Optimal dosing of angiotensin-converting enzyme inhibitors and β -blockers for acute coronary syndrome: up-titration remains a challenge

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ABSTRACT

Objectives Suboptimal dosing of angiotensin-converting enzyme inhibitors and β -blockers limits the mortality benefit for acute coronary syndrome patients. Recent National Institute for Health and Care Excellence (NICE) guidelines emphasise prompt initiation and up-titration from inpatient to community care to achieve this. The aim of this study was to assess the impact of simple interventions on inpatient and community up-titration of bisoprolol and ramipril for acute coronary syndrome patients admitted to Leeds General Infirmary. **Methods** An initial prospective audit of 37 acute coronary syndrome patients admitted to Leeds General Infirmary in January 2013 assessed inpatient up-titration of bisoprolol and ramipril, discharge advice and doses at 6 weeks after discharge. Following a collective multidisciplinary effort with education, posters and discharge advice templates, a re-audit of 34 acute coronary syndrome patients admitted from November to December 2014 assessed the impact of these interventions. The independent samples t test was used to compare the mean difference between doses of ramipril and bisoprolol from initiation to discharge to dose at 6 weeks after discharge before and after intervention.

Results There was a statistically significant improvement in the mean difference from initiation to discharge dose for both ramipril and bisoprolol ($p=0.012$ and $p=0.017$, respectively). However, there was little difference in community up-titration despite a 68% improvement in discharge advice.

Conclusions Simple multidisciplinary interventions improved inpatient up-titration of ramipril and bisoprolol but continued up-titration to achieve the target doses remains a challenge in primary care. Acute coronary syndrome patients are precluded from maximum mortality benefit due to suboptimal dosing after discharge.

INTRODUCTION

Acute coronary syndrome patients should have an ACE inhibitor (ACE-I) and β -blocker (BB) commenced promptly with up-titration to the maximum tolerated dose. The evidence demonstrating mortality benefit is derived from their early use at high target doses.^{1 2}

We believed that up-titration during admission was limited. A lack of discharge instructions for community up-titration leaves patients on suboptimal doses of ACE-I and BB despite adequate blood pressure, heart rate and renal function. In this small

interventional study, we audited up-titration of ACE-I and BB for acute coronary syndrome patients admitted to Leeds General Infirmary. We hypothesise that simple interventions can improve inpatient and primary care up-titration.

METHODS

Audit 1

An initial prospective audit was conducted from January to March 2013 for 37 consecutive patients with acute coronary syndrome. Data were collected on the day of discharge using the patient's notes, discharge summary and summary care record. A data collection proforma was used to record:

- ▶ Patient demographics (age, gender, diagnosis, presence of chronic kidney disease, diabetes or heart failure, duration of admission)
- ▶ Details of inpatient up-titration of bisoprolol and ramipril (starting doses, number and doses of titrations with corresponding heart rate, blood pressure and renal function, consultant team initiating and titrating)
- ▶ Doses on discharge
- ▶ Presence of discharge instructions.

At 6 weeks after discharge, the summary care record was used to note the doses of ramipril and bisoprolol and whether they had been titrated, stopped or changed.

Interventions

Following results of the initial audit, simple multidisciplinary interventions were implemented to improve up-titration and discharge advice:

- ▶ Education of junior doctors and pharmacists at departmental teaching sessions to promote awareness of the benefits of up-titration
- ▶ Summarised National Institute for Health and Care Excellence guidelines emailed to prompt senior colleagues to up-titrate on ward rounds
- ▶ Posters of prescribing guidance on wards and the intranet to enable quick reference
- ▶ Discharge template for acute coronary syndrome with guidelines for community up-titration
- ▶ A collective multidisciplinary effort to encourage appropriate up-titration.

Audit 2

From October 2014 to January 2015 a prospective re-audit of 34 acute coronary syndrome patients admitted to Leeds General Infirmary was conducted to assess the effect of the interventions. The same proforma was used to collect data on the day

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Table 1 Patient demographics, diagnosis, time as inpatient and comorbidities

	Audit 1 N=37	Audit 2 N=34
Median age (years)	70	68
IQR	60–77	59–79
Gender		
Male	20 (54%)	20 (59%)
Female	17 (46%)	14 (41%)
Diagnosis		
NSTEMI	19 (51%)	20 (59%)
STEMI	18 (49%)	14 (41%)
Average time as inpatient (days)	4.5	7.3
Chronic kidney disease	8 (22%)	5 (15%)
Diabetes	8 (22%)	6 (18%)
Heart failure	4 (11%)	2 (6%)

NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

of discharge and at 6 weeks after discharge to enable direct comparison with the initial audit.

We assessed up-titration for appropriate patients, excluding patients with contraindications and valid reasons preventing up-titration. Analysing up-titration of ramipril and bisoprolol before and after intervention enabled direct dose comparison.

The independent samples *t* test was used to compare the mean difference between doses of ramipril and bisoprolol from starting to discharge dose and from discharge dose to 6 weeks after discharge, before and after intervention (audit 1 vs audit 2). All data analyses were performed using SPSS V.20 (IBM, Chicago, Illinois, USA).

RESULTS

Demographics

In both audits the male to female ratio and age range were similar (table 1). In audit 2 marginally more patients had a non-ST-segment elevation myocardial infarction (59% vs 51%) and the average time as an inpatient was almost 3 days longer.

Ramipril and bisoprolol were the most commonly used ACE-I and BB in both audits. Of a combined total of 71 patients from both audits, 59 were on ramipril and 66 were on bisoprolol.

Discharge advice

There was a vast improvement in discharge letter advice after intervention: 3% from audit 1 vs 71% from audit 2.

Impact of interventions on inpatient up-titration

After intervention, the mean difference from starting to discharge dose for both ramipril and bisoprolol improved to a level of statistical significance (tables 2 and 3).

The mean discharge dose for ramipril improved from 2.7 to 4.4 mg daily after intervention, and was statistically significant ($p=0.016$). The mean discharge dose of bisoprolol improved from 3.17 to 4.4 mg daily.

Impact of interventions on community up-titration

While there was a trend towards improvement after intervention for the mean dose at 6 weeks after discharge, this was not statistically significant: bisoprolol mean dose improved from 3.5 to 3.8 mg daily and ramipril from 4.7 to 5.3 mg daily. The mean difference from discharge dose to dose at 6 weeks did not improve for either medication (tables 3 and 4).

Reasons preventing up-titration in both audits

Up-titration of BB during inpatient stay was prevented due to hypotension and bradycardia in both audits, with severe chronic obstructive pulmonary disease (COPD) as an additional reason in audit 2. Use and up-titration of ACE-I was prevented by poor renal function and hypotension in both audits, with severe aortic stenosis as an additional reason in audit 1.

DISCUSSION

ACE-I and BBs are standard secondary prevention medications for patients after acute coronary syndrome in addition to antiplatelet and statin therapy.

The mortality benefit of these medications is derived from use at their maximum target doses: ramipril 5 mg twice daily improved outcomes in the Acute Infarction Ramipril Efficacy (AIRE) study.³ Carvedilol was used at its maximum dose of 25 mg twice daily in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study (CAPRICORN).⁴

As these medications cannot be initiated at these high target doses, prompt up-titration is required to optimise prognostic benefit. This requires up-titration to begin during inpatient stay

Table 2 Inpatient up-titration: before intervention (audit 1) and after intervention (audit 2)

Inpatient	Audit 1 N=37		Audit 2 N=34	
	ACE-I	BB	ACE-I	BB
Up-titrated	4 (11%)	7 (19%)	12 (35%)	13 (38%)
Not up-titrated	14 (38%)	19 (51%)	5 (15%)	8 (24%)
Contraindicated/stopped for valid reason	6 (16%)	1 (3%)	3 (9%)	6 (18%)
Maximum dose prior to admission	2 (5%)	2 (5%)	4 (12%)	2 (6%)
Inpatient up-titration prevented for valid reason	6 (16%)	5 (14%)	5 (15%)	3 (9%)
Angiotensin II receptor blocker	4 (11%)	–	2 (6%)	–
Perindopril	1 (3%)	1 (3%)	1 (3%)	–
Enalapril	–	–	2 (6%)	–
Metoprolol	–	1 (3%)	–	–
Nebivolol	–	1 (3%)	–	1 (3%)
Atenolol	–	–	–	1 (3%)

Exclusions included patients not appropriate for up-titration (medication contraindicated/stopped or prevented for valid reason) and patients on different medications. ACE-I, ACE inhibitor; BB, β -blocker.

Table 3 Mean of difference between doses of ACE-I and BB from admission to discharge before intervention (audit 1) and after intervention (audit 2)

	ACE-I			BB		
	Audit 1	Audit 2	p Value	Audit 1	Audit 2	p Value
Mean of difference between dose from admission to discharge	0.49 N=18	1.9 N=17	0.012	0.53 N=16	2.14 N=21	0.017
Mean of difference between dose from discharge to 6 weeks after discharge	2.5 N=8	1.7 N=15	0.46	0.36 N=21	0.35 N=18	0.975

ACE-I, ACE inhibitor; BB, β -blocker.

as soon as haemodynamic stability is achieved, as emphasised in recent National Institute for Health and Care Excellence (NICE) guidelines.⁵ If titration to target dose is not reached during the inpatient stay, it should be achieved 4–6 weeks after discharge.⁵ This necessitates the provision of a clear discharge plan to the general practitioner (GP).

Suboptimal titration is a recognised problem; a 7-year study highlights prescribed doses of BBs at less than 50% of doses used in clinical trials providing mortality evidence.⁶

Simple multidisciplinary interventions, which could easily be adopted by any cardiac centre, have resulted in statistically significant improvement of up-titration of ramipril and bisoprolol during inpatient stay. The multi-disciplinary involvement within the cardiology department contributed to this; doctors and pharmacists promote, monitor and check the up-titration process while nursing colleagues note concordant changes in patient observations and side effects. Junior doctors have the responsibility of including up-titration instructions on discharge letters, but pharmacists were also able to prompt to add instructions when checking discharge medications if it had been missed.

The limitations of the interventions include rotation of junior doctors and pharmacists, as each new cohort would need to be educated about up-titration and incorporate this into their clinical practice.

Inpatient up-titration is limited by short inpatient stay; the longer patient stay in audit 2 may be one reason for the improved up-titration. Starting higher doses of ACE-I and BB at initiation would be a way to augment the dose on discharge. As inpatients are closely monitored, the doses could be easily decreased again if not tolerated. However, adverse effects may not become apparent until after discharge.

Despite the vast improvement in discharge instructions after the intervention, this did not impact on community up-titration to a level of statistical significance. Further challenges of

community up-titration need to be addressed to allow the discharge advice to be implemented.

The responsibility to continue up-titration is ultimately passed from a multidisciplinary team solely to the GP. Adequate monitoring of an individual patient's blood pressure, heart rate, renal function and adverse effects is more challenging in a community setting. GPs may feel that the initiating secondary care physician should manage medications started in secondary care. Implementation into the Quality and Outcomes Framework may improve compliance with up-titration.

Development of a community up-titration clinic in secondary care or routine review of doses at 6-week cardiology clinic follow-up would share some of the responsibility for community up-titration.

Limitations from these audits include small sample sizes after exclusions, particularly on analysis of community up-titration: in audit 1, just eight patients could be analysed after seven patients had a dose decrease, stopped or changed to an angiotensin II receptor blocker, likely for valid reasons. It would be useful to assess up-titration of additional ACE-I and BB choices to ramipril and bisoprolol. Up-titration of these may be less than for ramipril and bisoprolol due to unfamiliarity of doses among junior doctors.

Concluding points

- ▶ Acute coronary syndrome patients are precluded from maximum mortality benefit due to sub-optimal doses after discharge.
- ▶ Simple multidisciplinary interventions can improve inpatient up-titration of ramipril and bisoprolol, but this is limited by brief inpatient stay.
- ▶ Despite improvement in discharge advice, community up-titration remains a challenge.
- ▶ Development of a formal clinic review of doses at 6 weeks after discharge may improve community up-titration.

Table 4 Community up-titration at 6 weeks after discharge: before intervention (audit 1) and after intervention (audit 2)

Community	Audit 1		Audit 2	
	ACE-I N=18	BB N=26	ACE-I N=17	BB N=21
Up-titrated	6 (33%)	3 (12%)	6 (35%)	2 (10%)
Not up-titrated	2 (11%)	18 (69%)	9 (53%)	16 (76%)
Maximum dose on discharge	–	–	1 (6%)	3 (14%)
No GP	2 (11%)	2 (8%)	–	–
Death	1 (6%)	1 (4%)	–	–
Dose decreased	2 (11%)	2 (8%)	1 (6%)	–
Stopped	3 (17%)	–	–	–
Changed to angiotensin II receptor blocker	2 (11%)	–	–	–

ACE-I, ACE inhibitor; BB, β -blocker; GP, general practitioner.

Key messages

What is already known on this subject

- ▶ Angiotensin-converting enzyme inhibitors and β -blockers are standard secondary prevention medications after acute coronary syndrome.
- ▶ The evidence demonstrating mortality benefit is based on use of these medications at their high target doses.
- ▶ Suboptimal dosing is a recognised problem.

What this study adds

- ▶ Simple multidisciplinary interventions can improve inpatient up-titration to a level of statistical significance.
- ▶ Suboptimal dosing continues into primary care despite improved discharge advice.

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promoted education, distributed guidelines, created the discharge template and wrote the manuscript. Leanne Elder contributed to data collection for the second audit. RK ran statistical analyses on results.

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