Should all diabetic patients receive a statin? Results from recent trials

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Abstract

Diabetes is associated with the development of premature cardiovascular disease. In the three early trials of statin therapy for patients with established coronary heart disease there were many patients with diabetes; subgroup analysis has confirmed the benefits of cholesterol lowering with statin therapy in these patients. In the two early primary prevention trials, however, there were few patients with diabetes and so, initially, there was little evidence supporting the use of statins in diabetic patients without cardiovascular disease. The Heart Protection Study (HPS) and Collaborative AtoRvastatin Diabetes Study (CARDS) have now provided this evidence and firmly established that cholesterol lowering is of benefit in reducing cardiovascular events in patients with type 2 diabetes, regardless of the level of baseline cholesterol, or the presence or absence of cardiovascular disease. A few recent studies have failed to find benefit in diabetic patients but there are explanations for these negative findings. Ideally all patients with diabetes, especially the middle-aged and elderly, should be treated with statins but it remains uncertain at what age therapy should start and how low to reduce the cholesterol for maximum benefit.

Key words: diabetes, statins, cholesterol lowering.

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Introduction

The benefits of statins in people with diabetes are well established but the question "should all diabetic patients receive a statin?" has yet to be answered. This review examines the key evidence that exists for the use of lipid lowering with statins in patients with diabetes from recent, randomised, controlled trials. Different primary end points were used in some of the studies and subgroup analysis of diabetic patients has sometimes included different outcomes. We will focus on the study primary end points and on coronary events (coronary heart disease [CHD] death, non-fatal myocardial infarction [MI]) where these are available.

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Diabetic patients in secondary prevention trials

Results in diabetic patients in secondary prevention trials are summarised in table 1. In the Scandinavian Simvastatin Survival Study (4S)[1] a post-hoc subgroup analysis of the data from 202 diabetic patients was published in 1997.[2] Although there was a larger reduction in the primary end point of all-cause mortality in this group when compared to the whole trial population, this did not reach statistical significance (RR 0.57, p=0.087). This was likely a result of the small size of the subgroup (table 1). A significant reduction in major coronary events was observed from 44 events in the placebo group to 24 in the diabetic group (RR 0.45, p=0.002). This was the first trial-based evidence that cholesterol lowering reduced the risk of major CHD events and other atherosclerotic events in diabetic patients.

In the diabetic subgroup of the Cholesterol and Recurrent Events Study (CARE),[3] there were 586 patients (14% of the study population). They had similar low-density lipoprotein (LDL) cholesterol levels at baseline but they were more obese, had higher rates of hypertension and were older than non-diabetic subjects.[4] Treatment with pravastatin led to an insignificant reduction in the primary end point of death from coronary heart disease or non-fatal MI (RR 0.87, p=ns). A significant reduction was observed in an extended primary end point, however, that included revascularisations (RR 0.75, p=0.05), with a larger absolute risk reduction of coronary events in the diabetic subgroup than in the study population as a whole (8.1% *vs.* 5.2%), reflecting the fact that this subgroup had a higher level of risk in general (figure 1).

In the diabetic subgroup of the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study,[5] 1,077 subjects with type 2 diabetes were included in the cohort.[6] A 19% reduction in major coronary events was demonstrated in the diabetic subgroup but this was not quite statistically significant when compared to placebo (23.4% *vs.* 19.6% p=0.11). The absolute risk of a first CHD event was higher in the diabetes subgroup (23.4% *vs.* 14.5%), and the estimated number-needed-to-treat (NNT) with pravastatin therapy for six years to prevent one CHD-related event was 18 in the diabetes subgroup compared to 29 in the total study population. Comparisons of the reductions in major coronary events for people with diabetes compared to all subjects in 4S, CARE and LIPID are shown in figure 1.

Table 1. Results of end points for all subjects and subjects with diabetes in the three early secondary prevention studies and two early primary prevention studies with statins

	Drug	Total subjects n	Diabetic subjects n (%)	Primary end point all	Primary end point diabetes	Major coronary events (CHD death, non-fatal MI) all	Major coronary events (CHD death, non-fatal MI) diabetes	Comments
'Primary' prevention								
AFCAPS/TexCAPS	Lovastatin 20–40 mg	6,605	155 (2%)	Primary end point fatal or non-fatal MI, unstable angina, or sudden cardiac death reduced from 11–7%	Data not provided	Data not provided for combined end point	Data not provided	
WOSCOPS	Pravastatin 40 mg	6,595	76 (1%)	Reduced CHD mortality or non-fatal MI from 8–5.5%	Data not provided	Primary end point	Data not provided	
'Secondary' prevention								
4S	Simvastatin 20–40 mg	4,444	202 (5%)	Reduced total mortality from 12–8%	Reduced total mortality from 24–15% (NS)	Reduced from 28–19%	Reduced from 44–23%	
CARE	Pravastatin 40 mg	4,159	586 (14%)	Reduced CHD mortality or non-fatal MI from 13–10%	Insignificant effect	Primary end point	Primary end point, insignificant effect	Statistically significant reduction in expanded end point in diabetes (CHD death, MI, CABG, PTCA)
LIPID	Pravastatin 40 mg	9,014	1,077 (12%)	Reduced CHD mortality from 8–6%	Data not provided	Reduced from 15–12%	Reduced MACE from 23–19% (ns)	Statistically significant reduction in any cardiovascular end point in diabetes (CHD death, MI, CABG, PTCA, stroke)

Key: AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study; 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol And Recurrent Events; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; MI = myocardial Infarction; CHD = coronary heart disease; MACE =major adverse coronary events; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty

Diabetic patients in primary prevention trials

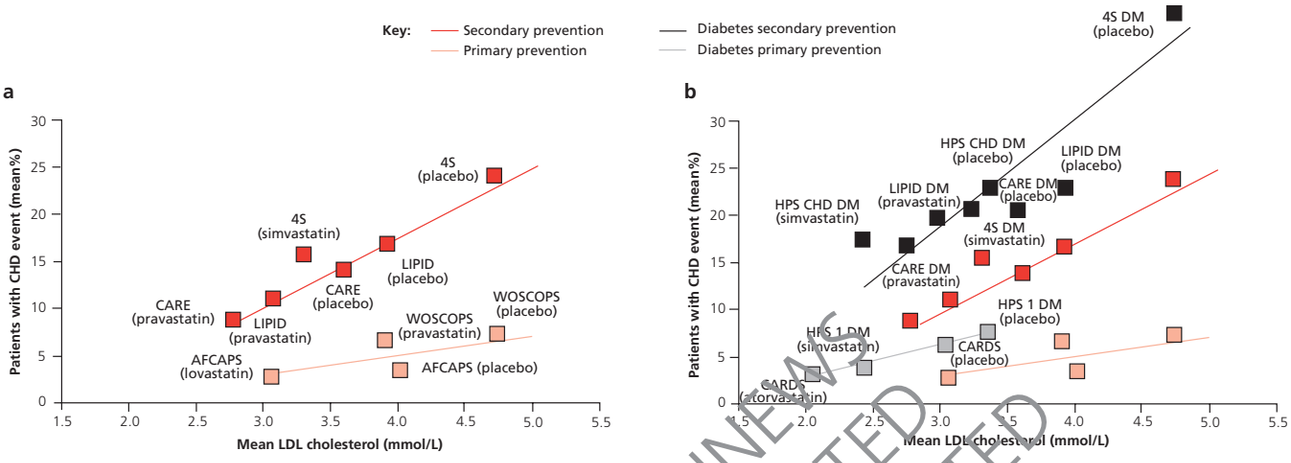
Abundant evidence exists for lowering cholesterol in patients with elevated cholesterol both in the presence or absence of other risk factors for CHD. The evidence that cholesterol lowering in diabetic patients plays a role in the primary prevention setting has been less compelling until recently. The classic West of Scotland Coronary Prevention Study (WOSCOPS) contained only 76 known diabetic patients,[7] and the Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) study had 155 people with diabetes (table 1).[8]

In the Heart Protection Study (HPS) there were 5,963 diabetic subjects within the overall study group of 20,536, of whom more than 90% had type 2 diabetes (table 2).[9] Amongst the diabetic subgroup there was a similar use of non-study statins and similar reduction in LDL cholesterol, of about 1 mmo/L, compared to the non-diabetic group.[10]

In the diabetic group on simvastatin there were highly significant reductions in coronary deaths (20%), major coronary events (27%), strokes (24%) and incidence of first revascularisation (17%). These figures are similar to the reductions seen with simvastatin in the non-diabetic, high-risk vascular patients.[9] There was also a significant reduction in prespecified, peripheral macrovascular complications in the diabetic subgroup including fewer amputations, leg ulcers, peripheral vascular angioplasty and surgery. When considered together, the reduction in first major vascular events in diabetic patients on simvastatin was 22%. An even greater reduction was seen in the diabetic group without previous coronary or occlusive vascular disease. Some 2,912 diabetic subjects had no cardiovascular disease and simvastatin reduced the primary end point of a first major vascular event from 13.5% to 9.3%, and of a first major coronary event from 6.5% to 3.7%. This effect was still seen regardless of age, sex, blood pressure, body mass index (BMI), HbA_{1C}, initial LDL cholesterol or type of diabetes, although there were very few patients with type 1 diabetes in the study group.[10]

Data on CHD events for people with diabetes is contained in figure 1. It can be seen that in the primary prevention cohort of diabetic patients in HPS the event rate was much higher than the event rates for all subjects in WOSCOPS and AFCAPS/TexCAPS,

Figure 1. Evidence for the benefits of lipid lowering with statins. Primary and secondary cholesterol-lowering statin trials illustrating the percentage of patients with a CHD event (CHD death or non-fatal myocardial infarction) against the mean LDL-cholesterol during the study in the statin intervention and placebo groups. Data for all subjects is in red (see graph **a**) and for subjects with diabetes is in black (see graph **b**). The event rate for diabetes secondary prevention is greater than for secondary prevention overall. The event rate for diabetes primary prevention is greater than for primary prevention overall, but not as high as secondary prevention overall



Key: CHD = coronary heart disease; LDL = low-density lipoprotein; AFCAPS = Airforce Coronary Atherosclerosis Prevention Study; CARDS = Collaborative AtoRvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events; HPS 1 DM = Heart Protection Study primary prevention diabetes subjects; HPS CHD DM = Heart Protection Study diabetes subjects with CHD; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; WOSCOPS = West of Scotland Coronary Prevention Study; 4S = Scandinavian Simvastatin Survival Study

but not as high as for secondary prevention subjects in 4S, CARE and LIPID.

Other recent trials

Other recent trials with statins in diabetic patients are summarised in table 2. Although the lipid lowering arm within the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT-LLA) contained a large number of diabetic patients (3,638 [35%]), the use of pravastatin did not show any statistically significant reduction in either the primary end point of all-cause mortality or in CHD events.[11] This trial is difficult to interpret, however, as many of the placebo group received open label statins and therefore there was only a very modest reduction in cholesterol in the treatment group.

Published shortly after ALLHAT in 2003, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA) was, similarly, a lipid-lowering arm of a hypertension study, comparing 10 mg of atorvastatin in patients with hypertension but no previous CHD.[12] This patient population was predominately white males and was younger than the ALLHAT population. Patients in ASCOT-LLA had uncontrolled hypertension and three or more pre-specified cardiovascular risk factors including type 2 diabetes. Average random total cholesterol was 5.5 mmol/L.

ASCOT-LLA was terminated early after a mean follow-up of 3.3 years (the intended follow-up period was five years). The primary end point of non-fatal MI and fatal CHD occurred in 100 patients treated with atorvastatin compared to 154 patients on placebo, a 36% reduction in primary end point in those on statin therapy with a 19% relative reduction in total cholesterol (1.0 mmol/L) and 29% reduction in LDL cholesterol (1.0 mmol/L). There was also a significant reduction in the incidence of total coronary events, total cardiovascular events and procedures, and strokes. Compliance with atorvastatin was approximately 87% while use of open-labelled statins in the placebo group was 9%.

Surprisingly, the effects of lipid lowering on the diabetic subgroup (2532 patients) did not show a benefit in primary end point, with an incidence of 38 (9.6%) events in the atorvastatin group *vs.* 46 (11.4%) events in the placebo group. All of the subjects had type 2 diabetes and made up 25% of the study population. The use of statins within the diabetic placebo group was notably higher than among the non-diabetic group at 14% and, like ALLHAT, the study was not powered to show a statistically different result with the subgroups analysed (table 2).

The diabetes subgroup in PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) had only 320 patients in the active treatment group and 303 participants in the placebo group.[13] It demonstrated a non-statistically significant increase in the composite primary end point of major CHD events and stroke, in the treatment group (70 events, 23.1%) compared to the placebo group (59 events, 18.4%).

CARDS

As recently discussed in the this journal,[14,15] the Collaborative Atorvastatin Diabetes Study (CARDS) is the first study which has attempted to assess the benefits of cholesterol reduction in the primary prevention setting in a cohort of subjects with type 2 diabetes.[16] Some 2,838 male and female participants were ran-

Table 2. Results of end points for all subjects and subjects with diabetes in the recent secondary prevention studies and primary prevention studies with statins

	Drug	Total subjects n	Diabetic subjects n (%)	Primary end point all	Primary end point diabetes	Major coronary events (CHD death, non-fatal MI) all	Major coronary events (CHD death, non-fatal MI) diabetes	Comments
HPS	Simvastatin 40 mg	20,536	5,963 (29%)	Reduced total mortality from 15–13%, reduced fatal or non-fatal vascular events from 25–20%	Reduced fatal or non-fatal vascular events from 25–20%	Reduced from 12–9%	Reduced from 13–9%	Diabetes subgroup contains patients with known CHD, other vascular disease, or no cardiovascular disease
ALLHAT-LLA	Pravastatin 40 mg	10,355	3,638 (35%)	No significant reduction in all-cause mortality	No significant reduction in all-cause mortality	No significant reduction	No significant reduction	Small difference in total cholesterol between groups, high rates of non-compliance in treatment group, high uptake of non-study statins in placebo group
ASCOT-LLA	Atorvastatin 10 mg	10,305 (25%)	2,532	Reduced fatal CHD and non-fatal MI from 3.0–1.9%	No significant reduction	Primary end point	Primary end point	Low number of total CHD events in diabetes group, high use of open-label statins in diabetes placebo group
PROSPER	Pravastatin 40 mg	5,804	623 (11%)	Reduced CHD death or non-fatal MI or fatal or non-fatal stroke from 16–14%	Higher rate of CHD death or non-fatal MI or fatal or non-fatal stroke in treatment group (23%) *vs.* placebo group (18%) (n.s)	Reduced from 12–10%	Data not provided	
CARDS	Atorvastatin 10 mg	2,838	2,838 (100%)	Significant reduction in acute CHD event, coronary revascularisation or stroke from 9–6%	Ditto	Significant reduction from 5.5–3.6%	Ditto	

Key: HPS = Heart Protection Study; ALLHAT-LLA = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (Lipid-Lowering Arm); ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial (Lipid-Lowering Arm); PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; CARDS = Collaborative Atorvastatin Diabetes Study; CHD = coronary heart disease; MI = myocardial infarction

domised in this UK multi-centre, double-blind, placebo-controlled trial. The participants, aged 40–75 years, all had type 2 diabetes and at least one other risk factor for cardiovascular disease. Entry serum LDL cholesterol was less than 4.14 mmol/L with a median of 3.1 mmol/L (i.e. not a markedly elevated cholesterol level).

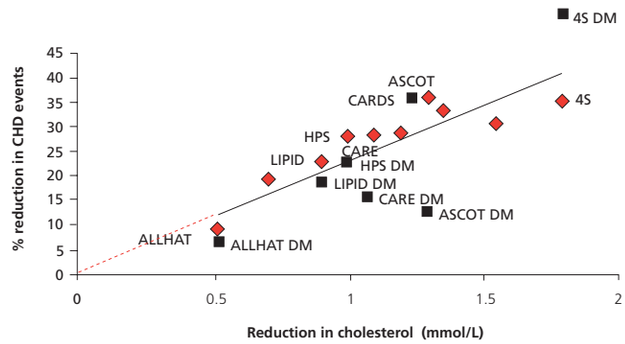
Follow-up was initially planned to be for a minimum of four years but the trial was stopped earlier than expected, in June 2003 after 210 events, when the second interim analysis showed a significant benefit in subjects taking atorvastatin. Daily treatment with atorvastatin 10 mg reduced major cardiovascular events by 37% (absolute risk reduction 3.2%; p=0.001) compared with placebo. The treatment effect was similar for each of the component end points: acute coronary events were reduced by 36% (absolute risk reduction 1.9%; p=0.013) while stroke – the single biggest cause of disability among adults – was reduced by 48% (absolute risk reduction 1.3%; p=0.016). Importantly, the benefit to patients was observed irrespective of their LDL-cholesterol or triglyceride levels at the start of the study.

Discussion

The benefit of cholesterol lowering with statins is well established for primary and secondary prevention of CHD in non-diabetic patients with both elevated and relatively 'normal' serum cholesterol levels.[1,3,5,7,8] The role of statins in secondary prevention of CHD in diabetic patients has also been established in the three key studies (4S, CARE, LIPID) described above.[2,4,6] Statins have effects other than simply lowering cholesterol, particularly anti-inflammatory actions. With emerging evidence to support the role of inflammation in atherosclerosis, this may prove to be an important consideration in the future. Nevertheless, the benefits of statins seem to be related to the degree of cholesterol lowering.[17]

Currently there are two studies with good evidence to support the role of statins in primary prevention for the diabetic population – HPS and CARDS.[10,16] Both had similar numbers of primary prevention patients and both were powered to show a statistical difference within this group. They included diabetic

Figure 2. Reduction in CHD events with statins, comparing the percentage reduction in CHD events with statin therapy against the reduction in cholesterol during the study in all subjects (red) and in subjects with diabetes (black). The % reduction in events is very similar in diabetic subjects. The greater the reduction in cholesterol, the greater the reduction in CHD events



Key: CHD = coronary heart disease; DM = diabetes mellitus; ALLHAT = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; CARDS = Collaborative AtoRvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events; HPS = Heart Protection Study; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; 4S = Scandinavian Simvastatin Survival Study

patients with few other CHD risk factors and still showed benefit within this subgroup. Although ASCOT and ALLHAT both addressed primary prevention in diabetes, their results did not confirm those of HPS or CARDS, due to a combination of low event rates, underpowering, non-compliance and use of non-study statins in the control group.

Statins in type 1 diabetics

An unresolved issue is the use of statins in patients with type 1 diabetes. Whereas this group does have a higher incidence of CHD than non-diabetic patients, the diabetes is usually diagnosed at a young age when the absolute incidence of CHD is negligible. The benefit of statin therapy in type 1 diabetes has not been proven, given the very small numbers of these patients included in statin trials. A small number of patients with type 1 diabetes were included in HPS and, although they received similar benefit to the diabetic group as a whole, this was not statistically significant because of the small size of the group. When to initiate therapy in people with type 1 diabetes remains uncertain. Nevertheless, it seems reasonable to extrapolate the trial data from type 2 diabetes to type 1 diabetes.

Risk estimation

Current risk estimation tables used for establishing CHD risk and influencing both statin and antihypertensive treatments for primary prevention (e.g. The Joint British Societies Coronary Risk Prediction Charts) do not adequately estimate the level of risk in the diabetic population. They also persistently underestimate the level of risk (although this is being addressed in the new Joint British Societies chart, which will be available soon). There are many reasons for this including the fact these tables are based on Framingham data which had few diabetic subjects.[18] This complicates the issue of deciding which diabetic patients should be treated with statins in the primary prevention setting, if the decision whether to treat is based on the estimated risk.

The high incidence of CHD in people with diabetes has led many to believe that diabetes should be considered as a CHD risk equivalent and therefore all patients should be given a statin. Haffner's data,[19] based on a diabetic population in Finland, indicated that the incidence of CHD events was as high in patients with diabetes as in non-diabetic patients with previous MI. Subsequent data from Tayside and elsewhere have disputed this evidence.[20] In a study from Tayside the event rate in people with diabetes without CHD, was much higher than in non-diabetic people without CHD but this was not as high as in the event rate in non-diabetic subjects with previous MI.[20] It can be seen in figure 1 that the risk of CHD events in the diabetic primary prevention patients in HPS was not as high as the risk of all secondary prevention subjects in 4S, CARE and LIPID, although these studies were performed in different geographical areas. It is clear, however, that diabetes confers significantly higher risk of CHD. This does raise the question – should we simply treat all people with diabetes with statin therapy?

Should all diabetics receive a statin?

There are a number of reasons why treating all diabetic patients with statins is not straightforward.[21] The cost implication of treating all diabetic patients with statins from the time of diagnosis of diabetes would be considerable. Given the rapid increase in the incidence of type 2 diabetes this, in itself, necessitates a targeting of statins to those diabetic patients most likely to benefit. The incidence of type 2 diabetes is also increasing within younger age

Key messages

- Evidence supports the use of statin therapy in all diabetic patients with previous cardiovascular disease
- Evidence supports the use of statin therapy in most diabetic patients for primary prevention of cardiovascular disease
- Current cardiovascular risk prediction tables should not be used to determine the use of statin therapy for primary prevention of cardiovascular disease in diabetic patients
- We recommend the use of simvastatin, pravastatin or atorvastatin in all diabetic patients over the age of 40 years regardless of previous cardiovascular disease or pre-treatment cholesterol

groups. Although the relative risk of CHD is high compared to age-matched non-diabetic subjects, the absolute incidence of CHD in these groups is relatively low and the short-term benefits of treating younger diabetic patients with statins would be less.

We believe a pragmatic approach for the time being is to treat all people with diabetes that would have been eligible for enrolment in HPS or CARDS i.e. all over 40 years old, and to consider the use of statins in higher-risk younger patients e.g. smokers or those with hypertension.

It remains unclear as to whether there are significant benefits to be gained from maximising the degree of cholesterol reduction. Although HPS does provide some indication as to target levels of cholesterol, it was not specifically designed to identify this. Nor did it address the issue of when to initiate statin therapy. A recent novel analysis of the reduction of CHD events with all forms of lipid-lowering therapy has been described.[17] Figure 2 shows the data for non-diabetic and diabetic subjects from the statin studies that we have described above.

In conclusion, all diabetic patients with cardiovascular disease and all diabetic patients without cardiovascular disease over 40 years of age should be treated with statins. Further information is required for patients with type 1 diabetes, and younger patients with type 2 diabetes. Studies that are currently in progress should confirm that lower cholesterol levels are almost certainly better for people with diabetes.

Conflict of interest

GM and CM – none. MF has served on advisory panels for AstraZeneca, Pfizer, and Novartis, plus received speaker's fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Pfizer. AB has received research grants from AstraZeneca UK, Merck Sharp & Dohme UK, and Boehringer Ingelheim Germany, plus served on speakers' bureau/advisory boards for AstraZeneca UK, Merck Sharp & Dohme UK, Pfizer UK, Bristol-Myers Squibb UK, Bayer Germany, Sanofi UK, and Servier France.

Editors' note

This is the first in a series of four articles on cardiovascular drugs in diabetes. Future articles will include:
'Should all patients with diabetes receive:
– angiotensin-converting enzyme (ACE) inhibitors
– aspirin
– beta blockers.

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