# Prescribing of ACE inhibitors and statins after bypass surgery: a missed opportunity for secondary prevention?

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**Abstract**

**Angiotensin-converting enzyme (ACE) inhibitors and statins improve prognosis in patients with coronary artery disease. Effective secondary prevention strategies, however, are frequently under-utilised. We sought to determine prescribing habits for ACE inhibitors and statins in 324 patients undergoing coronary artery bypass graft surgery (CABG) at two regional cardiac centres in the United Kingdom. We prospectively recorded ACE inhibitor and statin use on admission and discharge, ACE inhibitor and statin initiation and withdrawal during the hospital stay, and sought associations with treatment withdrawal. 82 (25.3%) patients were taking an ACE inhibitor on admission compared with 37 (11.4%) at discharge (p<0.0005). An ACE inhibitor was initiated during the hospital stay in five (1.5%) patients and was withdrawn in 50 (15.4%). On admission, 157 (48.5%) patients were receiving statin therapy compared with 154 (47.5%) at discharge (p=ns). Statin treatment was initiated in 23 (7.1%) patients, but was withdrawn in 20 (6.2%) others. Thus, only a minority of patients were receiving ACE inhibitors and statins on admission for isolated elective CABG. ACE inhibitor treatment was discontinued during the hospital stay in over 60% of these patients. Furthermore, statin therapy was no more common at discharge than on admission. This study highlights a missed opportunity for effective secondary prevention in a high risk population.**

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**Key words:** ACE inhibitors, statins, secondary prevention, CABG.

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## Introduction

The beneficial prognostic effects of angiotensin-converting enzyme (ACE) inhibitors are firmly established in patients with left ventricular systolic dysfunction.[1,2] Furthermore, recent data suggest that ACE inhibition improves outcome in patients with coronary artery disease and those at high risk of adverse cardiovascular events irrespective of ventricular function.[3] A significant proportion of patients undergoing coronary artery bypass graft surgery (CABG) would, therefore, be expected to derive prognostic benefit from ACE inhibitors both pre- and post-operatively.

For the statin group of drugs, large studies have shown unequivocal prognostic benefit in patients with coronary artery disease.[4-6] More specifically, the Post-CABG Trial has demonstrated retardation of angiographic progression of atherosclerosis in grafts and reductions in clinical end points by aggressive cholesterol lowering.[7,8] Further recent data from the CARE investigators have demonstrated reductions of over one third in coronary heart disease death, non-fatal myocardial infarction (MI), and stroke in patients with average cholesterol levels who had undergone revascularisation by CABG or percutaneous transluminal coronary angioplasty (PTCA) if they were treated with pravastatin rather than placebo.[9]

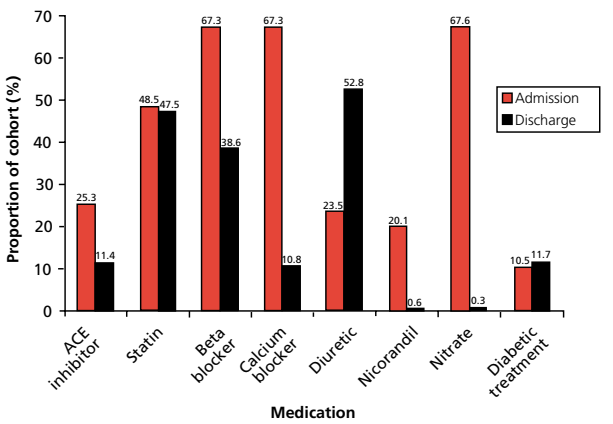
Despite increasingly robust evidence to support their use, strategies effective in the secondary prevention of coronary artery disease continue to be under-utilised in clinical practice.[10-12] Secondary prevention for patients with coronary disease and left ventricular dysfunction are stated priorities of the National Service Framework (NSF) for Coronary Heart Disease.[13] The aim of this observational study was to determine the prescribing habits for ACE inhibitors and statins in a population of patients undergoing CABG in order to assess whether this unique opportunity for secondary prevention is being fully exploited.

## Methods

### Study population

The study population comprised 340 patients recruited to a prospective study of atrial fibrillation (AF) after elective isolated CABG at two regional cardiac centres in the United Kingdom.[14] All patients gave informed consent and the study was approved

**Figure 1.** Medication on admission and discharge in 324 patients undergoing CABG




**Key:** ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft

by the ethics committees local to the participating centres.

## Data collection (see appendix)

Cardiac drug use (ACE inhibitors, statins, beta blockers, calcium channel blockers, nitrates, potassium channel openers, and diuretics), and the use of oral hypoglycaemic agents and insulin was recorded on hospital admission and discharge. Peri-operative drug use was not influenced by the study investigators. Left ventricular ejection fraction (LVEF) was estimated by a single experienced cardiologist (AGZ and NPC) at each centre from the pre-operative ventriculogram in the right anterior oblique projection.

## Statistical analysis

Data were stored electronically and analysed using SPSS for Windows statistical software. Associations with ACE inhibitor and statin treatment on admission and discharge were sought in the cohort as a whole. The subgroups taking an ACE inhibitor and a statin on admission were examined for variables associated with ACE inhibitor and statin withdrawal. Factors associated with ACE inhibitor withdrawal in patients with (LVEF $\leq$ 40%) and without important left ventricular systolic dysfunction were determined. Variables associated with ACE inhibitor treatment in patients receiving oral hypoglycaemic agents or insulin at admission were also examined. Proportions were compared using the chi square test. Variables with a univariate p value < 0.1 were entered into a logistic regression analysis to adjust for confounding factors.

# Results

Of 340 eligible patients, 16 either died prior to discharge or had incomplete angiographic or drug data. The remaining 324 patients form the basis for the results. The mean age was 63 years; 268 (83%) were male; mean LVEF was 56% and 49 (15%) patients had an ejection fraction $\leq$ 40%. An additional 70 (21.6%) patients had pre-operative ECG evidence of Q-wave MI. The mean number of grafts was three and the average post-operative hospital stay was 7.8 days.

**Table 1.** Significant univariate associations with ACE inhibitor treatment on admission

| | ACE inhibitor on admission n=82 | No ACE inhibitor on admission n=242 | p value |
|---|---|---|---|
| LVEF $\leq$ 40% | 23 (28.0%) | 26 (10.7%) | < 0.0005 |
| Pre-op Q waves | 38 (46.3%) | 61 (25.2%) | < 0.0005 |
| Beta blocker on admission | 38 (46.3%) | 180 (74.4%) | < 0.0005 |
| Diuretic on admission | 34 (41.4%) | 42 (17.4%) | < 0.0005 |
| Statin on admission | 50 (61.0%) | 107 (44.2%) | 0.009 |
| Beta blocker on discharge | 21 (25.6%) | 104 (43.0%) | 0.005 |
| Diabetic treatment on admission | 16 (19.5%) | 18 (7.4%) | 0.002 |
| Diabetic treatment on discharge | 17 (20.7%) | 21 (8.7%) | 0.003 |
| Pre-op urea > 7 mmol/L | 34 (41.5%) | 49 (20.2%) | < 0.0005 |
| Pre-op creatinine > 125 µmol/L | 25 (30.5%) | 36 (14.9%) | 0.002 |

**Key:** ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; Pre-op =pre-operative

Peri-operative drug usage is presented in figure 1. Eighty two (25.3%) patients were taking an ACE inhibitor on admission compared with 37 (11.4%) at discharge (p<0.0005). Before discharge, ACE inhibition was initiated in five (1.5%) patients and withdrawn in 50 (15.4%). On admission, 157 (48.5%) patients were receiving statin therapy compared with 154 (47.5%) at discharge (p=ns). Statin treatment was initiated during the hospital stay in 23 (7.1%) patients, but was withdrawn in 20 (6.2%) others.

## ACE inhibitor treatment on admission

Univariate associations with ACE inhibitor treatment on admission are presented in table 1. On multivariate analysis, the following variables were independently associated with ACE inhibitor treatment on admission: Q waves on the pre-operative ECG (p=0.006), diuretic (p=0.004) and statin (p=0.019) treatment on admission, and elevated pre-operative plasma urea concentration (p=0.046). Beta blocker treatment on admission was significantly less common (p=0.006) in ACE inhibitor treated patients.

## ACE inhibitor treatment on discharge

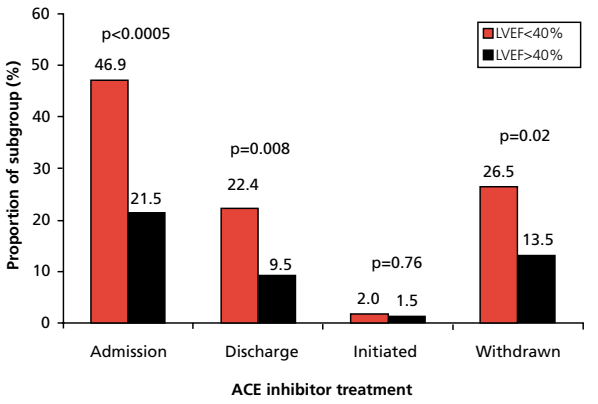
Univariate associations with ACE inhibitor treatment at discharge are presented in table 2. On multivariate analysis, discharge treatment with ACE inhibitors was associated with male gender

**Table 2.** Significant univariate associations with ACE inhibitor treatment on discharge

| | ACE inhibitor on admission n=37 | No ACE inhibitor on admission n=287 | p value |
|---|---|---|---|
| LVEF ≤ 40% | 11 (29.7%) | 38 (13.2%) | 0.008 |
| Males | 35 (94.6%) | 233 (81.2%) | 0.042 |
| Pre-op Q waves | 17 (45.9%) | 82 (28.6%) | 0.031 |
| Beta blocker on admission | 16 (43.2%) | 202 (70.4%) | 0.001 |
| Diuretic on admission | 14 (37.8%) | 62 (21.6%) | 0.028 |
| Pre-op urea > 7 mmol/L | 15 (40.5%) | 68 (23.8%) | 0.028 |
| Pre-op creatinine > 125 µmol/L | 14 (37.8%) | 47 (16.4%) | 0.002 |
| Grafts > 3 | 4 (10.8%) | 80 (27.9%) | 0.026 |

**Key:** ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; Pre-op = pre-operative

**Figure 2.** ACE inhibitor treatment before and after CABG in patients with and without left ventricular dysfunction




**Key:** ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction

(p=0.040); it was less common in patients treated with beta blockers (p=0.014) and calcium blockers (p=0.035) on admission.

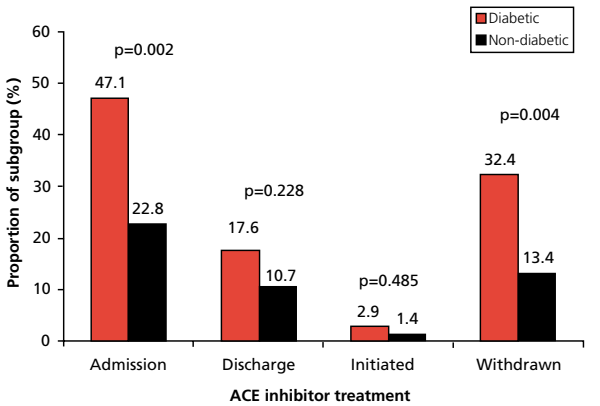
## ACE inhibitor withdrawal

Eleven out of 12 (91.7%) females taking an ACE inhibitor on admission had this discontinued compared with 39 out of 70 (55.7%) males (p=0.018). No other variables were associated with ACE inhibitor withdrawal.

## ACE inhibitor treatment in patients with left ventricular dysfunction

ACE inhibitor treatment was more common on admission (46.5% *vs.* 21.5%; p<0.0005) and at discharge (22.4% *vs.* 9.5%; p=0.008) in the 49 patients with left ventricular dysfunction (figure 2). Thirteen (56.5%) of the 23 patients with left ventricular dysfunction who were taking an ACE inhibitor on admission had it stopped during the hospital stay. Beta blocker treatment at discharge was significantly less common (0 *vs.* 30%; p=0.034) in the patients with left ventricular dysfunction who had had their ACE inhibitor discontinued.

**Figure 3.** ACE inhibitor treatment before and after CABG in diabetic patients




**Key:** ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft

## ACE inhibitor treatment in diabetic patients

ACE inhibitor treatment was significantly more common on admission (47.1% *vs.* 22.8%; p=0.002), but not at discharge (17.6% *vs.* 10.7%; p=0.228), in the 34 patients who were taking oral hypoglycaemic agents or insulin on admission (figure 3). In 11 (68.8%) of the 16 patients who were taking an ACE inhibitor on admission, it was stopped prior to discharge. Among these diabetic patients, ACE inhibitor treatment on admission was independently associated with pre-operative Q waves (p=0.043) and the absence of beta blocker treatment on admission (p=0.023). There were no significant associations with ACE inhibitor treatment on discharge or ACE inhibitor withdrawal in diabetic patients.

## Statin therapy

Statin therapy on admission was associated with the use of ACE inhibitors on admission (31.8% *vs.* 19.2%; p=0.009). Patients aged 60 years and over were less frequently prescribed statin therapy at discharge (61.7% *vs.* 71.2%; p=0.07) than younger patients though this difference was not statistically significant. There were no significant associations with withdrawal of statin therapy.

# Discussion

We have described the use of ACE inhibitors and statins in a group of patients undergoing elective isolated CABG. This study shows that (i) only a minority of patients are receiving ACE

inhibitors and statins on admission for CABG, (ii) ACE inhibitors are frequently discontinued after CABG and (iii) an opportunity to initiate ACE inhibitor and statin therapy in eligible patients is being missed.

## ACE inhibitor withdrawal in patients with left ventricular dysfunction

Current guidelines recommend that "all patients with symptomatic heart failure and those in functional class I with significantly reduced left ventricular function should be treated with an ACE inhibitor".[15] Furthermore, "ACE inhibitors should be continued indefinitely". The withdrawal of (anti-anginal) medication is a potential benefit of revascularisation and, in this study, anti-anginal therapy was discontinued in the majority of patients. Such treatment is symptomatic and (with the exception of beta blockers after MI) does not offer prognostic benefit. By contrast, it is questionable whether ACE inhibitors should be withdrawn post-operatively in patients with clinically important left ventricular dysfunction, yet this occurred in the majority of such patients who were taking an ACE inhibitor on admission.

There are some data to suggest that left ventricular function may improve following CABG. Such evidence, however, comes from non-randomised studies and many of the included patients had been shown pre-operatively to have hibernating myocardium. There has been considerable variation in the reported increases in ejection fraction but, even in these selected patients, the majority of studies have demonstrated an increase post-operatively of 10% or less,[16-18] a change that would not move these patients out of the group for whom ACE inhibitors are currently recommended.

## ACE inhibitor withdrawal in patients without left ventricular dysfunction

The recently published Heart Outcomes Prevention Evaluation (HOPE) Study investigated the effects of ramipril among over 9,000 patients without known left ventricular dysfunction at high risk for adverse cardiovascular events.[3] The majority (80.4%) had a history of coronary artery disease. The primary end point of MI, stroke, or death from cardiovascular causes was reached in 14.0% of ACE inhibitor treated patients compared with 17.8% in the placebo group (relative risk 0.78 (0.70–0.86); p<0.001). Additional significant reductions occurred in death from any cause, revascularisation procedures, cardiac arrest, heart failure, and complications related to diabetes. Similar benefit was observed in the 4,772 patients who were actually documented to have preserved ventricular function. Thus it can now be argued that the withdrawal of ACE inhibitors in all patients with coronary disease irrespective of left ventricular function is inappropriate, a situation that occurred in our study in 50 of 82 (61%) patients taking an ACE inhibitor on admission.

## ACE inhibitor withdrawal in diabetic patients

ACE inhibitors delay the progression of diabetic renal disease even in the absence of hypertension,[19,20] and improve prognosis in diabetic patients after MI.[21,22] In the HOPE study, ramipril lowered the risk of overt nephropathy in the 3,577 diabetic patients by 24% (3–40; p=0.027).[23] Furthermore, the risk of the combined primary end point of MI, stroke, or cardiovascular death was reduced by 25% (12–36; p=0.0004). Importantly, these patients had no standard indications for ACE inhibition (clinical proteinuria, uncontrolled hypertension or left ventricular dysfunction) at randomisation. The HOPE data have broadened the indications for ACE inhibition to include diabetic patients with coronary disease irrespective of left ventricular function. In this study, ACE inhibitor therapy was stopped during the hospital stay in over two thirds of the diabetic patients taking such treatment on admission.

## Statin therapy

Statin therapy is of unequivocal benefit in reducing adverse cardiovascular events in patients with coronary artery disease and plasma total cholesterol levels above 5 mmol/L. In the Cholesterol-Lowering Atherosclerosis Study, (non-statin) cholesterol lowering therapy produced retardation in overall (native vessel and graft) disease progression and a reduction in the proportion of subjects with new graft lesions and any adverse change in graft appearance.[24] More recently, the much larger Post-CABG Trial reported that aggressive cholesterol lowering (mean LDL concentration 2.4–2.5 mmol/L) by lovastatin was associated with a number of favourable angiographic outcomes on disease progression in vein grafts when compared with moderate cholesterol lowering (mean LDL 3.4–3.5 mmol/L).[7] These angiographic differences were associated with a reduction in revascularisation procedures and adverse clinical end points in the aggressively treated patients.[8] Further recent randomised trial data from the CARE investigators suggests that important reductions in coronary heart disease death, non-fatal MI, and stroke in revascularised patients with average cholesterol levels can be achieved with statin therapy.[9] Current concepts suggest that stabilisation of atheromatous plaques underlies both the retardation of disease progression and the reduction in adverse cardiovascular events caused by statin therapy.[25,26] Despite the evidence for statin use in the majority of CABG patients, in this study very few patients were commenced on a statin. This failure to initiate statin therapy is increasingly difficult to justify.

## Clinical implications

In the United Kingdom, 24,000 isolated CABG procedures are performed each year with a further 2,000 combined procedures.[27] This number is set to rise as the National Service Framework has targeted increased revascularisation rates.[13] If the data from the current study were extrapolated to the whole of this surgical population it would represent a fundamental failure to exploit an excellent opportunity for secondary prevention.

Most cardiologists no longer offer 'routine' follow-up to patients after CABG, partly because of service constraints. Thus, a problem of determining who should ensure optimum secondary prevention has been introduced into clinical practice. Should the cardiologist, surgeon, general practitioner, or even

**Key messages**

- A minority of patients admitted for CABG are receiving ACE inhibitors and statins
- ACE inhibitors are being discontinued inappropriately in hospital in the majority of patients post-CABG
- Evidence suggests patients with/without left ventricular dysfunction, and patients with coronary disease with diabetes, will benefit from ACE inhibition. Statin therapy has shown unequivocal benefits in patients with coronary heart disease
- A secondary prevention opportunity to initiate ACE inhibitors and statins in hospital is being missed – post-CABG patients should have their medications reviewed before discharge

the patient be responsible for the delivery of effective secondary prevention? Whatever the answer, a focused review of medications prior to discharge after CABG must be appropriate.

### Limitations

No assessment of post-operative left ventricular function was made. Plasma cholesterol levels were not measured although current NSF guidelines recommend statin use in all patients with coronary artery disease.[13] The number of female patients, and patients in the subgroups with left ventricular dysfunction and diabetes was relatively small. In addition, we did not examine reasons for ACE inhibitor and statin withdrawal.

## Conclusions

In this study, only a minority of patients admitted for elective isolated CABG were receiving ACE inhibitors and statins. ACE inhibitor treatment was discontinued and not recommenced prior to discharge in over 60% of patients who were taking an ACE inhibitor on admission. Such withdrawal of ACE inhibition is likely to have been inappropriate in the majority of cases. Furthermore, statin therapy was no more common at discharge than on admission. This study highlights a missed opportunity to take advantage of the proven secondary prevention benefits offered by these agents in a high-risk population.

## Appendix

The variables examined for associations with ACE inhibitor and statin treatment and withdrawal were age > 60 years, gender, LVEF $\leq$ 40%, Q waves on the pre-operative ECG, treatment on admission and discharge (beta blockers, calcium blockers, diuretics, statins, nitrates, nicorandil, digoxin, anti-arrhythmic agents, diabetic treatment), abnormal pre- and post-operative renal function (urea > 7 mmol/L, creatinine > 125 µmol/L) and post-operative increase in plasma creatinine concentration > 10 µmol/L, > 3 grafts.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