindications [4,5]. Nevertheless, large international studies have suggested a suboptimal use of these medications among patients with acute or chronic manifestations of CHD or other atherosclerotic diseases [6,7]. Diabetes is an additional indication for the use of hypolipidemic medications and ACE inhibitors. It is an increasing problem in Western countries and recently, a high proportion of patients with acute myocardial infarction (MI) was reported to have diabetes or impaired glucose tolerance [8,9]. It is not well known, however, to

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what extent cardiac and hypoglycemic medications are prescribed in routine clinical practice to survivors of an acute coronary syndrome (ACS) and what is the persistence of the patients to purchase their medications from a pharmacy during the months after the ACS.

We carried out a countrywide study assessing trends in the use of β-blockers, hypolipidemic medications, ACE inhibitors, and hypoglycaemic medications in all patients hospitalized for a first ever ACS during an 8-year period 1995–2003 in Finland. The use of medications was assessed at two different time points in relation to the first nonfatal ACS of the patient: 1–90 days after the first ACS, and 91–180 days after the first ACS. We particularly analysed the associations of age, sex, study year and diabetes with the drug use after the ACS, as well as on stopping the drug use 3–6 months after the ACS. We also examined the associations of persistent drug use during the first 6 months after the ACS with the risk of cardiovascular death or any recurrent cardiovascular event during the subsequent year.

Methods

Identification of first acute coronary syndromes

Data for the present report came from the Finnish Cardiovascular Disease Register Project. Its methods have been published previously [10] and details are also available on the Internet (http://www.ktl.fi/cvdr/). In brief, we used the National Hospital Discharge Register and the National Causes of Death Register to identify all nonfatal first ACS events among men and women aged 35–74 years in Finland. These countrywide registers cover all hospitalizations in Finland and all deaths of permanent residents of Finland. CHD diagnoses in these registers were recently validated [11]. Diagnoses in the registers are coded according to the International Classification of Diseases (ICD). The ninth edition (ICD-9) was used until the end of 1995 and the 10th edition (ICD-10) since 1 January, 1996. In the hospital discharge register, ICD-9 codes 410 and 4110, and ICD-10 codes I21-I22 and I20.0 either as the main diagnosis or as any of the additional diagnoses were taken as ACS events. A personal ID code, unique to every permanent resident of Finland, was used to check the hospital discharge register backwards in time for prior ACSs. If no other hospitalizations because of ACS were observed during the preceding 7 years, the ACS was considered as the first for that particular person. Only events where the patient survived at least 180 days after the ACS were included in the analyses. The survival status was checked using a record linkage with the National Causes of Death Register.

Data on drug use

At least 50% of the costs of all drugs prescribed by a doctor are reimbursed to the patient in Finland. The Social Insurance Institution keeps a database on all reimbursed drug purchases. We used the personal ID code to link our database on first ACSs to the individual level records of drug purchases. In the reimbursement database different drugs are coded according to the Anatomical Therapeutic Chemical (ATC) system, which is an international classification system of pharmaceuticals. Regarding medications in long-term use, at most a 3-month supply is given and reimbursed in one purchase. Accordingly, we simplified the analysis by assuming that if a patient had purchased a medication at least once during a 3-month period, he or she was considered as a user of the medication during that period. Conversely, if there were no purchases during a 3-month period, the patient was considered as a nonuser of the medication.

Diabetes

A proxy variable for diabetes was created as follows. If a patient had purchased hypoglycaemic medication, or if there was a diagnosis of diabetes among the hospital discharge diagnoses either for this hospitalization for ACS or for any earlier hospitalization since 1991, the patient was considered as diabetic, otherwise he or she was considered as nondiabetic.

Follow-up

New cardiovascular disease (CVD) events during the follow-up were identified with record linkage of the study data with the National Causes-of-Death Register and the National Hospital Discharge Register. Deaths with the ICD codes for CHD or stroke – the ICD-9 (Finnish modification) codes 410–414, 798, 430, 431, 433 (except 4330 × , 4331 × and 4339 ×), 434 (except 4349X) and 436 and the ICD-10 codes I20–I25, I46, R96, R98, I60, I61, I63 (except I63.6) and I64 – were taken as fatal CVD events. Hospitalizations with the ICD codes for MI, unstable angina, or stroke – ICD-9 (Finnish modification) codes 410, 4110, 430, 431, 433 (except 4330X, 4331X and 4339X), 434 (except 4349X) and 436, and ICD-10 codes I21–I22, I21.0, and I60, I61, I63 (except I63.6) and I64–were taken as nonfatal CVD events. Thanks to the use of the nationwide registers, the coverage of the follow-up was in practice 100%. Altogether, the time to event analyses included 49 521 person-years of follow-up for CVD deaths and 47 905 person-years of follow-up for nonfatal CVD events.

The Finnish Cardiovascular Disease Project is approved by the Ethical Committee of the National Public Health Institute and the study was carried out following the principles outlined in the declaration of Helsinki.

Statistical methods

Logistic regression was used for calculating the odds ratios (ORs) of purchasing a drug within 1–90 days after the first ACS as well as for calculating the ORs of

discontinuing the drug use after 3 months (no purchases within days 91–180 after the event). Age group, sex, study year, university hospital district, and diabetes status were included in the model. Cox proportional hazards regression models were used for calculating hazard ratios (HRs) of persistent drug use during months 0–6 for CVD mortality and fatal or nonfatal CVD events during the subsequent year (i.e., days 181–545, after the first ACS). Covariates were the same as listed above in the logistic regression models, except that the age was used as a continuous variable in the Cox models. Validity of the proportional hazards assumption was examined graphically and no violations were observed. Statistical analyses were carried out using SAS software [12].

Results

During the study period there were 53 353 hospitalized nonfatal ACSs in persons aged 35–74 years in Finland (36 589 in men and 16 764 in women). Of these ACS patients, 27 414 were aged 35–64 years and 25 439 were 65–74 years. Altogether, 8958 (16.8%) had diabetes.

The use of all medications after the ACS increased over time. The increase was most prominent in hypolipidemic medications and relatively modest in hypoglycemic medications and β-blockers (Table 1). Nevertheless, still in 2003 about 28 and 15% of the patients did not receive hypolipidemic medications or β-blockers, respectively, after their first ACS. The elderly age group, 65–74 years old, used hypoglycemic medications and ACE inhibitors more frequently, and β-blockers and hypolipidemic medications less frequently than the younger age group, 35–64 years old (Table 1). Women were using hypoglycemic medications more than men, but otherwise there were no treatment differences between the sexes. As expected, diabetic patients were using less β-blockers and more ACE inhibitors than the nondiabetic patients. Surprisingly, diabetic patients used less hypolipidemic medications than nondiabetic patients.

The overwhelming majority of patients, who had purchased a medication during days 1–90 after the event, continued buying it also during days 91–180, but for each medication there was a sizeable fraction of patients, who discontinued the use. For example, in 2003 6 and 10% of the patients stopped using hypolipidemic medications and β-blockers, respectively. Thus, 66% of the surviving patients were using hypolipidemic medications and 75% β-blockers 91–180 days after their first ACS. For hypoglycemic medication, study year was the only significant predictor of discontinuing the drug use indicating less discontinuation during more recent years (Table 2). For β-blockers, age, sex, study year, or diabetes were not associated with discontinuation. For ACE inhibitors, study year and the presence of diabetes were associated with smaller odds for discontinuation, but age and sex had no effect. For hypolidemic medications, female sex and more recent study years were associated with smaller likelihood of discontinuation. Surprisingly, the presence of diabetes was associated with a greater likelihood of discontinuing the hypolipidemic medication.

A more detailed analysis of diabetic patients revealed that still during this millennium – in 2000–2003 – only 49.9% [95% confidence interval (CI), 49.84–49.62%] of male and 49.6% (95% CI, 49.55–49.65%) of female diabetic patients used hypolipidemic medications after their first ACS event. Among nondiabetic patients the corresponding proportions were 54.8% (95% CI, 54.73–54.77%) and 52.1% (95% CI, 52.11–52.16%).

Patients who had purchased β-blockers or hypolipidemic medications during days 1–90 and 91–180 after their first ACS event had about 50% smaller risk of CVD death

Table 1 Odds ratios[a] (95% confidence intervals) for the use of medications after the first nonfatal acute coronary syndrome in Finland during 1995–2002

Predictor	Hypoglycemic medications	Beta blockers	ACE inhibitors	Hypolipidemic medications
Age group[b]	1.31 (1.24–1.38)	0.77 (0.74–0.81)	1.19 (1.15–1.24)	0.55 (0.53–0.58)
Women[c]	1.28 (1.22–1.35)	0.96 (0.91–1.00)	0.94 (0.90–0.98)	1.02 (0.98–1.06)
Study year[d]	1.04 (1.03–1.05)	1.05 (1.04–1.06)	1.13 (1.12–1.14)	1.35 (1.34–1.36)
Diabetes[e]		0.83 (0.79–0.88)	1.89 (1.81–1.99)	0.82 (0.78–0.86)

ACE, angiotensin-converting enzyme. [a]In addition to the variables listed, adjusted for the university hospital district. [b]65–74 years compared to 35–64 years. [c]Women compared to men. [d]Per 1-year increment, starting from 1995. [e]Compared to the nondiabetic patients.

Table 2 Odds ratios[a] (95% confidence intervals) for stopping the use of medications 91–180 days after the first acute coronary syndrome attack in Finland during 1993–2003

Predictor	Hypoglycemic medications	Beta–blockers	ACE inhibitors	Hypolipidemic medications
Age group[b]	1.03 (0.90–1.18)	0.99 (0.94–1.04)	0.95 (0.88–1.02)	1.03 (0.96–1.10)
Women[c]	1.08 (0.94–1.24)	0.96 (0.91–1.02)	0.96 (0.89–1.04)	0.92 (0.85–0.99)
Study year[d]	0.95 (0.93–0.98)	0.99 (0.98–1.00)	0.93 (0.92–0.95)	0.95 (0.94–0.97)
Diabetes[e]		1.00 (0.94–1.08)	0.87 (0.80–0.95)	1.15 (1.05–1.26)

ACE, angiotensin-converting enzyme. [a]In addition to the variables listed, adjusted for the university hospital district. [b]65–74 years compared to 35–64 years. [c]Women compared to men. [d]Per 1-year increment, starting from 1995. [e]Compared to the nondiabetic patients.

Table 3 Hazard ratios[a] (95% confidence intervals) for cardiovascular disease (CVD) death[b] or fatal or nonfatal CVD event[b] associated with consistent use[c] of medications after the first nonfatal acute coronary syndrome

Type of event	Beta-blockers	Hypolipidemic medications	ACE inhibitors
Cardiovascular disease death	0.54 (0.49–0.60)	0.47 (0.41–0.53)	1.25 (1.12–1.39)
Fatal or nonfatal cardiovascular disease event	0.73 (0.68–0.78)	0.70 (0.65–0.75)	1.08 (1.01–1.15)

ACE, angiotensin-converting enzyme. [a]Adjusted for age, sex, study year, university hospital district, and diabetes. [b]For CVD death $n=1502$ and for fatal or nonfatal CVD event $n=4194$. [c]Consistent use, used medication for 180 days after the first myocardial infarction. The follow-up time is 365 days after day 180. Patients who died during the first 180 days are excluded.

during the subsequent year (i.e., days 181–545) compared to the patients who had not purchased these medications at all or had purchased them only once soon after the ACS (Table 3). Patients who had consistently purchased ACE inhibitors had 25% higher risk of CVD death than those who had not purchased them. The risk of fatal or nonfatal CVD event was reduced by 27–30% among regular users of β-blockers or hypolipidemic medications. The use of ACE inhibitors was associated with a 25% increase in the risk of a fatal CVD event and an 8% increase in the risk of a fatal or nonfatal event combined. When all three medications (β-blockers, hypolipidemic medications, and ACE inhibitors) were included in the same model, the HRs did not change substantially.

Discussion

The present nationwide study included all nonfatal hospitalized ACS events in Finland during 1995–2003, and all purchases of drugs prescribed by a doctor to these patients up to 180 days after the event. We also followed up these patients for 1.5 years after the event for fatal and nonfatal CVD events. The use of all medications examined increased over time and the increase was particularly prominent for hypolipidemic medications and ACE inhibitors. Yet, still in 2003 about 28% of the patients did not receive hypolipidemic medications after their first ACS and a further 6% discontinued the use 3 months after the event. About 15% did not receive β-blockers after their first ACS and a further 10% discontinued the use 3 months after the event. Surprisingly, diabetic patients received less hypolipidemic medications and were more likely to discontinue their medication than the nondiabetic patients. It is also noteworthy that elderly patients received less β-blockers and hypolipidemic medications, although they would benefit from the treatment even more than the younger age groups [13–16].

Medication use in other studies

In the EUROASPIRE II survey [6] carried out in 1999–2002, 66.4% of patients with atherosclerotic manifestations were using β-blockers and 57.7% hypolipidemic medications. In the REACH registry [7], which collected its data during 2003 and 2004, 76.2% of patients with CHD were using statins. Our present results from the most recent years are generally in line with these large international studies and show that the use of evidence-based medications after a hospitalized ACS in Finland is comparable to the situation in other western countries. A register-based study, similar to ours, from Denmark [17] reported somewhat lower use of medications, presumably due to the inclusion of earlier years. It also reported that 78.6% of those who initially received statins, continued the use 1 year after their first MI. Advancing age and female sex were associated with better compliance in Denmark. In our study, female sex was associated with better compliance with hypolipidemic medications, but age did not play a significant role.

Medication use and the risk of subsequent adverse events

In the present study, Cox proportional hazards regression models indicated that consistent use of β-blockers or hypolipidemic medications was associated with 50% smaller risk of CVD death and 27–30% smaller risk of any CVD event compared with nonusers. Newby *et al.* [18] also investigated the HRs associated with consistent use of cardiovascular medications. They reported all-cause mortality HRs of 0.63 for users of β-blockers and 0.52 for users of lipid-lowering medications. Go *et al.* [19] reported from the ADVANCE study that, among patients with new-onset symptoms of CHD, recent use of statins and β-blockers was associated with substantially lower odds of presenting with an acute MI than with stable exertional angina. Wei *et al.* [20] from Dundee, Scotland, reported all-cause mortality HRs of 0.38 for users of β-blockers and 0.69 for users of statins. For non-fatal MI and CVD death their HRs were 0.40 and 0.82, respectively. In another European study, Feringa *et al.* [21] reported from the Netherlands that among patients with peripheral arterial disease the HR of all-cause deaths associated with the use of statins was 0.46 and with the use of β-blockers 0.68.

In all studies mentioned above the HRs were remarkably similar and well in line with our findings. Our HRs, however, need to be interpreted keeping in mind that the study was not a randomized clinical trial. Even though it is plausible that the lowered HRs associated with the use of β-blockers and hypolipidemic medications at least in part reflect the biologic action of these drugs, other factors may also play a part. It was reported from the Coronary Drug Project [22] that the regular use of placebo was also associated with lower mortality. The elevated HRs associated with the use of ACE inhibitors in our study naturally reflect the clinical indications for the use of these medications – heart failure, left ventricular dysfunction, and diabetes – which usually

are markers of a high risk of CVD death or a recurrent CHD event.

Hypoglycemic medications

The prevalence of diabetes is increasing in many western countries [23–25]. Recently, elevated blood glucose levels or overt diabetes has been found frequently among patients with MI [8,9]. In our study, the use of hypoglycemic medications among patients with their first ACS increased over time, but the increase was relatively modest. This, together with the low prevalence of diabetes diagnoses suggests that blood glucose levels may not have been actively examined among patients with hospitalized ACS in Finland. The use of hypoglycemic medications was clearly more common among female patients with ACS than among male patients. This is explained by the well-known fact that diabetes is a stronger risk factor of CHD among women than among men [26] and also by the fact that women are actively screened for diabetes and impaired glucose tolerance during pregnancy.

Limitations of the study

An obvious limitation of our study was the lack of clinical data and data on potential confounding factors such as socio-economic position. Therefore, we do not really know whether the treatment with medications included in the analyses was indicated or whether there were contraindications among the nonusers. As to the hypolipidemic medications and β-blockers, it can be safely assumed that the treatment was indicated in almost all patients after a hospitalized ACS, although a few patients may have had contraindications. In particular, the treatment with hypolipidemic medications should be indicated for diabetic patients with ACS and it was surprising that they used less hypolipidemic medications and were more likely to discontinue medication than nondiabetic patients. Another limitation was the lack of data on acetylsalicylic acid. It is an inexpensive drug, which is largely sold over the counter and not reimbursed. Therefore, it could not be included in these statistics.

Conclusion

This countrywide study showed that evidence-based use of medications was suboptimal particularly among elderly and diabetic patients, even though these groups could benefit most from active treatment. Data suggested that the regular use of β-blockers and hypolipidemic medications was associated with a significantly smaller risk of CVD death and reinfarction. Therefore, it is important that these medications are considered for every patient after the ACS.

References

1 Heart Protection Study Investigators. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**:7–22.

2 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **20(342)**:145–153.

3 Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; **26**: 1730–1737.

4 Smith SC Jr, Blair SN, Bonow RO, Brass LM, Cerqueira MD, Dracup K, *et al.* AHA/ACC Guidelines for Preventing Heart Attack and Death in Patients With Atherosclerotic Cardiovascular Disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol* 2001; **38**:1581–1583.

5 De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, *et al.* European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur J Cardiovasc Prev Rehabil* 2003; **10** (**Suppl 1**):S1–S78.

6 EUROASPIRE I and II Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. *Lancet* 2001; **357**:995–1001.

7 Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, *et al.* REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; **295**:180–189.

8 Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002; **359**:2140–2144.

9 Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J* 2004; **25**: 1990–1997.

10 Pajunen P, Pääkkönen R, Juolevi A, Hämäläinen H, Keskimäki I, Laatikainen T, *et al.* Trends in fatal and non-fatal coronary heart disease events in Finland during 1991–2001. *Scand Cardiovasc J* 2004; **38**:340–344.

11 Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Räihä P, Kärjä-Koskenkari P, *et al.* The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. *Eur J Cardiovasc Prev Rehabil* 2005; **12**:132–137.

12 SAS Institute, Inc. (1999) *Users guide, statistics*, Version 8. Cary, North Carolina: SAS Institute; 1999.

13 Williams MA, Fleg JL, Ades PA, Chaitman BR, Miller NH, Mohiuddin SM, *et al.* Secondary prevention of coronary heart disease in the elderly (with emphasis on patients > or =75 years of age): an American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. *Circulation* 2002; **105**:1735–1743.

14 Chen J, Marciniak TA, Radford MJ, Wang Y, Krumholz HM. Beta-blocker therapy for secondary prevention of myocardial infarction in elderly diabetic patients. Results from the National Cooperative Cardiovascular Project. *J Am Coll Cardiol* 1999; **34**:1388–1394.

15 Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998; **339**:489–497.

16 Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A, Marciniak TA. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA* 1998; **280**:623–629.

17 Gislason GH, Rasmussen JN, Abildstrøm SZ, Gadsbøll N, Buch P, Friberg J, *et al.* Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006; **27**:1153–1158.

18 Newby LK, LaPointe NMA, Chen AY, Kramer JM, Hammil BG, DeLong ER, *et al.* Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation* 2006; **113**:203–212.

19 Go AS, Iribarren C, Chandra M, Lathon PV, Fortmann SP, Quertermous T, Hlatky MA. For the Atherosclerotic Disease, Vascular Function and Genetic Epidemiology (ADVANCE) Study. Statin and beta-blocker therapy and the initial presentation of coronary heart disease. *Ann Intern Med* 2006; **144**:229–238.

20 Wei L, Ebrahim S, Bartlett C, Davey PG, Sullivan FM, MacDonald TM. Statin use in the secondary prevention of coronary heart disease in primary care: cohort study and comparison of inclusion and outcome with patients in randomised trials. *BMJ* 2005; **330**:821–824.

21 Feringa HHH, van Waning VH, Bax JJ, Elhendy A, Boersma E, Schouten O, *et al.* Cardioprotective medication is associated with improved survival

in patients with peripheral arterial disease. *J Am Coll Cardiol* 2006; **47**:1182–1187.
22 Coronary Drug Project Investigators. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. *N Engl J Med* 1980; **303**:1038–1041.
23 Green A, Hirsch NC, Pramming SK. The changing world demography of type 2 diabetes. *Diabetes Metab Res Rev* 2003; **19**:3–7.
24 Skyler JS, Oddo C. Diabetes trends in the USA. *Diabetes Metab Res Rev* 2002; **18** (**Suppl 3**):S21–S26.
25 Passa P. Diabetes trends in Europe. *Diabetes Metab Res Rev* 2002; **18** (**Suppl 3**):S3–S8.
26 Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006; **332**:73–78.