



## The pharmaco-economics of peri-operative beta-blocker and statin therapy in South Africa

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We conducted a pharmaco-economic analysis of the prospective peri-operative studies of beta-blocker and statin administration for major elective non-cardiac surgery, using the Discovery Health claims costs for 2004. This analysis shows that acute peri-operative beta-blockade and statin therapy could result in a cost saving through a reduction in major peri-operative cardiovascular complications in patients with an

expected peri-operative major cardiovascular complication rate exceeding 10% following elective major non-cardiac surgery. The validity of these findings is dependent on whether the incidence of cardiovascular complications following major non-cardiac surgery reported in the international literature is found to be similar in South Africa.

*S Afr Med J* 2006; **96**: 1199-1202.

Postoperative cardiovascular complications occur predominantly as a result of either prolonged myocardial ischaemia or rupture of unstable coronary plaques.<sup>1</sup> These pathophysiologies may be attenuated by both acute peri-operative beta-blockade or statin therapy.<sup>1,2</sup>

In previously published pharmaco-economic analyses of peri-operative beta-blocker and statin studies, we have shown that these drugs are cost-effective within the framework of the British National Health System (NHS).<sup>3,4</sup>

Using the same methodology previously employed,<sup>3,4</sup> we have now conducted a pharmaco-economic analysis for the use of beta-blocker and statin therapy in high-risk non-cardiac surgical patients using South African health care costs. Unfortunately, as there are no South African data available on peri-operative outcomes associated with acute peri-operative beta-blocker or statin therapy, we have continued to use the incidences reported in the American and European literature.<sup>5-15</sup> In this analysis, we have also considered the effect of the prevention of myocardial ischaemia with peri-operative beta-blockers on late postoperative cardiovascular complications,<sup>16,17</sup> which was not considered in our previous analysis.<sup>3</sup>

### Methods

#### Peri-operative beta-blocker therapy

This pharmaco-economic analysis compared the total expected cost of treating surgical patients with 200 mg metoprolol

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for 30 days versus placebo for 30 days peri-operatively and following elective surgery, as prescribed according to the POISE protocol.<sup>18</sup> We examined all the published prospective studies examining the utility of beta-blockers in the peri-operative period, and where major peri- and postoperative cardiovascular complications have been reported.<sup>5-13</sup> For these, we determined the overall incidences of all-cause mortality, non-fatal myocardial infarction and non-fatal cardiac arrest within 30 days of surgery in both the treated and control groups of these studies. In addition, we also noted the mortality reported in a subset of two of the studies at 2 years.<sup>16,17</sup> Because all drugs have potential adverse side-effects, we have attempted to determine the overall incidences of adverse cardiovascular outcomes potentially attributable to beta-blocker administration, including hypotension and bradycardia needing treatment, congestive heart failure, bronchospasm and cerebrovascular accident.

#### Peri-operative statin therapy

From the two prospective peri-operative statin studies in patients undergoing major vascular surgery,<sup>14,15</sup> we similarly determined the overall incidences of cardiac and all-cause death, myocardial infarction, unstable angina and stroke in the treated and control groups reported as in-hospital complications from the study by Schouten *et al.*<sup>14</sup> and up to 6 months from the study by Durazzo *et al.*<sup>15</sup> For this analysis we have assumed all patients to be on a therapeutic dose of atorvastatin (20 mg daily for 45 days) as per the protocol of Durazzo *et al.*<sup>15</sup> We also considered the cost of monitoring for, and treating, the complications associated with statin therapy. These included pre-operative hepatic and creatine kinase screening tests and four postoperative tests.<sup>14</sup> The incidence of peri-operative adverse events associated with statins is unknown. However it is likely to be more frequent than that recorded in medical patients as common risk factors for adverse peri-operative cardiac events have often been exclusion criteria in the statin trials of medical patients.<sup>1</sup> Indeed, in



surgical patients<sup>14</sup> the incidence of a peri-operative creatine kinase level > 10 times the upper limit of normal was found to be 40 times more common than that reported in large medical trials.<sup>1</sup> We assumed therefore that rhabdomyolysis in surgical patients may also be 40 times more common than reported in medical patients, giving a predicted incidence of 1.3% in surgical patients.<sup>4</sup> The incidence of elevated hepatic enzymes in the peri-operative period has been reported as 2%.<sup>15</sup>

For both the beta-blocker and statin pharmaco-economic analyses, we constructed a monetary balance sheet based on the reported cardiovascular and adverse drug events for all the patients reported in these trials.<sup>5-15</sup> All costs were derived from the Discovery Health claims costs for patients in the age band 61 - 75 years for 2004.<sup>18</sup> The mean or median ages of the patients reported in the beta-blocker studies range from 60 to 76 years,<sup>5-11,13</sup> and the mean age of the patients in the peri-operative statin study contributing nearly 91% of the patients to our analysis was 64 years.<sup>14</sup> The average total cost for all the events recorded in these studies is listed in Table I. The pharmaco-economic analyses of peri-operative beta-blocker and statin therapy (taking into account drug acquisition costs, managing adverse drug events and the cost of treating cardiovascular complications) was carried out as in our previous papers.<sup>3,4</sup>

## Results

### Peri-operative beta-blocker therapy

The reported clinical outcomes data of the 11 high-risk surgical studies of peri-operative beta-blockers<sup>5-13,16,17</sup> are presented in Table II. Acute peri-operative beta-blockade significantly decreased peri-operative myocardial infarction, late cardiovascular deaths and all postoperative deaths up to 2 years. The number-needed-to-treat (NNT) to prevent one major peri-operative cardiovascular event with acute peri-operative beta-blocker therapy was 20; and for peri-operative death alone the NNT was 72. The NNT to prevent both peri-operative and postoperative deaths for up to 2 years is 25, although this calculation does not include nearly 76% of the patients (for whom there are no available data), and thus the actual NNT is probably considerably smaller.<sup>5-7,9,10,12,13</sup> However, beta-blocked patients had significantly increased drug-associated adverse events in comparison to the controls.

Applying the Discovery Health claims costs for 2004<sup>19</sup> (Table I) to the reported incidences of cardiovascular complications and potential adverse drug events (Table II), we can show that acute peri-operative beta-blocker therapy may potentially save R869 per patient through the reduction in cardiovascular complications (Table III).

### Peri-operative statin therapy

The reported cardiovascular complications in the prospective studies of peri-operative statin therapy are shown in Table

**Table I. Costs of peri-operative beta-blocker and statin therapy and major cardiovascular complications for patients in the age band 61 - 75 years during 2004<sup>19</sup>**

Events recorded in this analysis	Cost in ZAR*
Direct and indirect costs of beta-blocker therapy	
Cost of 200 mg/day metoprolol for 30 days	378
Cost of adverse drug events	
Congestive heart failure	29 860
Hypotension, drug or unspecified	15 619
Bradycardia, unspecified	7 819
COPD with acute exacerbation	22 912
Cerebrovascular accident	17 438
Direct and indirect costs of statin therapy	
Cost of atorvastatin 20 mg for 45 days	373.50
Lipid profile (2 episodes)	360.60
AST, ALT, CK (5 episodes)	540.00
Cost of drug-associated adverse events	
Acute renal failure	44 056
Acute hepatitis/acute liver failure	12 168
Costs of peri-operative cardiovascular complications	
Sudden cardiac death	42 665
Non-fatal cardiac arrest	133 380
Non-fatal myocardial infarction	67 400
Angina pectoris	36 419
Cerebrovascular accident	17 438

COPD = chronic obstructive pulmonary disease; AST = aspartate transaminase; ALT = alanine transaminase; CK = creatine kinase.  
\* Costs are presented in South African rands (ZAR).

IV. Similarly, application of the Discovery Health claims costs for 2004<sup>18</sup> (Table I) show that statin therapy could potentially save R1 822 per patient treated, through a reduction in cardiovascular complications (Table V).

## Discussion

Using South African health care costs, this pharmaco-economic analysis suggests that both peri-operative beta-blocker and statin therapy (in addition to improving cardiovascular outcome in appropriately selected high-risk elective surgical patients) may result in cost-minimisation. However, these findings are based on cardiovascular outcomes reported in the international literature<sup>5-15</sup> and not in South African patients. Hence, our findings will only be valid if the same rate of peri-operative cardiovascular complications were to be found in South African patients. There is evidence, however, that the incidence of coronary artery disease is rapidly increasing in South African ethnic groups previously considered to be at low risk for coronary events,<sup>20</sup> while other specific ethnic groups in South Africa are already known to be at considerable cardiovascular risk including the South African Asian Indian population,<sup>21</sup> black patients with a history of cerebrovascular disease and hypertension,<sup>19,22</sup> and South Africans of European descent.<sup>20</sup>



**Table II. Reported cardiovascular complications and adverse events in the prospective studies of acute peri-operative beta-blocker therapy in high-risk surgical patients<sup>5-13,16,17</sup>**

	Beta-blocker therapy N = 642	No beta-blocker therapy N = 607	p-value*
<b>Cardiovascular complications</b>			
Non-fatal cardiac arrest	2 (0.3%)	5 (0.8%)	0.28
Non-fatal MI	24 (3.7%)	42 (6.9%)	0.02
Death within 30 days of surgery (A)	12 (1.9%)	20 (3.3%)	0.15
Death up to 2 years after hospital discharge <sup>†</sup> (B)	15/148 (10.1%)	30/145 (20.7%)	0.01
All deaths up to 2 years (C = A + B)	27 (4.2%)	50 (8.2%)	0.003
<b>Adverse events</b>			
Congestive heart failure	28 (4.4%)	17 (2.8%)	0.17
Hypotension needing treatment	200 (31.2%)	144 (23.7%)	0.004
Bradycardia needing treatment	63 (9.8%)	24 (4.0%)	< 0.0001
Bronchospasm	20 (3.2%)	19 (3.1%)	1.00
Non-fatal CVA	5 (0.8%)	1 (0.2%)	0.22
<b>Total</b>	<b>316 (49.2%)</b>	<b>205 (33.8%)</b>	<b>&lt; 0.0001</b>

MI = myocardial infarction; CVA = cerebrovascular accident.  
 \*p-values shown are calculated using a two-tailed Fisher exact test.  
<sup>†</sup>From the studies of Mangano *et al.*<sup>16</sup> and Poldermans *et al.*<sup>17</sup>

**Table III. Cost analysis of peri-operative beta-blocker therapy per patient\***

	Beta-blocker therapy	No beta-blocker therapy
Cost of peri-operative cardiovascular complications (A)	3 732.62	7 168.04
Cost of adverse drug events (B)	7 784.90	5 596.67
Cost of beta-blocker or placebo therapy (C)	378	0
Total cost (D = A + B + C)	11 895.52	12 764.71
Incremental cost of beta-blocker therapy (E = D with beta-blockers - D without beta-blockers)	-869.19	-

\*Costs are presented in South African rands (ZAR).

**Table IV. Reported adverse events in the prospective studies of statin therapy in vascular surgical patients<sup>14,15</sup>**

	Statin therapy N = 276	No statin therapy N = 805	p-value*
Death	6 (2.2%)	32 (4.0%)	0.19
Non-fatal myocardial infarction	18 (6.5%)	89 (11.1%)	0.03
Unstable angina	0	1 (0.1%)	1.000
Cerebrovascular accident	0	2 (0.2%)	1.000
<b>Total</b>	<b>24 (8.7%)</b>	<b>124 (15.4%)</b>	<b>0.004</b>

\*p-values shown are calculated using a two-tailed Fisher exact test.

**Table V. Cost analysis of peri-operative statin therapy per patient\***

	Statin therapy	No statin therapy
Cost of peri-operative cardiovascular complications (A)	5 323.15	9 236.24
Cost of statin therapy (B)	2 090.19	-
Total cost (C = A + B)	7 413.34	9 236.24
Incremental cost of statin therapy (D = C with statins - A without statins)	-1 822.90	-

\*Costs are presented in South African rands (ZAR).



## How to identify patients likely to benefit from peri-operative beta-blocker or statin therapy

Our findings suggest that beta-blockers are only potentially cost-effective for patients with an expected major cardiovascular complication rate exceeding 10% following major non-cardiac surgery. This is an important strategic point, as when all risk groups are included the cardioprotective efficacy of acute peri-operative beta-blockade is inconclusive.<sup>23</sup> Similarly, peri-operative statin therapy is only potentially cost-effective for patients undergoing vascular surgery with an expected major cardiovascular complication rate of 15.4%.

## Minimising side-effects associated with peri-operative beta-blocker therapy in high-risk surgical patients

Administering beta-blockers to high-risk patients is associated with a significantly increased risk of associated adverse drug events (Table II). This may be partly due to overdosage, but also to a small group with significant ventricular-wall motion abnormality unresponsive to peri-operative beta-blockers.<sup>24</sup> The high incidence of major peri-operative cardiovascular events in the untreated patients (11%) suggests that all these patients should routinely have further cardiac investigation prior to surgery. Identification of a subgroup of patients who require optimisation of ventricular function as opposed to beta-blockade is important.<sup>24</sup>

## Comparing the cost of peri-operative beta-blocker and statin therapy with accepted medical (or non-surgical) indications

The cost analyses summarised in Tables III and V show that the reduction in peri-operative cardiovascular events offsets the total additional cost of peri-operative beta-blocker or statin therapy. This compares favourably with secondary prevention in high-risk medical patients. We have calculated that the cost in the UK of preventing a death at 2 years with peri-operative beta-blockade is 33% of the cost of preventing the same event in a medical patient after myocardial infarction,<sup>25</sup> and that the cost of preventing a peri-operative death with statin therapy is 72% of the cost of preventing the same complication in the highest risk cohort of the Health Protection Study (unpublished observations).

From the available data in the literature, we have not been able to evaluate the effect of peri-operative statin therapy on long-term cardiovascular outcomes, although it is likely that this therapy would also positively affect outcome.<sup>1</sup>

## Conclusions

Acute peri-operative beta-blocker and statin therapy may be cost-effective in high-risk surgical patients undergoing major

non-cardiac surgery and vascular surgery respectively in South Africa.

Acknowledgements: Dr B A Ruff and Dr D W C Jacobs of Clinical Risk Management, Discovery Health (Pty) Ltd South Africa.

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Accepted 16 June 2006.