



## Use of evidence-based management for acute coronary syndrome

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### Abstract:

**Aims** This study compared the management of acute coronary syndrome (ACS) for patients admitted to Dunedin Coronary Care with evidence-based recommendations from the American College of Cardiology / American Heart Association in 1999 and 2002 and with management reported in international and local registries.

**Methods** All patients with ACS from 2001-2002 were included.

**Results** Guidelines stated that aspirin, beta-blockers, statins, and ACE-inhibitors/angiotensin-II-blockers are appropriate treatment for acute coronary syndrome. These medications were prescribed respectively in 98%, 80%, 70% and 55% of patients on discharge. In patients with documented dyslipidaemia, Statins was prescribed in 80% on discharge. The use of ACE inhibitors was 73% in patients with impaired left ventricular function, 79% in patients with clinical heart failure and 84% in patients with anterior ST-elevation myocardial infarction (STEMI). For patients with STEMI, 67% received coronary angiography, 50% had PCI and 7% underwent inpatient coronary artery bypass grafting. For Non-ST-elevation myocardial infarction (NSTEMI), the respective numbers were 73%, 38% and 21%. Our use of evidence-based medications was consistent with published guidelines and comparable to results of international registries (CRUSADE, EUROESPIRE II, GRACE) in 2001–2002.

**Conclusion** There is good adherence to the use of evidence-based management for acute coronary syndrome in Dunedin Coronary Care Unit.

Findings from major clinical trials constitute the basis for evidence-based management (EBM) of acute coronary syndrome (ACS) which are summarised by various professional bodies to produce official treatment guidelines.<sup>1,2</sup> Data from international Registries often revealed significant differences between published guidelines and real life clinical practice in managing ACS.<sup>3,4</sup>

Our study aims to compare our local practice in Dunedin Hospital in the years 2001–2002 with what was published in:

- The 1999 American College of Cardiology (ACC) / American Heart Association (AHA) Practice Guidelines,<sup>1</sup> and
- The 2002 updated ACC/AHA Practice Guidelines<sup>2</sup> (Appendix 1); as well as with
- International & local Registry data from 1999 to 2002 including EUROASPIRE II<sup>5</sup> (European Action on Secondary Prevention through Intervention to Reduce Events), GRACE<sup>6</sup> (Global Registry for Acute Coronary Syndrome), CRUSADE<sup>7</sup> (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?), and the

New Zealand Acute Coronary Syndrome Audit<sup>8</sup> (NZACS) conducted in May 2002.

## Methods

**Patient identification**—We identified (retrospectively) all consecutive patients admitted into Coronary Care in Dunedin Hospital from 1 January 2001 to 31 December 2002 with ACS. Relevant information was extracted from clinical notes. All patients had ACS as their discharge diagnosis and were above 18 years of age. Patients were excluded if the ACS was precipitated or accompanied by morbid conditions such as sepsis, trauma, or major surgery. Our Coronary Care Unit acted also as a tertiary referral centre for Oamaru Hospital, Dunstan Hospital, Kew Hospital (in Invercargill), and Lakes District Health (in Queenstown) with a catchment area including both Otago and Southland (population 286,700; June 2003).<sup>9</sup>

**Data collection**—A systematic approach was made to collect data on demographic characteristics, presenting symptoms, medical history, inpatient management, treatment, and inpatient outcome.

ACS was divided into

- ST elevation myocardial infarction (STEMI): defined as having ST segment elevation  $\geq 1$  mm in two contiguous leads (or  $\geq 2$  mm in  $V_1$  to  $V_3$  leads) or new left bundle branch block together with evidence of myonecrosis with elevated troponin I (Abbott AxSYM assay)  $\geq 2.0$  mcg/L and / or chest pain for  $>30$  minutes.
- Non-ST elevation myocardial infarction (NSTEMI): defined as no ST elevation on ECG despite elevated troponin I (Abbott AxSYM assay)  $\geq 2.0$  mcg/L and chest pain for more than 30 minutes.
- Unstable angina: defined as having clinical characteristics of ischaemic chest pain lasting more than 30 minutes (with or without ischaemic ECG changes) but no evidence of myonecrosis or ST elevation.

**Statistical analysis**—Statistical analysis was prepared on SPSS for Macintosh Version 10. Data are presented as mean  $\pm$  standard deviation or proportions as appropriate. Chi-squared tests were used to compare proportions. The test was double-sided and considered to be statistically significant at  $\alpha < 0.05$ .

**Definition of other analysed parameters**—The diagnosis of diabetes was recorded based on the patient's history. Dyslipidaemia was defined as total fasting cholesterol of  $\geq 5.5$  mmol/L measured during the index admission. Left ventricular ejection function (EF) was assessed semi-quantitatively by echocardiography or left ventriculography during cardiac catheterisation and was classified as normal (EF  $\geq 50\%$ ), mildly impaired (EF = 35–49%), moderately impaired (EF = 25–34%) or severely impaired (EF  $< 25\%$ ). Heart failure was recorded if the attending cardiologist had made the diagnosis, if there was radiographic evidence of pulmonary congestion, or if a loop diuretic was commenced during hospitalisation.

## Results

In 2001–2002, 815 patients were admitted into Coronary Care, of which 577 satisfied our inclusion criteria. Table 1 shows the demographics of the 577 patients in this study (195 with STEMI, 239 with NSTEMI, and 143 with unstable angina).

**Pharmacological management of ACS**—Table 2 showed the use of aspirin, beta-blockers, statins, and ACE inhibitors.

In the 577 ACS patients, 98%, 80%, and 70% were discharged on aspirin, beta-blockers, and statins respectively. Furthermore, 61% of patients with diabetes and 82% of patients with documented fasting total cholesterol of  $\geq 5.5$  mmol/L were prescribed statins.

With respect to ACE-inhibitor or angiotension-II-antagonist, 55% of ACS patients, 79% of patients with a history of heart failure, and 80% of patients with anterior STEMI were prescribed either of the medications on discharge. These medications

were used in 82% of patients with  $\geq$  moderate and 73% in patients with  $\geq$  mild left ventricular impairment.

**Use of heparin in NSTEMI / unstable angina**—Of the 382 patients with NSTEMI or unstable angina, 93% were commenced on IV heparin or low molecular weight heparin in the first 24 hours during the admission.

**Use of clopidogrel and glycoprotein IIb/IIIa inhibitors in NSTEMI**—Of the 239 patients with NSTEMI, 59% received clopidogrel and 37% received glycoprotein IIb/IIIa inhibitors. For the 65 patients who only had medical treatment without angiography, 4(6.1%) had clopidogrel and 4(6.1%) had glycoprotein IIb/IIIa inhibitors. The remaining 174 patients (representing 73% of NSTEMI patients) underwent angiography  $\pm$  revascularisation and amongst them 75% received clopidogrel and 46% received glycoprotein IIb/IIIa inhibitors either prior to or during the procedure.

**Early angiography-directed revascularisation for NSTEMI**—For these 174 patients, 89 had angiography-directed medical management, 91 had percutaneous coronary intervention (PCI), and 49 had inpatient coronary bypass graft for revascularisation. Thus, of all 239 patients with NSTEMI, PCI was performed in 38% and coronary bypass graft in 21%.

**Management of STEMI**—For the 195 patients with STEMI, 75% received thrombolysis. For the remaining 25% not having thrombolysis, the reasons included late presentations (9.7%), clear contraindication(s) for thrombolysis (6.7%), inappropriate clinical decisions (4.6%), and primary angioplasty (4.0%).

For patients who were thrombolysed, 46% received streptokinase and 54% reteplases. The mean door-to-needle time from arrival into the Emergency Department to thrombolysis was 49 minutes.

When thrombolysis was conducted in Coronary Care from August 2000 to May 2002 (N=101), the time was 62 minutes but this shortened to 38 minutes since thrombolysis was initiated in the Accident and Emergency Department of Dunedin Hospital in July 2002.

Amongst the 195 patients with STEMI, 67% (n=131) had inpatient coronary angiography, 51% (n=99) had inpatient PCI, including 8 patients with primary PCI and 14 patients with rescue PCI after failed thrombolysis which was defined as persistent pain with ST elevation 120 minutes post-thrombolysis.

Of the 99 who had PCI, the majority (n=77) had deferred PCI which was mostly preformed 24 hours later. Thirteen patients (7%) received inpatient coronary artery bypass graft. Overall, 91% of STEMI admissions received reperfusion and/or revascularisation therapy.

**Comparison with other registry data**—The management of patients with ACS in Dunedin was compared with EUROASPIRE II<sup>5</sup> 1999–2000 (N=8181), GRACE<sup>6</sup> 1999–2000 (N=12,666), CRUSADE<sup>7</sup> 2002 (N=19,000), and the NZACS Audit<sup>8</sup> 2002 (N=721). Compared with the CRUSADE registry, there was more frequent use of less expensive medications (aspirin, beta-blockers, and heparin) and a less frequent use of the more expensive glycoprotein IIb/IIIa inhibitors and clopidogrel in Dunedin (Table 3).

**Table 1. Patient demographics (N=577)**

STEMI	33.8%
NSTEMI	41.4%
Unstable angina	24.8%
Male Gender	62.8%
Age (mean±SD)	65 ± 12.6
History of ischaemic heart disease	47.1%
History of hypertension	50.3%
History of diabetes mellitus	15.1%
Fasting cholesterol ≥ 5.5mmol/L	62.0%
History of coronary artery bypass graft	8.0%
On beta-blocker on arrival	36.7%
Family history of ischaemic heart disease (1° relative <60 years old )	36.7%
Past or present cigarette use	57.0%
Blood pressure on admission (mean ± SD)	138/76 ± 23/18 mmHg
Creatinine (mean ± SD)	0.103 ± 0.049 mmol/L,

**Table 2. Use of medications amongst patients admitted with ACS 2001–2002**

Medication	First 24 hours of admission	At discharge
Aspirin	99%	98%
B-blocker	83%	80%
Statins	38%	70%
ACE-I/AIIA	No data	55%

**Table 3. Medications used in the first 24 hours during the index admission**

Admission medications	CRUSADE*	DUNEDIN†	P value
Aspirin	90%	99%	p<0.0005
Beta-blocker	76 %	83%	p<0.0005
Heparin	83%	87%	p=0.01
GP IIb/IIIa inhibitors	31%	20%	p<0.0005
Clopidogrel	35%	30%	p=0.01

\*19,000 ACS patients treated at 300 US hospitals during 2002; †577 ACS patients admitted into Dunedin CCU in 2001–2002

Table 4 reported the comparisons with EUROASPIRE II, GRACE, CRUSADE, and the NZACS Audit. At discharge, the use of aspirin in Dunedin was the highest amongst the five registries (p<0.0005). The use of beta-blockers in Dunedin was equal to CRUSADE but higher than the other registries (p<0.0005); while the use of aspirin, statins, and beta-blockers exceeded NZACS (p<0.05).

**Table 4. Comparison of discharge medications**

Discharge Medications	DUNEDIN <sup>α</sup>	NZ ACS <sup>γ</sup> (Range of values)	EURO- ASPIRE II <sup>Ω</sup>	GRACE <sup>δ</sup>	CRUSADE <sup>+</sup>
Statins	70 %	52–62%*	43%**	47%**	77%**
Aspirin	98%	80–89%**	90%**	93%**	88%**
ACE-I/AIIA	55%	39–51%	38%**	55%	59%
Beta blocker	80%	59–70%**	66%**	71%**	80%

<sup>α</sup> 577 ACS patients admitted into Dunedin CCU in 2001-2002

<sup>γ</sup> 721 ACS patients from all hospitals in New Zealand over 2 weeks in May 2002

<sup>Ω</sup> 8,181 patients with myocardial infarction admitted into 15 European countries in 1999-2000

<sup>δ</sup> 6,312 patients from the Global Registry for ACS in 1999-2000

<sup>+</sup> 19,000 ACS patients treated at 300 US hospitals during 2002

For comparison with NZACS<sup>γ</sup>, P-value was derived from the highest value of the range:

\* P<0.05 compared to Dunedin

\*\* P<0.0005 compared to Dunedin

**Comparison of the use of revascularisation for STEMI in Dunedin with registry data**—The rate of revascularisation (coronary angiography, PCI or in-patient CABG) for patients with STEMI was higher in Dunedin than in the NZACS Audit<sup>10</sup> or GRACE<sup>11</sup> (Table 5).

**Table 5. Comparison of angiography and revascularisation rates for STEMI**

	Dunedin <sup>α</sup>	NZACS <sup>γ</sup>	GRACE <sup>δ</sup>
Coronary angiography	68%	31%**	55%**
PCI	51%	13%**	40%**
Inpatient CABG	7%	4%**	4%**

<sup>α</sup> 577 ACS patients admitted into Dunedin CCU in 2001-2002

<sup>γ</sup> 721 ACS patients from all hospitals in New Zealand over 2 weeks in May 2002

<sup>δ</sup> 6,312 patients from the Global Registry for ACS in 1999-2000

\*\* P<0.0005 compared to Dunedin

**Management of NSTEMI in Dunedin, GRACE and NZACS**—For patients with NSTEMI, the use of glycoprotein IIb/IIIa inhibitors was 37% in Dunedin, compared to 52% in GRACE/US,<sup>12</sup> 27% in GRACE/EUROPE,<sup>12</sup> and 20% in GRACE/Australasia-Canada.<sup>12</sup>

Table 6 shows higher rate of revascularisation (coronary angiography, PCI or in-patient CABG) for patients with NSTEMI in Dunedin compared to NZACS<sup>10</sup> and GRACE.<sup>11</sup> Dunedin's PCI rate (38%) was comparable to GRACE/US<sup>12</sup> (39%), GRACE/Europe<sup>12</sup> (35%) and GRACE/Latin-America<sup>12</sup> (34%). The PCI rate in GRACE/Australasia-Canada<sup>12</sup> was 25%.

**Table 6 Comparison of angiography and revascularisation rates for NSTEMI**

	Dunedin <sup>α</sup>	NZACS <sup>γ</sup>	GRACE <sup>δ</sup>
Coronary angiography	73%	25%**	53%**
PCI	38%	8%**	28%**
Inpatient CABG	21%	3%**	15%**

<sup>α</sup> 577 ACS patients admitted into Dunedin CCU in 2001-2002

<sup>γ</sup> 721 ACS patients from all hospitals in New Zealand over 2 weeks in May 2002

<sup>δ</sup> 6,312 patients from the Global Registry for ACS in 1999-2000

\*\* P<0.0005 compared to Dunedin

## Discussion

This registry study complements the NZACS audit in documenting the cardiology practice in New Zealand. Our patient population likely represents a higher risk subgroup than the NZACS Audit<sup>8</sup> conducted during the two-week period in May 2002. NZACS included all patients admitted with a suspected or definite ACS to any hospital (interventional and non-interventional) throughout New Zealand. Because Dunedin served as a referral centre for the whole Otago and Southland District, the current study had a higher proportion of STEMI (34%) than the NZACS Audit (11%). The NSTEMI rate was 41% for Dunedin and 40% for NZACS. For unstable angina the rate was 25% and 46% respectively.

**Aspirin and beta-blockers**—In Dunedin, the common use of aspirin (98%) exceeded that of NZACS (80–90%), EUROASPIRE II (90%), GRACE (93%), and the CRUSADE (88%). Our rate of prescribing beta-blocker (80%) on discharge was comparable to local and internationally published registries.

**Statins**—As of 2001-2002, statins were not fully funded in New Zealand unless the patient's condition satisfies the PHARMAC rules. The underuse of statins has also been discussed in the NZACS Audit<sup>8</sup> because clear-cut evidence of benefit has been shown in the Scandinavian Simvastatin Survival Study<sup>13</sup> and the British Heart Protection Study.<sup>14</sup>

Before 2002, PHARMAC rule for statins-use was a fasting cholesterol of  $\geq 5.5$  mmol/L despite 3 months of diet modification; or a fasting cholesterol of  $\geq 5.0$  mmol/L in patients who have undergone coronary artery bypass grafting.

In ACC/AHA recommendations in 2002 (Appendix 1), the use of statins was recommended concurrently with diet modification if LDL was  $\geq 2.5$  mmol/L, preferably commenced in hospital to ensure compliance. It is interesting to note that the use of statins in Dunedin in 2001–2002 (70% on discharge) was higher than contemporary registries such as EUROASPIRE II (43%), GRACE (47%), and NZACS (52–62%).

**Use of ACE-inhibitor / angiotensin-II-antagonist**—ACE-inhibitor has a Class I indication (AHA/ACC 1999 and 2002 Guidelines<sup>1</sup>) for patients who have a history of heart failure or anterior STEMI and a Class IIa indication in patients with mild left-ventricular impairment post myocardial infarction, regardless of symptoms (Appendix 1).

In Dunedin, the medications were used in 79% of heart failure patients and 84% of patients with anterior STEMI. The HOPE Study<sup>15</sup> has shown the benefit of ramipril in all patients with arterial occlusive disease and coronary risk factors. Following the publication of CHARM<sup>16</sup> and EUROPA,<sup>17</sup> ACE-inhibitors may be considered for all patients with coronary artery disease.<sup>18,19</sup> The PEACE Trial<sup>20</sup> however, shows that patients with stable coronary artery disease and normal systolic function treated with intensive medical therapy and appropriately revascularised would not benefit from ACE inhibitor.

From Table 4 reporting the use of discharge medications, it is worth noting that the EUROASPIRE II and GRACE registries contained only patients with STEMI and NSTEMI, and they had higher risk than patients with unstable angina who were also included in both the current study and the NZACS audit.<sup>8</sup> While concerns has been raised that the use of EBM for ACS in New Zealand in general could be suboptimal,<sup>8</sup> we found the use of EBM in Dunedin Coronary Care comparable to international practice.

**Use of revascularisation for NSTEMI**—The optimal treatment for unstable angina/non-STEMI was controversial in 2001-2002. Earlier studies like TIMI IIIb<sup>21</sup> and VANQWISH<sup>22</sup> failed to show significant benefit in an early invasive strategy in reducing cardiovascular morbidity and mortality. These earlier studies predated the use of stents and glycoprotein inhibitors. They included relatively small numbers of patients and there was only a small difference in revascularisation rate between the conservative and invasive arms of the studies.

More recent studies such as FRISC II<sup>23</sup> (2000), TACTICS TIMI-18<sup>24</sup> (2001) and RITA-III<sup>25</sup> (2002) all showed definite benefit from revascularisation in reducing recurrent ischaemia, re-infarction and re-hospitalisation. These three landmark trials were incorporated in the 2002 ACC/AHA Guidelines for NSTEMI / unstable angina<sup>2</sup> recommending routine use of early invasive revascularisation for higher risk patients. In Dunedin, a selective invasive strategy for patients with NSTEMI was used, as reflected by a high rate of inpatient routine coronary angiography (73%), PCI (38%) and coronary artery bypass graft (21%).

This rate of PCI (38%) for NSTEMI was comparable to GRACE/USA<sup>12</sup> at 40%, GRACE/Europe<sup>12</sup> (35%), GRACE/Latin-America<sup>12</sup> (34%) and higher than the GRACE/Australasia-Canada rate (25%). Of note, the rate of PCI in NZACS was 8%.

**Clopidogrel and glycoprotein IIb/IIIa inhibitors**—The indication for clopidogrel has changed in the last 5 years. The 2002 ACC/AHA Guidelines<sup>2</sup> for clopidogrel became Class I for NSTEMI / unstable angina following the CURE<sup>26</sup> study, which showed a 2.2% absolute reduction in the composite end-point of cardiovascular death, myocardial infarction or stroke in patients with unstable angina / NSTEMI over 9 months, with a 1% absolute excess risk of major bleeding.

The upstream use of glycoprotein IIb/IIIa inhibitors, concurrently with aspirin and heparin, is now universally recommended for non-STEMI / unstable angina on admission if PCI is planned. In Dunedin the use of clopidogrel (59%) and glycoprotein IIb/IIIa inhibitors (37%) in NSTEMI was consistent with the higher use of angiography and interventions.

**Primary PCI and revascularisation for STEMI**—The ACC/AHA Guidelines for PTCA in STEMI have not changed between 1999 and 2002. Only 4% of STEMI presented to our Coronary Care received primary PCI, which had a Class I indication. Dunedin Hospital does not provide a 24-hour primary PCI service. Routine deferred PCI post-thrombolysis was not recommended in the 2002 ACC/AHA Guidelines.<sup>2</sup>

Our use of deferred PCI in 40% (n=77) of STEMI patients might represent a more pharmacoinvasive approach than was recommended. GRACIA-1,<sup>27</sup> published in 2004, showed routine early catheterisation post thrombolysis (<24 hours) for STEMI is safe (without any increase of major bleeding and vascular complications) and also beneficial. There was less revascularisation for symptomatic ischaemia after discharge up to one year in the invasive group compared to the conservative group (4% vs 12%, p=0.001), although the difference in the rate of death or reinfarction was not statistically significant (7% vs 12%, p=0.07).

**Clinical implications**—The use of EBM was variable in New Zealand hospitals as reflected by the different results between the current study and the NZACS audit. However, both studies revealed room for improvement in treating ACS. The MINAP<sup>28</sup> audit database from the UK demonstrates how an ongoing national electronic audit system with feedback to clinicians could increase the prescribing rate of proven secondary therapy in ACS. By 2002–2003, after 3 years of implementation, the MINAP registry has a discharge rate of aspirin at 90%, beta-blocker 83%, ACE-inhibitor 72%, and statins 84%. These figures are quite impressive and a similar database may be set up in New Zealand to provide clinicians with treatment audits and continuous feedback to increase the prescribing of EBM.

Evidence is mounting in daily practice outside the context of clinical trials supporting the use of EBM in reducing mortality in patients with ACS. Mukherjee<sup>29</sup> showed a progressive and independent survival benefit with incremental reduction in 6-month mortality when aspirin, beta-blocker, statins and ACE-inhibitor were increasingly prescribed. One year follow up data by Schiele<sup>30</sup> demonstrated superior survival rate in patients who adhered more to EBM and revascularisation therapy following myocardial infarction, regardless of their baseline risk.

Whether the adherence to EBM and the use of more aggressive revascularisation strategy for STEMI and NSTEMI translate into better long-term outcomes in New Zealand will be the subject of future studies.

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## Appendix 1 AHA/ACC Guidelines for medical treatment of ACS<sup>1,2</sup>

	1999	2002
Aspirin	Early	Early
B-blocker	<12 hour	<12 hour
Statins		NCEP— ATP III <sup>A</sup>
	<b>Class I:</b> Dietary modification for 3 months If LDL still > 3.2mmol/L, start drug to keep LDL < 2.5 mmol/L If HDL < 0.9mmol/L, start exercise.	<b>Class I:</b> Fibrate or niacin if HDL < 1.0mmol/L <b>Class IIa:</b> Statins and diet if LDL > 2.5mmol/L and commence 24-96 hours after admission
ACE-I/AIIA	<b>Class I (CCF or &lt;24 hours post anterior STEMI)</b> <b>Class IIa</b> (mild LV impairment post MI; Asymptomatic)	<b>Class I (CCF or &lt;24 hours post anterior STEMI)</b> <b>Class IIa</b> (mild LV impairment post MI; Asymptomatic)

<sup>A</sup>Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.

**Class I:** Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective

**Class IIa:** Weight of evidence/opinion is in favour of usefulness/efficacy