



CONTENTS

This Issue in the Journal

A summary of the original articles featured in this issue

Editorials

Heart attacks and unstable angina (acute coronary syndromes) have doubled in New Zealand since 1989: how do we best manage the epidemic?

John Elliot, Mark Richards

Original Articles

Cardiovascular medications in primary care: treatment gaps and targeting by absolute risk

Natasha Rafter, Jennie Connor, Jason Hall, Rod Jackson, Isobel Martin, Varsha Parag, Stephen Vander Hoorn, Anthony Rodgers

Systematic review and meta-analysis of the risk of major cardiovascular events with etoricoxib therapy

Sarah Aldington, Philippa Shirtcliffe, Mark Weatherall, Richard Beasley

Directly eroding tobacco industry power as a tobacco control strategy: lessons for New Zealand?

George Thomson, Nick Wilson

Use of evidence-based management for acute coronary syndrome

Eng Wei Tang, Cheuk-Kit Wong, Gerard Wilkins, Peter Herbison, Michael Williams, Patrick Kay, Norma Restieaux

Special Articles

ST-elevation myocardial infarction: New Zealand management guidelines

ST-Elevation Myocardial Infarction Guidelines Group and the New Zealand Branch of the Cardiac Society of Australia and New Zealand

Non ST-elevation myocardial infarction: New Zealand management guidelines

Non ST-Elevation Myocardial Infarction Guidelines Group and the New Zealand Branch of The Cardiac Society of Australia and New Zealand

Case Reports

Severe hypothermia in association with sodium valproate overdose

Philip Robinson, Chris Abbott

Systemic side effects from topical imiquimod

Carl Hanger, Judith Dalrymple, David Hepburn

Viewpoint

Capturing data on medicines usage: the potential of community pharmacy databases

Kathleen Ryan, Pauline Norris, Gordon Becket

Special Series

Going against the flow: the impact of PHARMAC not funding COX-2 inhibitors for chronic arthritis

Rachel Grocott, Scott Metcalfe

100 Years Ago in the NZMJ

Modern medical literature

Medical Image

Acute abdominal pain and palpable mass

K Sudeep, M John

Methuselah

Selected excerpts from Methuselah

Letter

New Zealand Quality of Healthcare Study: what about hindsight bias?

Don Mackie



This Issue in the Journal

Cardiovascular medications in primary care: treatment gaps and targeting by absolute risk

N Rafter, J Connor, J Hall, R Jackson, I Martin, V Parag, S Vander Hoorn, A Rodgers

Guidelines recommend people at high risk of heart attack or stroke receive lifestyle interventions, aspirin and therapy to lower their blood pressure and cholesterol. Analysis of primary care data showed only 28% of those with a previous heart attack or stroke and 16% of those at high risk due to a mixture of factors (e.g. smoking, blood pressure, age) received both blood pressure lowering and cholesterol lowering medicines during 2000. This suggests gaps in treatment exist and will have implications for the successful implementation of guidelines.

Systematic review and meta-analysis of the risk of major cardiovascular events with etoricoxib therapy

S Aldington, P Shirtcliffe, M Weatherall, R Beasley

There has been recent worldwide interest in the cardiovascular side effects of COX-2 inhibitors. Following the withdrawal of VIOXX due to its cardiovascular toxicity, there became a need to assess the potential of the other drugs in this class for similar effects. This paper conducts an analysis on etoricoxib to establish whether a class effect exists with respect to cardiovascular side effects. The results indicate an increased risk of cardiovascular events with etoricoxib consistent with a class effect.

Directly eroding tobacco industry power as a tobacco control strategy: lessons for New Zealand?

G Thomson, N Wilson

Government policies that could reduce tobacco industry power include requiring better health warnings; more comprehensive promotion and marketing restrictions; disclosure and fire safety requirements; inquiries into the industry; limits on associations with the industry; government litigation against the industry; and mass media campaigns with anti-industry themes. This analysis examined a number of such policies used elsewhere in the world, and found that their use in New Zealand could potentially improve tobacco control here.

Use of evidence-based management for acute coronary syndrome

E W Tang, C-K Wong, G Wilkins, P Herbison, M Williams, P Kay, N Restieaux

Our study examined the use of evidence-based medications (aspirin, anticoagulation drugs, beta-blockers and ACE inhibitors) and revascularisation (angioplasty or bypass surgery) treatment for patients with heart attack admitted into Dunedin Coronary Care Unit in the years 2001-2002. While our therapies were overall consistent with international guidelines and comparable to other registries, we recognised from our data and those of the recent New Zealand Acute Coronary Syndrome Audit that there were discrepancies among different centres in the country.



Heart attacks and unstable angina (acute coronary syndromes) have doubled in New Zealand since 1989: how do we best manage the epidemic?

John Elliott, Mark Richards

While falls in age-standardised mortality have been well publicised over the last 30 years, heart disease continues to account for 30% of all deaths in New Zealand.¹ There were 5973 deaths in 2000 and 6368 deaths in 2001 due to disease of the coronary (heart) arteries. Recent surveys also suggest a large number of older New Zealanders have been diagnosed with coronary artery disease. Indeed, 40% of those aged over 75, and 30% of those aged 65 to 74, have symptoms of coronary disease.² Therefore, it is important to treat such a prevalent disease well to optimise wellbeing of (and minimise costs to) individuals, the health system, and our society.

The treatment of acute coronary syndromes (ACS) in New Zealand was audited in 2002 in a nationwide study in which data was collected on all patients presenting with suspected or definite ACS to all 36 hospitals in the country accepting such admissions.³ Over a 14-day period in May 2002, there were 721 patients with a confirmed ACS (101 were diagnosed with ST-elevation myocardial infarction, 287 with non ST-elevation myocardial infarction, and 333 with unstable angina); this translates to nearly 19,000 New Zealanders requiring treatment over 1 calendar year.

Results suggested low levels of appropriate investigations and evidence-based treatments compared with contemporary international guidelines, including revascularisation before discharge. Furthermore, treatments received varied between one region and another, and depended on whether the hospital had on-site angiography or cardiac catheterisation facilities. If there was no angiography facility on-site, the chances of having an angiogram or in-hospital revascularisation were significantly lower.⁴

In this issue of the *Journal*, New Zealand Guidelines formulated by New Zealanders for New Zealanders are published.^{5,6} These Guidelines outline appropriate standards of care for in-hospital treatment of people presenting with ST-elevation myocardial infarction (STEMI) or non ST-elevation acute coronary syndromes (nonSTEACS). There is a gap between the standards of care outlined in these guidelines and the treatments received by New Zealanders in 2002.³ Before estimating the extra resources required to close the gap, we need to know just how many New Zealanders are presenting to hospitals with STEMI or nonSTEACs each year.

Age- and gender-specific data on the incidence of ACS was extracted from an annual publication titled *Selected Hospital Morbidity and Mortality Data* for calendar years till 1995 inclusive then for financial years including 1995/96 through 2000/2001. Unpublished data for 2001/02 and 2002/03 was kindly supplied by the New Zealand Health Information Service.

Total hospital discharges

Between 1989 and 2002/2003, hospital discharges for acute myocardial infarction have more than doubled from 5496 to 11,454 per year or 31 each day in New Zealand, increasing by an average of 4% per year from 1989 to 1999/2000 then by 17% per year till 2002/2003 (Figure 1). During the same period, hospital discharges for all acute coronary syndromes combined increased by 5% per year from 14,777 to peak at 25,692 in 2000/2001 and then fell to 23,978 or 66 each day in 2002/2003 (Figure 2).

Figure 1. Hospitalisation for treatment of acute myocardial infarction (DRG 410 up to and including 1999/2000, thereafter code I21) in all New Zealanders (closed squares), men (closed circles), and women (open circles)

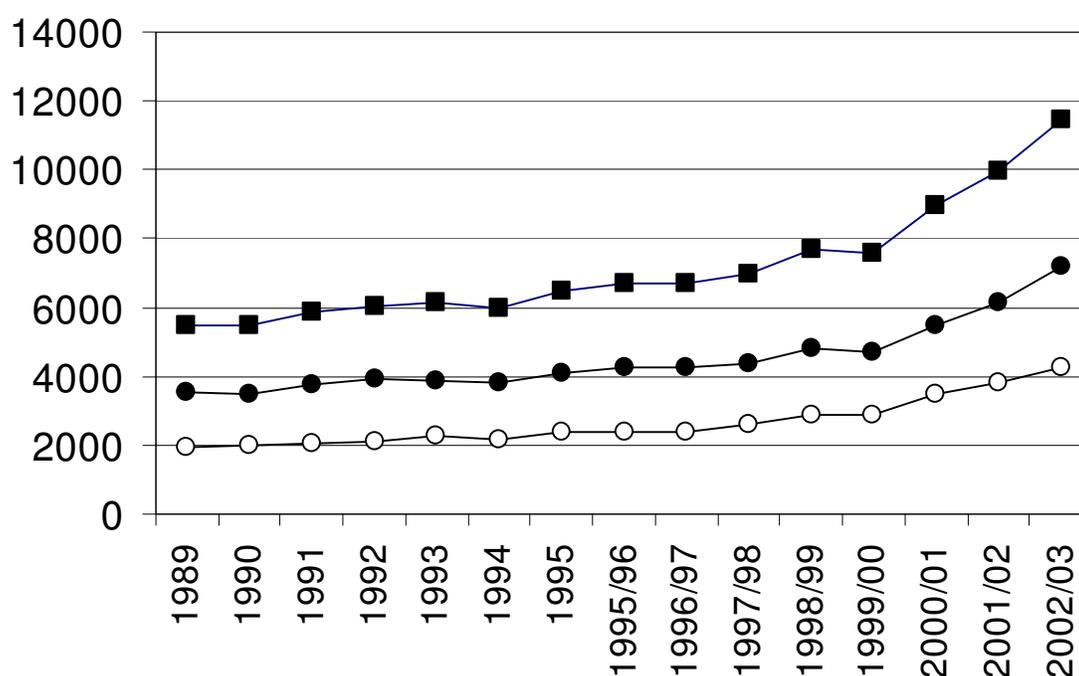
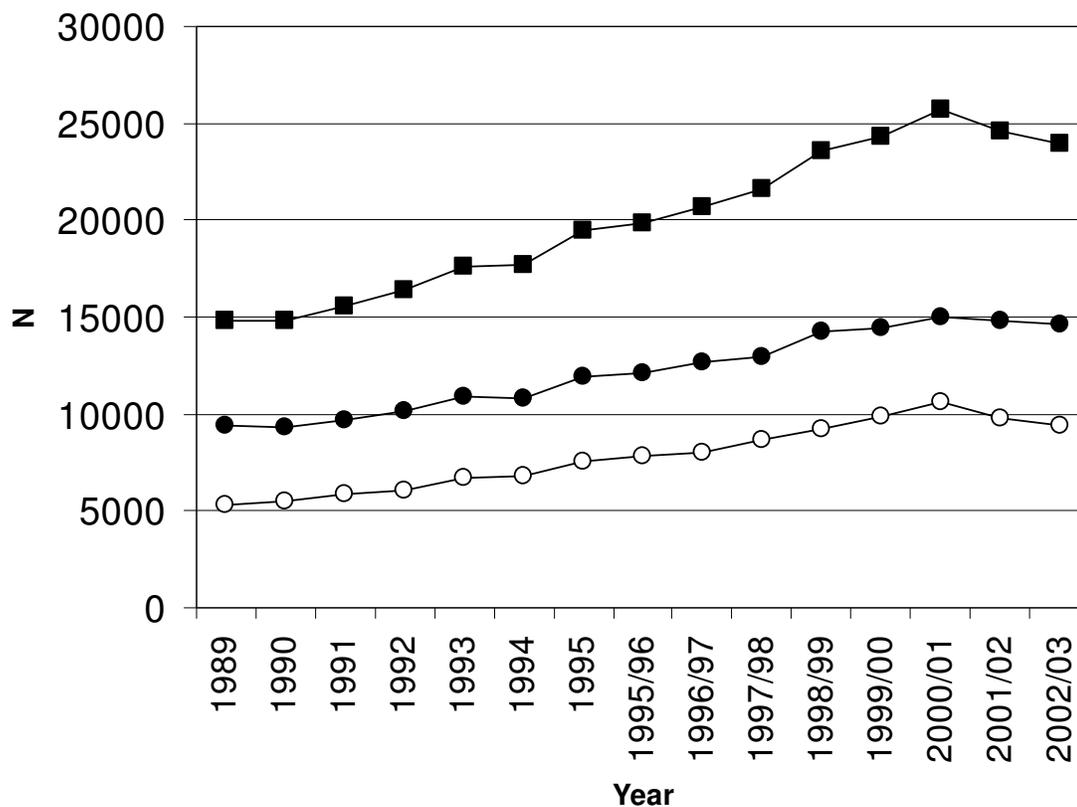


Figure 2. Hospitalisation for treatment of acute coronary syndromes in all New Zealanders (closed squares), men (closed circles), and women (open circles)



The recent accelerated increase in the number of acute myocardial infarctions (AMIs) per year may be due to changes in the definition of AMI. Rises in troponin T and troponin I are specific for myocardial cell necrosis. Guidelines for the diagnosis and treatment of AMI have been changed to incorporate the use of troponins in differentiating between AMI and unstable angina. This has increased the number of AMI diagnosed by at least 20% in the GRACE registry, a contemporary international ACS registry.⁷

The risk of death and reinfarction in the years after these “small” infarcts, with raised troponins but normal creatine kinase levels, is the same as that after “bigger” heart attacks with raised creatine kinase levels. Therefore, international guidelines have recommended that these “small” AMIs diagnosed using troponin levels should be investigated and treated in the same way as AMI with raised creatine kinase. Thus, however they are defined, all patients currently diagnosed with AMI must be considered for in-hospital angiography and revascularisation as appropriate. The redefinition of AMI in no way confounds the observed increase in total admissions for ACS (although it clearly recategorised a significant minority from unstable angina to AMI within the overall population incurring ACS).

It is not known how many of the 11,454 AMIs in 2002/2003 presented with ST-elevation and required immediate thrombolysis or direct angioplasty. The coding

system is based on primary discharge diagnosis and does not categorise AMI according to ECG changes at presentation. Also there are no discharge codes for thrombolysis, direct angioplasty, or glycoprotein IIb/IIIa inhibitors. This has two important consequences: there is no data on how many New Zealanders receive these treatments, and DHBs who choose to use these interventions do not receive any extra payment for the extra costs of evidence-based treatment in these subgroups. Coding updates that have been adopted in Australia in recent years have not been adopted in New Zealand pending reassessment of the cost implications. In the NZ ACS Audit, 26% of all infarcts presented with ST elevation.³

ACS may be increasing more rapidly in women than in men. Between 1989 and 2002/2003, AMI has increased by 102% in men and 119% in women. In 1989, 35% of AMI were in women, this has increased to 38% in 1999/2000 and 37% in 2002/03. The proportion of women with acute coronary syndromes has increased from 36% to 39%.

ACS is also increasing more rapidly in Maori and Pacific Island groups than in other New Zealanders. Between 1995/96 and 2000/2001, acute coronary syndromes overall increased by 15% per year in Maori (15% in men and women), 25% per year in Pacific Islanders (26% in men and 24% in women), and 5% per year in other New Zealanders (4.1% in men and 6.4% in women) (Figure 3).

In 1995/96, 5.5% of all New Zealanders discharged with ACS were Maori and 1.6% were Pacific Islanders, this increased to 7.2% and 2.7% in 2000/01. Discharge after treatment for AMI increased by 14% per year in Maori (17% in men and 13% in women) and 4% in other New Zealanders. In 1995/96, 5.5% of AMI were in Maori, this increased to 6.7% in 2000/01. Data on AMI in Pacific Islanders was not published.

Age and age-specific discharge rates.

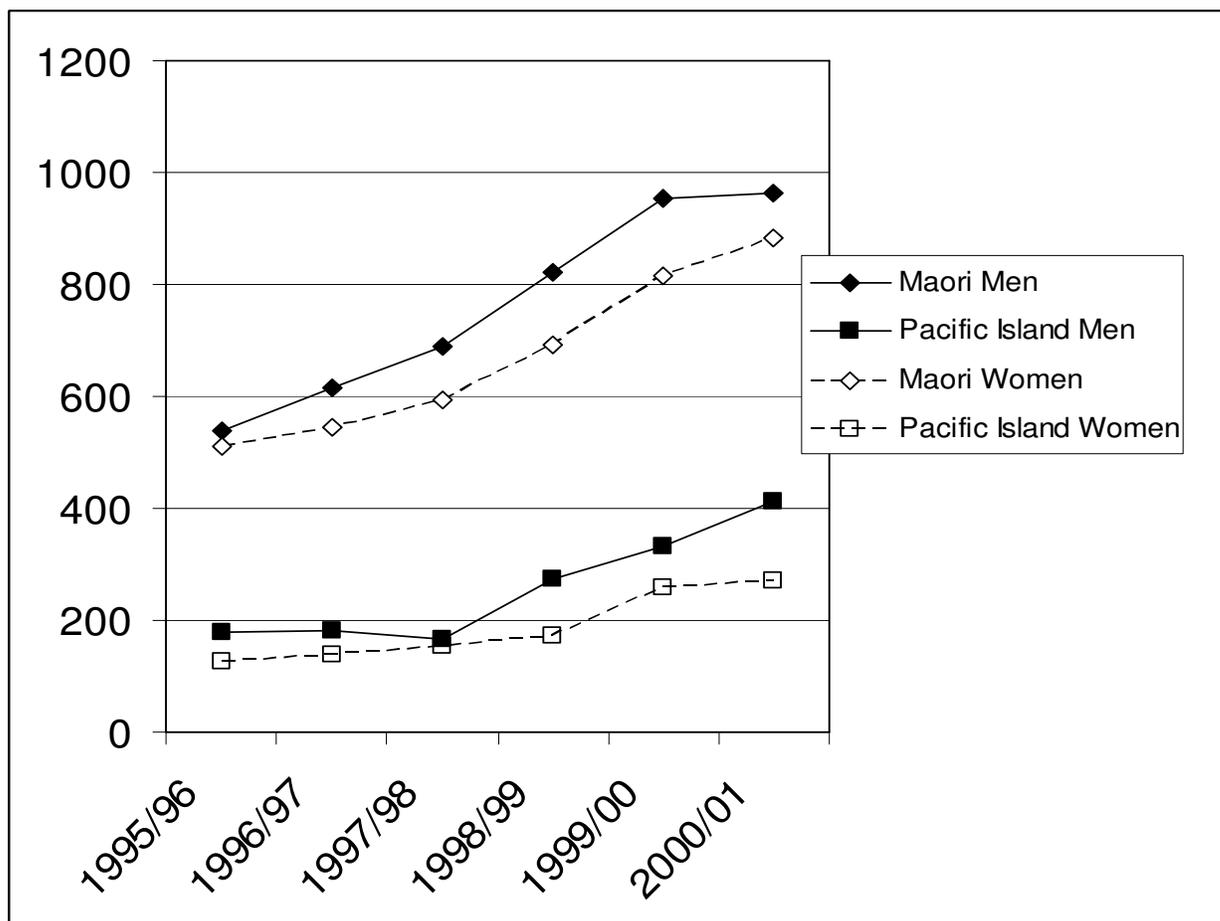
We have calculated age-specific data for ACS hospital discharges for all New Zealand men from 1991 to 2000 by adjusting increases in hospital discharges for increases in population numbers for each age group using 1991 and 2001 census data. There were increases in all age groups with the greatest absolute increase in numbers in the 65 to 74 year age group, but the largest percentage change in the age-specific discharge rates was in the youngest age group of men aged 25 to 34 years. Age-specific discharge rates increased by 2 to 3% per year in all age groups except those aged 55-64 where the increase was just over 1% per year. Similar changes were present in women. Thus the increases in numbers of patients are not confined to elderly age groups.

Implications

In 2002/2003, more than twice as many New Zealanders had a heart attack than in 1989, and 9,000 more New Zealanders were admitted to hospital with ACS than in 1989. While these data may be influenced by changes in coding systems over the last 15 years, and do not distinguish repeat admissions from first admissions, our observations suggest an epidemic in acute coronary syndromes is in progress. The aging population contributes to this epidemic but increases have occurred in men and

women of all age groups. Of further concern, increases in the incidence of ACS in Maori and Pacific Islanders appear to outstrip trends in other New Zealanders.

Figure 3 Hospitalisation with acute coronary syndromes in Maori men (closed diamonds), Maori women (open diamonds), Pacific Island men (closed squares), and Pacific Island women (open squares) from 1995/96 to 2000/01



These findings have important implications for resource allocation and planning, particularly as this increase in numbers of New Zealanders hospitalised with ACS has coincided with a wealth of evidence that supports more aggressive and invasive treatments to improve prognosis and outcomes (see Guidelines published in this issue of the *Journal*).

The cost of treating New Zealanders with “best practice” treatments, which have been available for more than 10 years, needs to be acknowledged by funders by urgently updating the coding system to include codes for such treatments. It is indefensible that DHBs are not compensated for the costs of treating patients with thrombolysis or IIbIIIa inhibitors because these proven agents have not made it into the coding system.

The lack of a code or payment for direct angioplasty for STEMI patients will impede appropriate development of such services. Pre-discharge angioplasty or bypass surgery attracts 1.84 fewer case weights or approximately \$5000 less than discharge without appropriate investigation with later elective readmission for angiography then further admission for revascularisation in those who have survived this stepwise process. The funding system is backward and broken and will hamper efforts by providers or DHBs to follow the Guidelines.

Hospital funding will also have to keep pace with the epidemic until primary prevention efforts become more effective and adverse trends in smoking in the young, and insufficient exercise as well as obesity in all age groups, are reversed.²

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Cardiovascular medications in primary care: treatment gaps and targeting by absolute risk

Natasha Rafter, Jennie Connor, Jason Hall, Rod Jackson, Isobel Martin, Varsha Parag, Stephen Vander Hoorn, Anthony Rodgers

Abstract

Aim To measure the use of three major types of cardiovascular medications (antiplatelet, blood pressure lowering, and cholesterol lowering) in primary care, and their level of targeting to individuals at high absolute risk of a cardiovascular event.

Methods Demographic, risk factor, and prescribing data from the Dunedin Royal New Zealand College of General Practitioners Research Unit database were analysed. The data set consisted of 25,384 individuals, men aged at least 45 years and women at least 55 years, who consulted a doctor in 2000 in a practice which supplied electronic clinical notes. People with congestive heart failure were excluded. Five-year risk of a cardiovascular event was estimated using a history of vascular disease or the Framingham risk equation, and correlated with prescribed medications.

Results Cardiovascular risk could be estimated for only one-third of the study population due to missing risk factor information. Data were largely unavailable on antiplatelet agents and so lipid lowering and blood pressure lowering medications were used to assess the “treatment gap”. This combination was prescribed to only 28% of those with documented cardiovascular disease. For the remainder without a history of disease and for whom 5-year absolute risk of cardiovascular disease could be estimated, prescription of combination therapy ranged from 8% in the lowest risk group (<5% 5-year risk) to 14-16% in the other risk categories.

Conclusions Among this primary care population, more than two-thirds of people with vascular disease were not receiving guideline-recommended medications and there was little evidence of targeting by absolute risk for those without disease. However limited conclusions can be made for the latter group because of lack of documented risk factor information. While these treatment gaps may be less now, for example due to increased access to statins, it is probable that substantial gaps remain.

Recent national and international guidelines recommend that individuals with a past history of cardiovascular disease receive three classes of cardiovascular medication (antiplatelet, blood pressure lowering, and cholesterol lowering), largely irrespective of risk factor levels.^{1,2} For those with no vascular history but who have a calculated 5-year cardiovascular risk of 15% or more individualised lifestyle interventions and treatment to lower all their modifiable risk factors is advised.¹

However significant treatment gaps have been shown in New Zealand and overseas studies examining single modality therapy.^{3,4} In addition, targeting by absolute risk rather than by risk factor thresholds represents a shift in paradigm for many doctors (and patients), potentially resulting in even greater gaps.

The objective of this paper was to measure the use of cardiovascular medications in primary care and establish whether prescribing is targeted to those at high absolute risk of an event.

Methods

Study population—Demographic, risk factor, and prescribing data from the Dunedin Royal New Zealand College of General Practitioners (RNZCGP) Research Unit were analysed. Their database comprises a non-random sample of general practices that contribute non-identifiable clinical data including demographic, consultation and prescription information. The study population was men aged at least 45 years and women at least 55 years, who were recorded in the RNZCGP network as consulting a general practitioner during 2000 (1 January to 31 December inclusive), and whose practice provided full computerised clinical notes.

For each patient the RNZCGP provided a unique identifier, demographics (age, sex, NZDep2001,⁵ community services card (CSC, entitles families on low to modest incomes to a subsidy on GP visits and prescriptions), high user health card (HUHC, entitles the bearer to the same subsidies as the CSC and can be applied for if a person has visited the GP 12 or more times in the previous 12 months), cardiovascular risk factor information (blood pressure and cholesterol measurements in 2000, diabetes, smoking status), past history of cardiovascular disease or congestive heart failure, and prescriptions of cardiovascular medication during 2000.

Patients were classified as having diabetes if they had a prescription for oral hypoglycaemics or insulin or a Read code diagnosis of diabetes; and as cigarette smokers if there was evidence from free text searching or Read codes of regular daily smoking or cessation within the last 12 months. The mean of the latest two systolic blood pressure, total cholesterol and high density lipoprotein (HDL) measurements in 2000 were obtained from free text searching, laboratory results and patient measurements tables. Unaggregated data could not be provided due to privacy concerns.

Identification of cardiovascular history—A cardiovascular history was defined as a history of angina, myocardial infarction, angioplasty, coronary artery bypass graft, transient ischaemic attack, ischaemic stroke, or peripheral vascular disease.¹ Congestive heart failure was not included because of its specialised management and patients with congestive heart failure were excluded from the study population.⁶

Evidence of a history of cardiovascular and/or congestive heart failure was obtained from primary and secondary care data over a five-year period (1996-2000 inclusive). The RNZCGP primary care data set was searched using Read codes and free text queries of clinical notes. Public hospital diagnoses in the form of International Classification of Disease (ICD-9) codes were obtained from the National Minimum Data Set (NMDS) using an encrypted National Health Index number to link the study population with the NMDS. Cardiovascular history as identified by diagnostic coding (Read and ICD-9) was used in the main analyses and the free text search results were included in the sensitivity analyses.

The ICD-9 codes used in the NMDS search for cardiovascular history were: ischaemic heart disease (410-414, 429.0-429.2, 429.71, 429.72, 429.9), ischaemic cerebrovascular events (433-438), and peripheral vascular disease (440-444); and for congestive heart failure history: congestive heart failure (428.0), left heart failure (428.1) and heart failure unspecified (428.9). These codes were matched to Read codes to query consultation notes in the RNZCGP data set. Free text searching was necessary because many patient records in the RNZCGP data set did not contain any Read coding. The patient notes ensuing from the free text search were scanned for prescription of a nitrate medication at any time in the previous five years and where present it was assumed that there was a positive history of cardiovascular disease. The remainder, without a nitrate prescription, were then visually scanned to determine whether cardiovascular disease was present. All of the search results for heart failure were visually scanned.

Calculating cardiovascular risk—Individuals with a cardiovascular history were classified at greater than 20% risk of a cardiovascular event over the next five years.¹ Five-year absolute risk of a cardiovascular event was calculated only for individuals without a past history of cardiovascular disease and with blood pressure and cholesterol measurements by means of the Framingham-based (Anderson⁷) risk equation, as currently used in New Zealand.^{1,8} Variables included in the equation are sex, age, systolic blood pressure, smoking, total cholesterol, HDL, diabetes, ECG left ventricular hypertrophy (LVH). The variable ECG LVH was set to zero. Estimated five-year risk was grouped into

categories: < 5%, 5 - 10%, 10 - 15%, 15 - 20%, and \geq 20%. Demographics of those with and without estimated cardiovascular risks were compared using t-tests for continuous variables and chi-squared for categorical. Analyses were performed using SAS version 8.02 software.⁹

Medication groups—Cardiovascular medicines were grouped as follows:

- Antiplatelet agents—aspirin, clopidogrel, dipyridole.
- Blood pressure lowering agents—angiotensin converting enzyme inhibitors, alpha adrenoceptor blockers, angiotensin II antagonists, beta adrenoceptor blockers, centrally acting agents, dihydropyridine calcium channel blockers, other calcium channel blockers, potassium-sparing diuretics, thiazides and related diuretics, vasodilators.
- Cholesterol lowering agents – HMG CoA reductase inhibitors (statins), fibrates, resins, nicotinic acid.

In sensitivity analyses medicines with blood pressure lowering effects (e.g. loop diuretics, long acting nitrates, and antiarrhythmics) but other primary indications were included in the blood pressure lowering group.

Assessing the treatment gap—Cross-tabulations were performed of absolute risk categories and use of one, two, or three medication types. Predictors of the simultaneous use of medications from both classes (lipid lowering and blood pressure lowering) were determined using multivariate logistic regression models. Explanatory variables included were sex, age, systolic blood pressure, smoking, cholesterol, diabetes, cardiovascular history, absolute five-year cardiovascular risk, NZDep2001, HUHC and CSC status.

Results

Twenty practices were eligible and 99,796 patients consulted these practices during the study year. Date of birth or sex was missing from the records of 865 (0.9%) patients. From the remainder, 27,184 fitted the age criteria. After excluding those with history of congestive heart failure (1,800 or 6.7%), the study population consisted of 25,384 individuals. Approximately 28% had documented cholesterol measurements (7,231 had total cholesterol and 6,937 had HDL) and 64% (16,191) had a systolic blood pressure. A quarter (5,994) of the sample population had all three of these risk factor levels documented.

Cardiovascular risk—A history of cardiovascular disease based on ICD-9 or Read codes was present in 3,855 individuals (15%). In the more sensitive strategy, which included free text searching and nitrate prescriptions, this increased to 22% (n=5,615). Absolute risk category could be calculated for 8,434 (33%) individuals, consisting of the 3,855 with a cardiovascular history and 4,579 without a history but with data on risk factors levels. Cardiovascular risk could not be calculated for 16,950 individuals (67%). Those with a cardiovascular risk score were more likely to be older, smokers, have diabetes, and be holders of CSC or HUHC (Table 1).

Medication use by absolute risk—Data were provided on cardiovascular prescriptions for 11,293 individuals. Prescriptions for one or more antiplatelet agents, blood pressure or cholesterol lowering drugs were recorded for 5%, 34%, and 10% of the study population respectively. However since many patients purchase aspirin over-the-counter it is likely that the data set did not fully capture actual antiplatelet use. Hence the main analyses are performed for prescription of blood pressure and lipid lowering medicines only.

Table 1. Demographics of those with and without a cardiovascular (CV) risk estimate

Demographics	CV risk not calculated (n=16,950)	CV risk calculated (n=8,434)
% Female	43.9	44.5
Mean age (years)	63.6	66.3*
% CSC holders	45.8	58.5*
% HUHC holders	2.8	5.7*
% Smoker	7.5	14.1*
% Diabetes	6.4	17.2*

*p<0.0001; CSC=Community Services Card, HUHC=High User Health Card—subsidised health and medicines.

The correlation between absolute cardiovascular risk and treatment is shown in Table 2 below. Overall 72-84% of those potentially eligible under current guidelines were not receiving both blood pressure and lipid lowering medications, with the lowest gap in those with a past history of cardiovascular disease. Prescribing of combination therapy was predominantly influenced by vascular history with little evidence of targeting by absolute risk. Only blood pressure medication prescribing showed an upward trend with increasing absolute risk levels. Use of combination therapy was very low for the group in whom risk was unable to be estimated.

Table 2. Proportion in each 5-year absolute cardiovascular (CV) risk group prescribed at least one medicine from each class of medication

Variable	CV history	No CV history					
		≥20%	15–20%	10–15%	5–10%	<5%	Risk not estimable
5-yr CV risk (Number in group)	≥20% (n=3855)	≥20% (n=570)	(n=515)	(n=1005)	(n=1507)	(n=979)	(n=16,950)
BP-lowering medication	67%	62%	58%	53%	44%	30%	23%
Lipid-lowering medication	33%	21%	23%	20%	21%	15%	2%
Combination (BP & lipid lowering)	28%	16%	16%	14%	14%	8%	1%

Sensitivity analyses that included additional cardiovascular medicines with blood pressure lowering capability or excluded potassium-sparing diuretics showed similar results. Using the more sensitive definition of cardiovascular history, i.e. including free text searching as well as ICD-9 and Read codes, indicated only 23% with a past cardiovascular history were receiving combination therapy.

Imputing missing values using age and sex means from the data set increased the treatment gap in those without a past history of cardiovascular disease. Individuals

with missing cardiovascular risk calculations had lower prescribing of lipid lowering and blood pressure lowering medication.

A past history of vascular disease was the strongest predictor of combination therapy; those with a history were three times more likely to be prescribed the combination compared to those with less than 7.5% 5-year risk (Table 3). There was no trend of increasing odds between the high risk ($\geq 15\%$) and moderate risk ($\geq 7.5\%$ - $< 15\%$) groups when compared with the lowest risk group in those without a past history (odds ratios 1.6 and 1.5 respectively). Having a high user health card was associated with greater provision of combination therapy. People living in the most deprived areas (NZDep2001 groups 8-10) were less likely to be on the combination than those in less deprived areas.

Table 3. Predictors of combination therapy use

Variable	Odds ratio	95% confidence interval
Cardiovascular risk		
- Past history of vascular disease	3.2	(2.7–3.8)
- 5-year CV risk $\geq 15\%$ (no past history)	1.6	(1.3–2.0)
- 5-year CV risk 7.5%–15%	1.5	(1.2–1.8)
- 5-year CV risk $< 7.5\%$	1.0	
Community Services Card holder		
- Yes	1.1	(1.0–1.3)
- No	1.0	
High User Health Card holder		
- Yes	1.4	(1.1–1.7)
- No	1.0	
NZDep2001		
- Deciles 1–4	1.3	(1.1–1.5)
- Deciles 5–7	1.4	(1.2–1.6)
- Deciles 8–10	1.0	

In a separate model increasing blood pressure levels were not predictive of combination therapy but there was a trend for increasing prescription with reducing cholesterol, although these were on treatment values and analysed independent of cardiovascular history. Males were more likely to be on the combination (odds ratio 1.4, 95% confidence interval 1.3–1.6) and there was increasing likelihood of prescription in higher age groups until 75 years and above. Smoking status and diabetes status were not predictive.

Discussion

This research shows there is a significant gap between guideline recommendations and practice in cardiovascular prevention. The large majority of people with vascular disease do not receive recommended medication. There was little evidence of targeting by absolute risk in those without disease. This research also highlights the extent of missing risk factor data in a recent primary care database.

Findings from other research have been similar. During 1999–2000 use of beta-blockers in coronary heart disease patients ranged from 47% to 88% across Europe

with persistent low use of statins (40-75%).⁴ A British survey conducted over two years from 1999 showed that less than half of women with a history of myocardial infarction or stroke were taking antiplatelet medication and only one in five were receiving a statin.¹⁰

Missing data are a significant concern and highlight the difficulty in retrieving information that is not stored in an easily accessible electronic format and is not routinely extracted. Due to resource constraints risk factor levels in one year only were searched. Cholesterol may be less frequently checked than blood pressure and this will result in selection of people with a recent cholesterol measurement. Smoking is likely to be significantly underestimated due to infrequent documenting in consultation notes and the lack of coding.

More resources and support for the development of accurate and timely primary care data collection are required on a national level in order to increase the utility of these data sets in monitoring treatment gaps. Missing data may also be due to failure to collect and/or document cardiovascular risk factors. Implementation of the New Zealand cardiovascular risk guideline provides an opportunity for consistent documentation of risk factors as part of initiatives to systematically risk assess and manage the eligible population.¹

This research examined medicines in broad classes. Cardiovascular medications prescribed during 2000 were included regardless of their actual dose and intended use. They were not analysed according to whether prescriptions were ongoing. These factors will tend to underestimate the gap. Aspirin use could not be reliably evaluated and this means the gap will be underestimated for the combination of three treatment modalities.

Further research into this area should explore ways of capturing data on over-the-counter medications. Patients who have a recent diagnosis of cardiovascular disease may be receiving their medication from specialist clinics and hence the treatment gap may be overestimated in this primary care database. The gap may also be affected by incomplete data due to patient migration to non-contributing practices and deaths early in the study year.

We did not differentiate by risk factor level in those at 15-20% 5-year risk without a history of vascular disease. In this group the presence of very low blood pressure or cholesterol levels may mean combination drug treatment aimed at all risk factors is not required. Therefore our analysis may slightly overestimate the gap, although we would expect a low prevalence of such risk factor levels in this population.

During the time period examined, access to statins was under Special Authority (restricting subsidy to individuals with cardiovascular disease and total cholesterol above 4.5-6 mmol/L or, if no history, total cholesterol greater than 9) and statin use has increased since 2000. A 2001 audit in Auckland of 147 patients with coronary artery disease found 71% were receiving statins, however this was a group recently discharged from hospital following an acute event and this high percentage is unlikely to accurately reflect chronic usage in primary care.³ The Special Authority requirement was removed in early 2002 and in 2003 statin prescribing had increased by 65%.¹¹ Nonetheless our data suggest a large treatment gap is still likely to exist since the baseline was so low.

As with any medical records-based research, the Dunedin RNZCGP Research Unit database has limitations. Doctors contributing to the database are a selected subgroup. However an investigation of biases by the Unit found the data collected to have similar patient morbidity and prescribing but reduced rates of laboratory investigation when compared to a random sample of general practitioners.¹²

There are no legal requirements in New Zealand to maintain patient records on paper in addition to those recorded on practice computers and this means that if computers are used to store practice records at all, they store more comprehensive patient data than in other countries.¹³ The Research Unit recently showed that key demographic variables such as patient age, National Health Index, sex, and health card status were very well recorded, but only 23% of consultations were Read coded and ethnicity recorded for 35%.¹⁴

In conclusion, there are large treatment gaps for cardiovascular disease. This has implications for the successful implementation of the recent New Zealand Guidelines Group guideline on management of cardiovascular risk.¹ Many different strategies, ranging from district wide programmes of risk assessment to individual education of doctors and patients about absolute risk, and initiatives to enhance primary care access and support for chronic care management out of hospital, are likely to be required to achieve widespread identification and management of those at high cardiovascular risk.

Primary health organisations may be ideally positioned to monitor these gaps through systematic approaches to risk assessment and the development of risk registers and methods of evaluating appropriate management.

Competing interests: Anthony Rodgers, Natasha Rafter, Jennie Connor, Rod Jackson, and Stephen Vander Hoorn are investigators on a randomised controlled trial of combination cardiovascular medication.

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Systematic review and meta-analysis of the risk of major cardiovascular events with etoricoxib therapy

Sarah Aldington, Philippa Shirtcliffe, Mark Weatherall, Richard Beasley

Abstract

Objective To determine the risk of thromboembolic cardiovascular events associated with the use of etoricoxib, a COX-2 inhibitor.

Design Systematic review and meta-analysis of placebo-controlled randomised double-blind clinical trials of etoricoxib that were of at least 6 weeks duration and presented data on cardiovascular thromboembolic events.

Data sources Six databases including Medline and EMBASE.

Methods The main outcome measure was cardiovascular thromboembolic events. A secondary analysis was undertaken to identify the presence or absence of predefined features that allowed determination of major cardiovascular events in a clinical trial.

Results There were five studies with a total of 2,919 subjects included in the meta-analysis. There were 7 cardiovascular thromboembolic events in 1,441 patients (0.5%) treated with etoricoxib, and 1 event in 906 patients (0.1%) on placebo. A pooled fixed effect estimate of the absolute risk difference was 0.5% (95% CI 0.1–1.0). The odds ratio for the risk of cardiovascular events with etoricoxib was 1.49 (0.42–5.31).

Conclusion The clinical trials of etoricoxib provide limited data on major cardiovascular thromboembolic events as they were neither designed nor powered to assess the potential cardiovascular risks with etoricoxib therapy. However, the limited data that were available provide weak evidence of an increased cardiovascular risk with etoricoxib consistent with a class effect for COX-2 inhibitors.

The demonstration of an increased risk of cardiovascular thromboembolic events with rofecoxib therapy has raised the important issue of whether it was specific to rofecoxib or represented an effect of the class of COX-2 inhibitors.^{1–4} In support of a class effect is the plausible biological mechanism in which COX-2 inhibition reduces the production of prostacyclin but not thromboxane which is prothrombotic.^{5,6}

In terms of other COX-2 inhibitors, valdecoxib and its prodrug parecoxib have been shown to markedly increase the risk of major cardiovascular thromboembolic events when administered following cardiac surgery^{7,8}—and the recent National Cancer Institute Celecoxib Trial has reported a similar increased risk with long-term celecoxib therapy.⁹

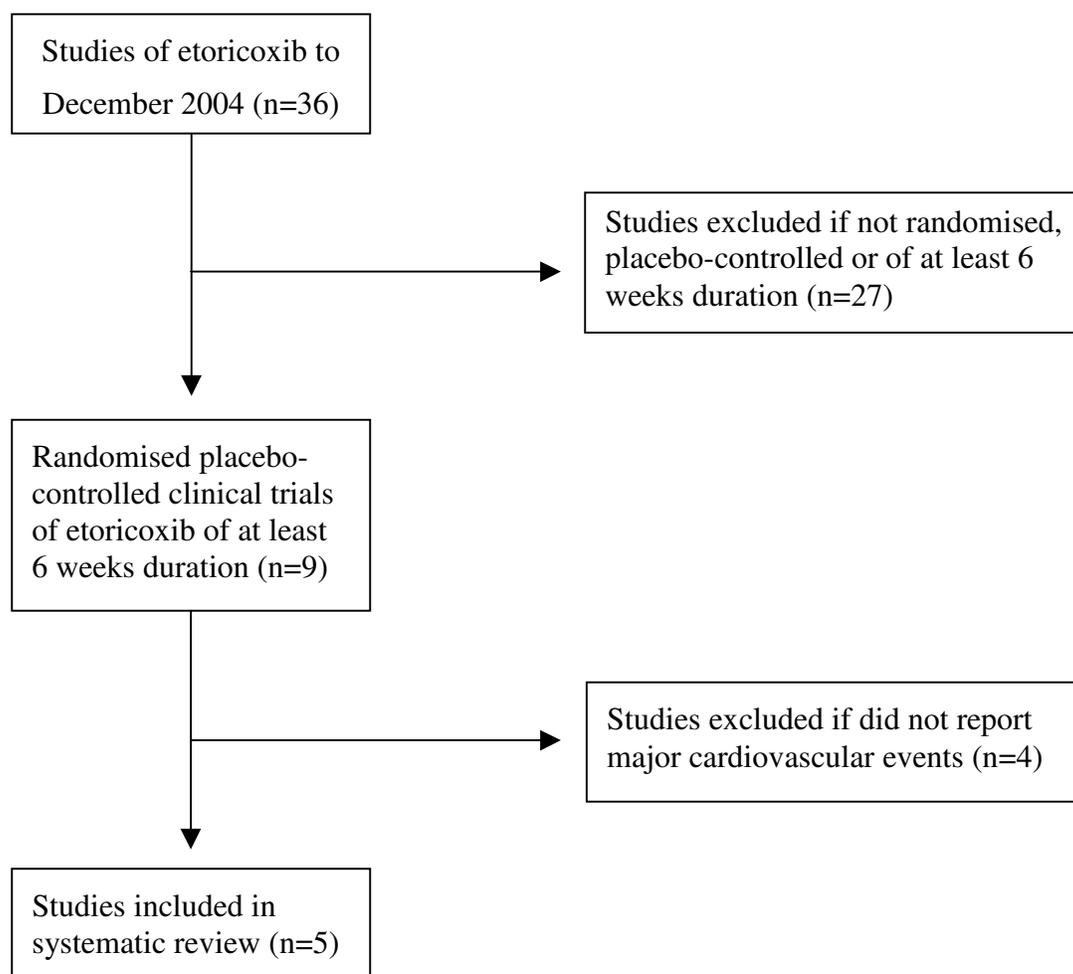
Etoricoxib has a greater COX-2 selectivity than rofecoxib¹⁰ and therefore if the cardiovascular risk seen with rofecoxib is a class effect, it should also be present with the long-term use of etoricoxib. To determine if there is an increased risk of cardiovascular thromboembolic events associated with etoricoxib therapy, we undertook a meta-analysis of all double-blind randomised clinical trials that have

compared etoricoxib with other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol or placebo.

Methods

Search strategy—A search to January 2005 of studies containing the key words “etoricoxib” or “COX-2 inhibitors and cardiovascular events” was conducted from Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ACP Journal Club, Database of Abstracts of Review of Effects, and EMBASE. Two researchers independently examined each paper for inclusion. The reference lists of relevant studies were also examined. Merck, the manufacturer of etoricoxib, was approached for details of all relevant studies; no additional data was provided. The search strategy as recommended by the QUOROM statement is shown in Figure 1.

Figure 1. Process of inclusion of studies in systematic review



Inclusion criteria—To be included in the systematic review, studies had to be randomised double-blind, controlled clinical trials of at least 6 weeks duration and report major cardiovascular thromboembolic events. The primary outcome variable was major cardiovascular thromboembolic events. The presence or absence of predefined features that allowed determination of major cardiovascular events in a clinical trial was also recorded.

Analysis—The number of subjects with cardiovascular thromboembolic events associated with etoricoxib, placebo, and non-steroidal anti-inflammatory drugs (NSAIDs) was stated. The pooled fixed effects estimates for the odds ratio for risk of cardiovascular events for the use of the active treatment

were calculated by standard methods using the inverse variance weighting method.¹¹ The I-squared inconsistency statistic was also calculated.¹² The pooled fixed effect estimate of the absolute probability difference in cardiovascular events between treatments was calculated, together with the point estimate of the number of subjects needed to harm.¹¹

Results

The systematic review included five studies with a total of 2,919 subjects (Table 1).^{13–17} Treatment was for rheumatoid arthritis,^{13,14} osteoarthritis,^{15,16} and chronic lower back pain.¹⁷ The duration of treatment ranged from 6 to 12 weeks. The doses of etoricoxib studied were 30 mg (n=102), 60 mg (n=445) and 90 mg (n=894). Data relating to 5 mg and 10 mg doses of etoricoxib, which were examined in one study, were not included as these doses are lower than the recommended dose range. Three studies included the NSAID naproxen as the comparator treatment.

There were 7 major cardiovascular thromboembolic events in the 1,441 patients (0.49%) treated with etoricoxib, including 1 pulmonary embolism, 1 deep vein thrombosis, 1 myocardial infarction, 2 unstable angina, 1 cerebrovascular accident, and 1 transient ischaemic attack.

The one major cardiovascular thromboembolic event in the 906 patients (0.11%) treated with placebo was thrombophlebitis. In one study, there were no cardiovascular events in either the placebo or etoricoxib arms,¹⁵ and in a further three studies, no events in the placebo arms.^{14,16,17} There were no cardiovascular thromboembolic events in the 572 patients receiving naproxen.

The infrequent occurrence of major cardiovascular events made a standard estimate of the pooled risk, based on the inverse variance weighting method for odds ratios, highly sensitive to the method used to deal with the zero cell counts. We used the standard method of adding 0.5 to all cell counts to give a fixed effects point estimate for all five studies. The odds ratio for the risk of cardiovascular events in the etoricoxib arm was 1.49 (0.42 to 5.31) with an I-squared statistic of 0% (0% to 45%).

Four of the five studies had at least one event in one of the arms of the trials. These studies can be used to estimate the difference in absolute probabilities of an event, and its equivalent measurement the numbers of subjects needed to harm, as shown in Table 2. The pooled fixed effect estimate of the absolute probability difference was 0.5% (0.1–1.0). This is equivalent to a point estimate of numbers needed to harm of 197 (105–1553).

Table 1. Characteristics of included studies

Study (reference)	Condition*	Duration (weeks)	Etoricoxib treatment		Comparator† treatment	
			No. of subjects	Daily dose (mg)	No. of subjects	Treatment
Collantes ¹³	RA	12	353	90	357, 181	Pl, Na
Matsumoto ¹⁴	RA	12	323	90	323, 170	Pl, Na
Leung ¹⁵	OA	12	224	60	56, 221	Pl, Na
Gottesdiener ¹	OA	6	102, 112, 112	30, 69, 90	60	Pl
Pallay ¹⁷	CBP	12	109, 106	60, 90	110	Pl

*RA=rheumatoid arthritis, OA=osteoarthritis, CBP= chronic back pain.

†Pl=placebo; Na=naproxen.

Table 2. The probability of a cardiovascular thromboembolic event with etoricoxib therapy

Study ^[Ref]	Etoricoxib events/ number of subjects	Placebo events/ number of subjects	Probability difference (95% CI)
Pallay ¹⁷	1/215	0/110	0.5 % (-0.4 to 1.4)
Matsumoto ¹⁴	2/323	0/323	0.6 % (-0.2 to 1.5)
Collantes ¹³	2/353	1/357	0.3 % (-0.7 to 1.2)
Gottesdiener ¹⁶	2/326	0/60	0.6 % (-0.2 to 1.5)

Systematic review of the individual clinical trials of etoricoxib also identified that they were neither designed nor powered to assess the potential cardiovascular risk associated with its use (Table 3).

Table 3: Characteristics of studies included in systematic review*

Item	Yes	No
Adequate sample size to determine cardiovascular events	0	5
Duration of study ≥6 months	0	5
Major cardiovascular events as stated objectives	0	5
Subjects excluded due to cardiovascular disease	4	1
Subjects on aspirin excluded	1	4
ECG pre- and post-	1	4
External board for review of cardiovascular events	4	1
Stated lost to follow up and <1%	0	5

*The presence or absence of predefined features that allowed determination of cardiovascular events in a clinical trial.

Discussion

The major finding of this systematic review was that the clinical trials of etoricoxib provided limited data on cardiovascular events as they were neither designed nor powered to assess the potential cardiovascular risks with etoricoxib therapy. The common limitations with these studies included subjects being excluded if they were pre-existing cardiovascular disease; serious cardiovascular events not being systematically investigated; an inadequate number of subjects studied; and a short study duration.

These major limitations in the etoricoxib clinical trial programme were present despite all but one study stating that it was designed to assess the safety and tolerability of etoricoxib. It is disappointing that having been alerted to the potential risks of COX-2 inhibitors with publication of the VIGOR study almost 5 years ago,² there has been such a paucity of research specifically undertaken to assess the cardiovascular risk of etoricoxib.

However the limited data that were available did provide weak evidence of an increased cardiovascular risk with etoricoxib. The proportion of patients on etoricoxib therapy with a major cardiovascular thromboembolic event was 0.5%, compared with 0.1% on placebo. This resulted in a pooled fixed effect estimate of the absolute probability difference of 0.5%. However, there were only eight major cardiovascular events overall, which severely limited the ability to determine an odds ratio for the risk of cardiovascular events using standard meta-analytic methods. This was

illustrated by the wide 95% confidence intervals for the odds ratio for the risk of cardiovascular events with etoricoxib therapy (1.49, 95% CI 0.42–5.3).

This risk of cardiovascular thromboembolic events with etoricoxib is broadly concordant with the 2.4-fold increased risk for rofecoxib also determined from a meta-analysis of randomised clinical trials.⁴ The risk is also similar to the 2.5- and 3.4-fold increased risk reported for the 400 mg and 800 mg doses of celecoxib,⁹ and the 3- to 5-fold greater risk with parecoxib/valdecoxib in the postcardiac surgery situation.^{7,8} Together these findings indicate that there is a class effect of increased cardiovascular risk with COX-2 inhibitors.

We conclude that the limited available evidence provides weak evidence of an increased risk of cardiovascular thromboembolic events with etoricoxib therapy, consistent with a class effect of COX-2 inhibitors increasing cardiovascular risk.

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Directly eroding tobacco industry power as a tobacco control strategy: lessons for New Zealand?

George Thomson, Nick Wilson

Abstract

Aims To examine some recent examples of tobacco control policies used elsewhere that seek to directly erode tobacco industry power, and to consider the relevance of these to New Zealand.

Methods A literature search was supplemented with six key informant interviews, with World Health Organization (WHO) officials, and Canadian officials and advocates.

Results The Provincial Government of British Columbia (BC) from 1997 to 2001 had an explicit objective of 'denormalising' the tobacco industry. Legal action was started against the industry to recover healthcare costs. The Canadian Government has been involved in defending its comprehensive tobacco control legislation in court against the industry since 1988. The policies to directly erode industry power, of both Canada overall and at the province level (BC), have been temporally associated with significant declines in smoking prevalence. Since 1998, WHO has conducted a series of inquiries into tobacco industry influence within WHO, and at regional and national levels. Its research and publishing focus on the industry has supported the creation of the Framework Convention on Tobacco Control, which has sections with the potential to assist national governments in strengthening strategies to erode tobacco industry power. The limitations of such strategies, and the uncertainties with using these approaches in the New Zealand context, suggests the need for careful planning and ongoing evaluation.

Conclusions Recent experience (in several jurisdictions and organisations) suggests that policies to directly erode tobacco industry power may contribute to the effectiveness of comprehensive tobacco control programmes. Some of these lessons could be incorporated into New Zealand's tobacco-control strategy.

Until the 1990s, tobacco control in many countries tended to concentrate on smoking behaviour or on protecting non-smokers, as shown by the predominance of the particular interventions used.¹ Except for some notable exceptions,²⁻⁴ attention to the control of the tobacco industry was largely limited in scope and not a particular goal in itself. Because of complex factors in different jurisdictions,⁵⁻⁷ a perspective began to emerge that saw the direct erosion of industry power as an equally important part of a comprehensive tobacco control strategy.⁸ In part, the move was towards seeing the industry as the problem,⁹ rather than the addicted smoker.

This article examines some recent (post-1997) tobacco control policies that seek to *directly erode industry power*, in contrast to those that concentrate on smoking behaviour or on protecting non-smokers. 'Directly eroding industry power' is defined as directly controlling tobacco companies' ability to operate, to hide and to obscure

their behaviour, and their ability to neglect the externalities of their products and escape responsibility for them.

In contrast, changing smoking behaviour can *indirectly* reduce industry power by reducing their profits. The approaches that directly erode industry power include requiring health warnings; promotion and marketing bans; disclosure and fire safety requirements; inquiries into the industry; limits on associations with the industry; government litigation against the industry; and mass media campaigns with anti-industry themes. New Zealand has already partly utilised the first two of these approaches.

This definition is not meant to be exhaustive, with other policies also contributing to the erosion of industry power. Many policies (such as warnings and advertising bans) will both erode industry power *and* influence smoking or protect non-smokers. There is extensive evidence of the tobacco industry's marketing and political activity as determinants of both smoking and tobacco control policies.¹⁰⁻¹²

The term 'denormalisation' is sometimes used for some parts of strategies that aim to directly erode tobacco industry power. However, when referring to the tobacco industry, the term is generally used to mean 'making the industry appear less legitimate to the public'. Our aim is to examine a far wider range of policy options around eroding tobacco industry power.

Methods

Medline, EBSCO, Proquest, Tobacco.org, and Google electronic databases were searched, using the search terms: *tobacco, industry, tobacco control, anti-industry, social marketing, denormalisation, countermarketing, legislation, litigation, inquiry, and policy*. From the literature found, we selected three recent disparate policy examples. The criteria for selection was that they were substantial and explicit policies that were intended to directly erode industry power, and had high potential relevance for the future of New Zealand tobacco control. The examples can also be considered as very brief intrinsic case studies, of interest in themselves.¹³

The examples were: British Columbia, as a case of a jurisdiction legislating to enable litigation against the industry; Canada, as a case of long-term resistance to the industry in court; and the Tobacco Free Initiative of the World Health Organization (WHO) as a case involving effective inquiries into links with the industry. To provide additional information, six interviews were conducted with officials and advocates in the cities of Geneva, Ottawa, and Victoria (British Columbia [BC]) during 2003.

Results

Actions by the Government of British Columbia

Since 1997, the Provincial Government of BC has operated a tobacco control programme with a considerable focus on directly eroding tobacco industry power. In 1997, that Government adopted two main tobacco-control strategies which were complementary:

- To prevent smoking uptake; and
- To 'denormalise' the industry.

Denormalisation is an approach which places the industry as outside normal society, because of its consistently and inherently unacceptable behaviour. At one level, it is the destruction of the industry's desired image, and its replacement by one based on the industry's adverse effects on health, equity, the economy, life and other social costs. While a subsequent and more conservative BC Government has diminished some aspects of tobacco control efforts since early 2002, much of the industry focus has continued.

From 1997, industry activity was framed as 'Big Tobacco', legal action was started against the industry to recover healthcare costs, and retail sales were further restricted from 1998 with regulations under the *Tobacco Sales Act 1994*.¹⁴ The industry was required to publicly disclose the material, additives and harmful products from each brand.¹⁵ The BC Government has legislated twice to enable the court action to go ahead (the first action was defeated by the industry on constitutional grounds).¹⁶ In 2004, it won an Appeal Court action to be able to continue the court action, and the industry's Supreme Court appeal against this was heard in June 2005.¹⁷ The BC legislation established 'the province's right of action to recover costs from tobacco companies; the province's right to pursue claims on an aggregate basis; (and) the validity of placing the onus of proof on the tobacco industry on issues where the industry has superior knowledge'.¹⁶

The litigation is paid for and controlled by the BC Provincial Health Department, ensuring that the action meets health objectives, and is also not vulnerable to the priorities of other agencies. The litigation has created free publicity, and has helped make public internal industry documents that could be used for advocacy and health promotion.¹⁸ It has also helped set the tone of political and public attitudes to, and discourse about, the industry.

Actions by the Canadian Federal Government

The aspects of the national Canadian tobacco control strategy that directly erode tobacco industry power include legal action, mandated health warnings, advertising restrictions, and research into industry activities. The industry launched a legal attack on the 1988 Canadian tobacco control legislation that banned advertising, winning a judgement against the Government in 1995 on constitutional grounds. The Government then passed a new Act in 1997 which was again challenged by the industry. In December 2002, the Government won a comprehensive victory, with the Act being upheld, including the right to require large picture warnings on packages. This judgement was very largely upheld on appeal in 2005.¹⁹

This court action required a large commitment by Government and officials over several years, with the Government defence depended on indepth research in several fields. Besides the upholding of legislation, other immediate results of the court action included evidence of document destruction and concealment by the industry.²⁰ Several other Government-initiated court cases against tobacco companies are underway in Canada.^{21,22}

This long experience of litigation appears to have produced a number of downstream effects in Canada. These include the sensitising of the public and politicians to industry misconduct, and the accumulation and use of internal tobacco industry documents.^{20,23} The willingness to confront the industry has included the passage by the Canadian Parliament of a Bill regulating the fire safety of cigarettes.²⁴

The Canadian Government has been exploring the adoption of industry denormalisation as a basic tobacco control strategy. Political considerations meant that the brief adoption of denormalisation in 1999 (as part of the official tobacco control policy at the Federal level) was followed by the suspension of the policy in 2000 and the replacement of it by a 'harm reduction' policy in 2001.²⁵ Currently, the strategy does not specifically include industry denormalisation,²⁶ despite the continued government court actions.

WHO's Tobacco Free Initiative (TFI)

In 1998, the incoming WHO management was persuaded that the tobacco industry was a threat to both WHO and to WHO tobacco control plans.²⁷ This understanding was achieved by the production of internal tobacco industry documents and by skilled advocacy. Lawyers who had just won the Minnesota case against the industry and had a grasp of the industry's pernicious and deceitful behaviour,^{28,29} helped demonstrate the need for research and action against the industry.³⁰

An independent investigation committee with indepth skills in organisational, policy, and corruption inquiries was assembled by WHO. The committee found that the industry had deliberately subverted the purposes of WHO's tobacco control programmes, by elaborate plans over many years.³¹ The report and its recommendations enabled the WHO to establish conflict-of-influence policies that would help limit tobacco industry influence.³² The report also enabled a mandate from the World Health Assembly (WHO's political masters) to 'inform Member States on activities of the tobacco industry that have negative impact on tobacco control efforts'.³³

In turn, that mandate enabled WHO's regional offices to commission regional case studies that further demonstrated the harmful effect of industry influence, (for instance in Latin America).³⁴ Further WHO inquiries are being conducted for national governments that have requested them. The results of the reports were taken out to workshops and conferences, to emphasise the need for awareness and action to limit industry influence.

The TFI has also helped point to a number of research and action needs. These included the countering of industry marketing to youth by a range of tactics, including the use of industry documents,³⁵ and research on the international activity of tobacco companies and policies to control those activities.³⁶ Examples of such research were published by the TFI. Of particular note is the report for the TFI on litigation and public inquiries as effective tools for tobacco control.³⁷

Work for the TFI was conducted in parallel with the development of the WHO Framework Convention on Tobacco Control (FCTC) and was supportive of that process. The efforts of NGOs, particularly through the Framework Convention Alliance, has been significant in supporting and enabling the success of the official FCTC process.³⁸

The FCTC may provide opportunities for governments to directly erode tobacco industry power. In particular, one part appears to give a wide obligation and mandate: '*Parties shall act [to protect public health] from commercial and other vested interests of the tobacco industry in accordance with national law*' (Article 5, section

3). This section appears to support government legislation and action to control tobacco-industry activities.

Other examples of government activity to directly erode tobacco industry power

Media campaigns that have focused on the tobacco industry have included those of California (from 1990),³⁹ Florida (from 1998),⁴⁰ the American Legacy Foundation across the USA⁴¹, Norway,⁴² and Quebec, Canada.⁴³

Government legal action continues in the USA, with the Department of Justice case against the tobacco industry.⁴⁴ The European Community has taken a legal action against tobacco companies on several issues. These include smuggling cigarettes into Iraq, in contravention of the UN embargo.⁴⁵ Elsewhere, countries such as Singapore, Thailand, and Brazil are requiring graphic health warnings on cigarette packs.⁴⁶

Inquiries into tobacco industry activity have been conducted by the United Kingdom (UK) Parliamentary Health Select Committee,⁴⁷ the UK Department of Trade and Industry (from 2000),⁴⁸ the Irish Parliament (as part of a wider inquiry, with reports in 1999 and 2001),⁴⁹ and the Australian Senate (1994), amongst others. The Australian Competition and Consumer Commission has investigated the industry to see if the terms 'light' and 'mild' were deceptive, and forced their removal from tobacco brands.⁵⁰

The possible impact of policies to erode industry power

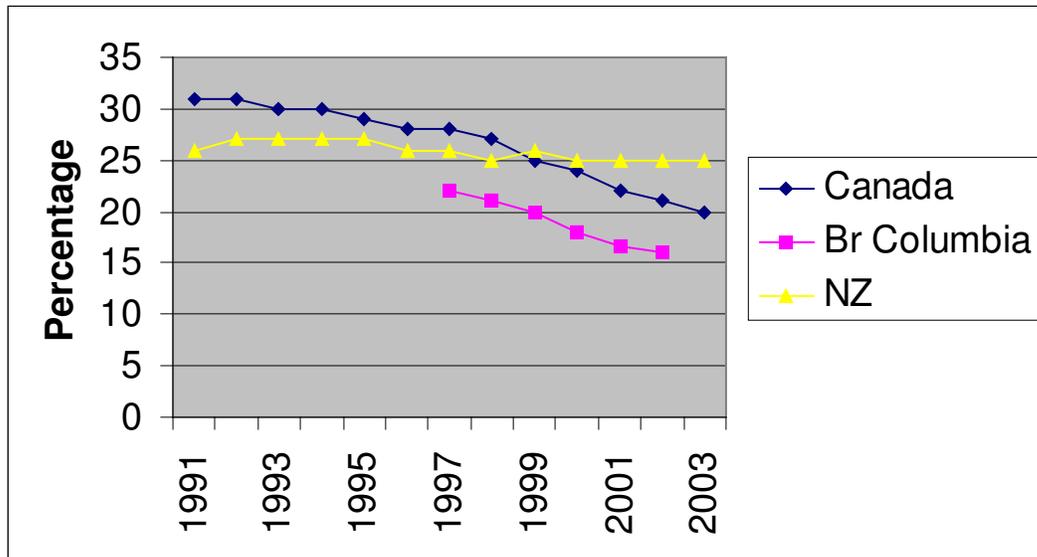
In conjunction with other tobacco-control activities at a provincial and federal level (including significant tobacco tax rises and smokefree environments policies) the BC tobacco-control strategy has been associated in time with a reduction in smoking prevalence (for the 15 years plus age group) from 22% to 15% between 1997 and 2004 (i.e. 1% per year for 7 years in absolute terms).^{51,52}

This decline is even faster than the most successful periods in California and New Zealand. In California, the greatest prevalence reduction was during 1991 to 1994, at 1% per year.⁵³ In New Zealand, smoking prevalence fell from 30% to 26% during 1987–91.⁵⁴ The health and other cost savings to government from the smoking prevalence reduction in BC were successfully used to argue for the programme's continuance. The legislative and legal focus on the industry in Canada since 1987 (part of a comprehensive tobacco control strategy) accompanied a decline in smoking prevalence from over 30% in 1991 to 20% in 2004 (for the 15 years plus age group)⁵⁵ (Figure 1).

There is disagreement about the evidence for the impact of anti-industry advertising. Goldman and Glantz have suggested that 'industry manipulation' media strategies are one of the two most effective themes in the USA.⁵⁶ Other authors have suggested caution about these conclusions.⁵⁷ Farrelly et al argue that anti-industry advertising can be highly effective in changing youth attitudes to smoking.⁵⁸ Pechmann et al suggest that the industry's deception is one of four themes that are effective in preventing youth uptake.⁵⁹ However, in a later article, they cast doubt on the effectiveness for youth of anti-industry advertisements, compared to some other tobacco control themes.⁶⁰ Three recent evaluations of 'Truth' campaigns add support to such campaigns being effective.⁶¹⁻⁶³ A review of counter-marketing programmes

indicates the difficulty for such evaluations in allowing for the effects of other tobacco control programmes and for context.⁶⁴

Figure 1: Adult smoking prevalence in Canada overall, Canada's British Columbia Province, and New Zealand from 1991 to 2003



Political commitment to policies that erode industry power

In several jurisdictions it appears that a reduction in political commitment to policies that erode tobacco industry power can limit the effectiveness of this approach. In California, the reduced commitment (for a period from 1992) blunted the effectiveness of the media campaign exposing the industry, resulting in a significant decline in the extent to which smoking prevalence was being reduced.^{39,53} Similar damage to industry-focused media campaigns occurred in Florida.⁶⁵ In British Columbia, the change to a new conservative government in 2002 was associated with the reduction of tobacco control policy staff from 18 to 3, and the halting of tobacco control mass media campaigns.

Discussion

The limitations of this analysis

This analysis is limited in the scope of the type of jurisdictions and organisations examined, and the period covered. The three main examples examined have distinctive political and other contexts, potentially limiting the value of comparisons with New Zealand. The operation of active tobacco-control policies could in each case be partly due to unique political windows of opportunity.

We emphasise that temporal associations between interventions and declines in smoking prevalence provide only weak support for causation in the absence of other evidence. Furthermore, a complicating factor with assessing the impact of an 'eroding

industry power' policy on tobacco control outcomes is that such policies are generally bundled with other components of tobacco control programmes. In particular, changes in smoking prevalence depends on the interactions and combinations of many factors within comprehensive programmes.⁶⁶

Furthermore, the gradient of the smoking prevalence decline in Figure 1 may suggest that there was no extra effect from the particular industry focus from 1997 in British Columbia on the tobacco industry, compared to Canada overall. However, it may be that the particular focus in BC contributed to the decline in smoking prevalence to continue to below 20%. The data on the smoking prevalence trend in the two jurisdictions over the next few years may help to clarify this issue.

The major themes identified

In considering the direct erosion of tobacco industry power via government policies, several principles emerge for consideration. They include the need for:

- A comprehensive approach for tobacco control;
- Effective political defences for such programmes;
- A firm research base; and
- Periodic new approaches within the industry focus theme.

Directly eroding industry power should be just one part of programmes that include appropriately high tobacco-price levels, effective smoking-cessation support, education, creating smokefree environments, research, and advocacy. Because the political commitment to a policy of eroding industry power may vary, it would be necessary to both embed that policy (by legislation, organisational, and other structural means) and to ensure that supplementary tobacco-control strategies are present. Most importantly, it would be necessary to accurately gauge public attitudes to such policies.

The experience of the WHO's TFI suggests other particular lessons. They include the value of an inquiry into industry activity, which can produce new information, sensitise policy makers and the media, and help mandate action. The experience of the WHO indicates the need for explicit and comprehensive conflict-of-interest policies to prevent industry influence of the policy process.

The process to bring the FCTC to life underlines the mutual dependence of nations in the face of the multi-national tobacco industry, and the need for seeing tobacco control as a cross-border issue. Unless nation states have the advantages of such international law, and have regional neighbours with comparative strengths in tobacco control policies, advances within states will be both more difficult, and more likely to be sidestepped by international industry activity. This is particularly relevant for New Zealand's efforts to support health and development among Pacific Island countries.

Should additional policies to erode industry power be adopted in New Zealand?

Despite the limitations of the analysis, the temporal association between the implementation of policies that erode industry power and tobacco-control outcomes (including declines in smoking prevalence) suggests that such policies need to be

considered. Furthermore, the strength of tobacco industry resistance to such approaches provides some indirect evidence that such policies benefit tobacco control.⁶⁷⁻⁷⁰ Although much of the tobacco control progress in Canada and British Columbia could be attributed to tobacco price changes, the rapid progress compared to New Zealand may have been augmented by the industry erosion policies.

Denormalising the industry may also benefit tobacco control in general, by making political support more likely and political action more acceptable. Although more research is required to clarify the issues, it would seem prudent that the New Zealand Government and NGOs continue to implement policies that erode industry power where circumstances permit and to evaluate these wherever possible. These approaches would be consistent with past New Zealand efforts to require health warnings, and to restrict tobacco promotion by tobacco companies. Sustainable new policies may also need a minimum of research and policy infrastructure, and work with WHO and with other jurisdictions to boost local, regional and international tobacco control efforts that have an industry focus.

What would the costs be of an industry focus approach? Any government that stands up to the industry risks being the focus of large hostile industry resources.⁶⁷⁻⁷⁰ However, New Zealand has a record of not only being a successful leader in adopting tobacco control legislation in the face of tobacco industry antagonism, but successfully confronting another powerful group of multinationals—the pharmaceutical industry. The New Zealand Government agency, PHARMAC, has been very effective in using legal actions to defend government policy in that area.^{71,72}

Any costs of an industry focus approach needs to be compared with the tangible costs to the New Zealand economy of tobacco industry activity, estimated at 1.7% of GDP annually, and the social cost of consequent illness and premature death.⁷³ The costs also need to be seen in the context of the low level of spending on tobacco control over the last 20 years, and the level of tobacco tax revenue gained by Government. Less than NZ\$250 million (2004 dollars) was spent on tobacco control, which was less than 2.5% of tobacco tax revenue collected during the period.^{74,75}

Would an industry approach help narrow health inequalities in the impact of tobacco use? Insofar as it may more clearly demonstrate the exploitation of disadvantaged groups (such as Maori) by a powerful industry, the approach could provide a better foundation for the rejection of that industry by those groups.

The possible options for policies to erode industry power in New Zealand

Within an increased focus on eroding industry power as part of tobacco control, the options for New Zealand include media and community campaigns about industry behaviour, requirements for better warnings on packets, industry monitoring, legal action (in court or by official inquiries), increased and more effective advocacy, and more research about industry processes, strategies, and activities. More fundamentally, an increased focus on the industry within New Zealand tobacco control could require a substantial reorientation of government and NGO processes and policies. Such a reorientation could involve all sectors of Government taking a more critical stance to the industry, and taking a deliberate strategy of distancing themselves from the industry.

The assumption by some New Zealanders that the tobacco industry is a 'legitimate' industry indicates the need for well-resourced media campaigns to fully inform the public of the risks from this industry's behaviour.^{11,76} In particular, information could be given in such campaigns on the international industry's refusal to take responsibility for its long-term denial of tobacco use risks; its continued refusal to admit to the health risks of secondhand smoke exposure; its misuse of product design; its marketing to youth; its opposition to tobacco-control measures; and its perversion of the research and political policies worldwide.^{3,4,10-12,28,29}

The possible uses of statute law to limit industry behaviour, and to make the activity more visible and understood, include legislation on marketing (for instance shop displays), on information disclosure, and to open the avenues of litigation.^{37,77} Legislation could set up a regulatory control body for tobacco control that could have powers over the manufacturers, importers, distributors, exporters and retailers.⁷⁸⁻⁸⁰ Legislation could require tobacco companies to both disclose information, and to answer questions put to them.⁸⁰

Within tobacco-control *research*, several options could be considered to enable a greater focus on the industry. These include monitoring programmes for industry marketing efforts;⁸¹ and the mapping of the associations between business and professional organisations and individuals, and the tobacco industry.⁸² Much of industry erosion efforts depend on a better understanding by both Government and NGOs of the industry, its associates, and their activities.⁸³⁻⁵

A comprehensive approach to eroding industry power

Any comprehensive strategy for a greater focus on eroding tobacco industry power within the New Zealand context may benefit from at least three features:

- The framing of tobacco industry behaviour as both an international and regional problem, where jurisdictions need to actively work on international and regional schemes to deal with the industry;
- A well-resourced plan that involves allies from a wide range of sectors, and which frames the industry as unsustainable socially and economically – a problem and liability for all sectors within the country; and
- An effective research capacity to enable the organisations concerned to have a sufficient understanding of industry processes and strategies, and to understand the arenas in which the erosion of industry power is to be achieved.

To strengthen regional and international tobacco control action, the New Zealand Government could contribute to getting the FCTC ratified in other countries (particularly those in the Pacific). NGO advocates can also encourage a greater involvement by Government in the building of the capacity to target the industry (e.g. through the programmes of the WHO's Tobacco Free Initiative). Without such international cooperation, the ultimate contribution of these industry-focus policies to global tobacco control is likely to be undermined by the capacity and coordination ability of the multinational tobacco industry.

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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.^{1,2} Data from international Registries often revealed significant differences between published guidelines and real life clinical practice in managing ACS.^{3,4}

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,¹ and
- The 2002 updated ACC/AHA Practice Guidelines² (Appendix 1); as well as with
- International & local Registry data from 1999 to 2002 including EUROASPIRE II⁵ (European Action on Secondary Prevention through Intervention to Reduce Events), GRACE⁶ (Global Registry for Acute Coronary Syndrome), CRUSADE⁷ (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 Audit⁸ (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).⁹

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 ≥ 1 mm in two contiguous leads (or ≥ 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) ≥ 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) ≥ 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 ≥ 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 ≥ 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 II⁵ 1999–2000 (N=8181), GRACE⁶ 1999–2000 (N=12,666), CRUSADE⁷ 2002 (N=19,000), and the NZACS Audit⁸ 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 ^α	NZ ACS ^γ (Range of values)	EURO- ASPIRE II ^Ω	GRACE ^δ	CRUSADE ⁺
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%

^α 577 ACS patients admitted into Dunedin CCU in 2001-2002

^γ 721 ACS patients from all hospitals in New Zealand over 2 weeks in May 2002

^Ω 8,181 patients with myocardial infarction admitted into 15 European countries in 1999-2000

^δ 6,312 patients from the Global Registry for ACS in 1999-2000

⁺ 19,000 ACS patients treated at 300 US hospitals during 2002

For comparison with NZACS^γ, 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 Audit¹⁰ or GRACE¹¹ (Table 5).

Table 5. Comparison of angiography and revascularisation rates for STEMI

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

^α 577 ACS patients admitted into Dunedin CCU in 2001-2002

^γ 721 ACS patients from all hospitals in New Zealand over 2 weeks in May 2002

^δ 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,¹² 27% in GRACE/EUROPE,¹² and 20% in GRACE/Australasia-Canada.¹²

Table 6 shows higher rate of revascularisation (coronary angiography, PCI or in-patient CABG) for patients with NSTEMI in Dunedin compared to NZACS¹⁰ and GRACE.¹¹ Dunedin's PCI rate (38%) was comparable to GRACE/US¹² (39%), GRACE/Europe¹² (35%) and GRACE/Latin-America¹² (34%). The PCI rate in GRACE/Australasia-Canada¹² was 25%.

Table 6 Comparison of angiography and revascularisation rates for NSTEMI

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

^α 577 ACS patients admitted into Dunedin CCU in 2001-2002

^γ 721 ACS patients from all hospitals in New Zealand over 2 weeks in May 2002

^δ 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 Audit⁸ 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 Audit⁸ because clear-cut evidence of benefit has been shown in the Scandinavian Simvastatin Survival Study¹³ and the British Heart Protection Study.¹⁴

Before 2002, PHARMAC rule for statins-use was a fasting cholesterol of ≥ 5.5 mmol/L despite 3 months of diet modification; or a fasting cholesterol of ≥ 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 ≥ 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 Guidelines¹) 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 Study¹⁵ has shown the benefit of ramipril in all patients with arterial occlusive disease and coronary risk factors. Following the publication of CHARM¹⁶ and EUROPA,¹⁷ ACE-inhibitors may be considered for all patients with coronary artery disease.^{18,19} The PEACE Trial²⁰ 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.⁸ While concerns has been raised that the use of EBM for ACS in New Zealand in general could be suboptimal,⁸ 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 IIIb²¹ and VANQWISH²² 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 II²³ (2000), TACTICS TIMI-18²⁴ (2001) and RITA-III²⁵ (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 angina² 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/USA¹² at 40%, GRACE/Europe¹² (35%), GRACE/Latin-America¹² (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 Guidelines² for clopidogrel became Class I for NSTEMI / unstable angina following the CURE²⁶ 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.²

Our use of deferred PCI in 40% (n=77) of STEMI patients might represent a more pharmacoinvasive approach than was recommended. GRACIA-1,²⁷ 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 MINAP²⁸ 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. Mukherjee²⁹ 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 Schiele³⁰ 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^{1,2}

	1999	2002
Aspirin	Early	Early
B-blocker	<12 hour	<12 hour
Statins		NCEP— ATP III ^A
	Class I: 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.	Class I: Fibrate or niacin if HDL < 1.0mmol/L Class IIa: Statins and diet if LDL > 2.5mmol/L and commence 24-96 hours after admission
ACE-I/AIIA	Class I (CCF or <24 hours post anterior STEMI) Class IIa (mild LV impairment post MI; Asymptomatic)	Class I (CCF or <24 hours post anterior STEMI) Class IIa (mild LV impairment post MI; Asymptomatic)

^AExpert 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

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ST-elevation myocardial infarction: New Zealand management guidelines

ST-Elevation Myocardial Infarction Guidelines Group and the New Zealand Branch of the Cardiac Society of Australia and New Zealand

Glossary

ACS	Acute coronary syndromes
ACE	Angiotensin converting enzyme
CAPTIM	Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study
ECG	Electrocardiogram
ED	Emergency department
FT	Fibrinolytic therapy
GRACIA	Grupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA) trial
IRA	Infarct related artery
LBBS	Left bundle branch block
LV	Left ventricular
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PRAGUE	Primary Angioplasty in AMI Patients From General Community Hospitals Transported to PTCA Units Versus Emergency Thrombolysis (PRAGUE-2) study
SHOCK	Should we Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction

Purpose

These guidelines apply to the management of patients with ST-elevation myocardial infarction (STEMI). The purpose of these guidelines are to provide a summary of the most up-to-date New Zealand and overseas evidence and to make recommendations based on the evidence that will lead to the best practice for patients with STEMI in New Zealand. The guidelines are aimed at all health providers who care for patients with STEMI.

For a detailed description of the levels of evidence cited in these guidelines, please see Appendix 2. These guidelines are intended for best clinical practice. Where physicians or hospitals are not able to meet the guidelines it is important that there is documentation that there have been communications between clinicians and managers clearly defining the clinical implications of any resource shortages.

Management

Sustained ST segment elevation on the electrocardiogram (ECG) in the context of an acute coronary syndrome (ACS) is usually indicative of an occluded epicardial artery. Included within this subset are those patients presenting with presumed new left bundle branch block pattern on the initial ECG.

When patients first present with ischaemic symptoms (chest pain or a surrogate) lasting for more than 20 minutes, their management (Figure 1) depends on whether ST elevation is present on the ECG or not. If the symptoms are within 12 hours, urgent reperfusion; fibrinolytic, or catheter-based reperfusion is mandatory.1++A (See Appendix 2 for explanation)

Good nursing care is a very important component of the care of patients with STEMI.

Diagnosis

The diagnosis of STEMI is defined as ST elevation of ≥ 2 mm in chest leads V_{1-3} or ≥ 1 mm in 2 contiguous leads or presumed new left bundle branch block (LBBB).

Investigations

ECGs

An ECG should be performed and reviewed immediately on first assessment. All patients with inferior infarctions must have V_3R and V_4R leads recorded to detect right ventricular infarction. Posterior recordings (V_7-V_9) should be performed if a posterior infarction is suspected.

If the initial ECG is normal, and there is a high clinical suspicion of ongoing MI, serial ECGs should be performed at 5 to 10 minute intervals and optimally continuous ST segment monitoring should be performed. ECGs should be obtained every 6 to 8 hours in all other patients until an established diagnosis has been made.**D4**

The criteria required are:

- New or presumed new ST-elevation at the J point in 2 or more contiguous leads.
- ST elevation ≥ 0.2 mV (2 small squares) in leads V_1 , V_2 , or V_3 , **or** ≥ 0.1 mV (1 small square) in other leads.

Patients who present with a history consistent with acute myocardial ischaemia and have an ECG with new or presumed new LBBB should be classified and managed as a STEMI. In this context, the presence of one of three of the following ECG criteria adds independent diagnostic value:

- ST elevation ≥ 0.1 mV in leads with a positive QRS complex.
- ST depression ≥ 0.1 mV in V_1 to V_3 .
- ST elevation ≥ 0.5 mV in leads with a negative QRS complex.

The ECG leads in which ST segment changes occur are helpful in localising the regions of ischaemia of the left ventricular myocardium and this in turn can help predict the culprit coronary artery involved:

- Anterior wall ischaemia $\rightarrow V_2$ to V_4 .
- Anteroseptal ischaemia \rightarrow Leads V_1 to V_3 .
- Apical or lateral ischaemia \rightarrow Leads V_4 to V_6 .
- Inferior wall ischaemia \rightarrow Leads II, III, and aVF.
- Posterior wall ischaemia \rightarrow ST depression in leads V_1 and V_2 with upright T waves or (more sensitively) presence of ST elevation in posterior chest leads (V_7-V_9).

Q waves:

- Development of any Q wave in leads V_1 through V_3 , **or**

- The development of a Q wave ≥ 30 ms (0.03 s) in leads I, II, aVL, AVF, V₄, V₅, V₆.
- Q-wave changes must be present in 2 contiguous leads and be ≥ 1 mm in depth.
- “Q-wave equivalent” in a posterior MI is the presence of a dominant R wave in leads V₁ and V₂.

The absence of ST elevation or a new LBBB pattern does not exclude the presence of complete epicardial coronary artery occlusion, but the benefit of reperfusion has not been demonstrated among these patients. With a posterior MI due to circumflex artery occlusion there may be marked ST segment depression in leads V₁ to V₄ associated with tall R waves and upright T waves in the right precordial leads (V₁ to V₃).

In patients with STEMI, initiation of reperfusion therapy based on the initial ECG should take priority over cardiac marker analysis. Subsequent confirmation of MI can be determined by initial and subsequent biomarker levels.

Cardiac biomarkers

Blood samples for measurement of troponin levels, which are the preferred cardiac markers for ACS,¹ should be obtained within 10 minutes of presentation.**D4**

Measurement should be repeated 6 to 8 hours later particularly if the baseline level was normal. Troponin levels assessed 8 hours after admission will detect most MIs but requires 12 hours after the onset of symptoms to detect all MIs.

Many patients who present within 3 to 6 hours of the onset of symptoms will have normal troponin and CKMB levels. Myoglobin levels will usually be elevated in these patients and maybe of clinical value to guide management when there is uncertainty about the diagnosis of STEMI particularly in patients with LBBB.

Due to its rapid rise and fall CKMB is preferred over troponin T or I (which may remain elevated for 2 weeks) for the diagnosis of re-infarction.

Troponins (which are the most specific cardiac markers), however, may be elevated in conditions other than an ACS.

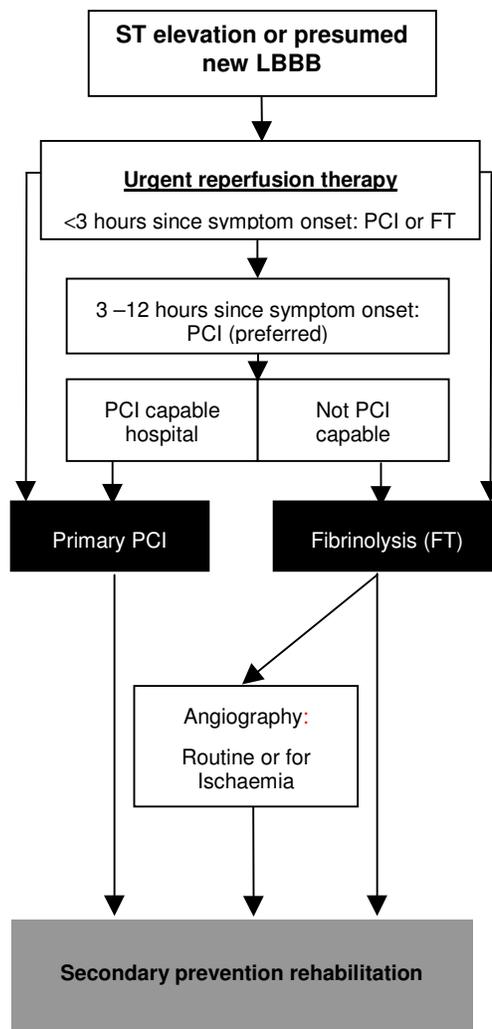
Other blood tests

Blood should also be obtained for FBC, electrolytes, glucose, liver function, renal function and lipids. A CXR should be performed (but in the absence of clinical features suggesting aortic dissection or other differential diagnoses), not before initiation of treatment.**D4**

Echocardiography

On occasions acute echocardiography demonstrating a regional wall motion abnormality may be a useful adjunct for diagnosis and assessment of complications such as ventricular septal defect, sub acute rupture and LV thrombus. In situations where left bundle-branch block is present on the initial electrocardiogram an early rising cardiac marker such as myoglobin may aid diagnosis.**D4**

Figure 1. Management of ST-elevation acute coronary syndromes



Management

Early risk stratification

There are a number of risk scores. The TIMI STEMI risk score for early risk stratification in patients with STEMI is used most commonly for predicting mortality 30 days after the MI (Table 1).² Risk assessment plays an important role in predicting patient prognosis and initiating appropriate evidence-based therapies in patients who are most likely to benefit from them.D4

Reperfusion therapy in patients with ST elevation

Urgent reperfusion of the ischaemic myocardium by restoration of flow in the occluded epicardial coronary artery is the primary therapeutic goal in patients with STEMI who present within 12 hours of symptom onset. If reperfusion therapies are initiated early after symptom onset, the infarctions are smaller, complications are

reduced and survival benefit is greater. When epicardial flow is restored within 30 minutes of occlusion infarction can be aborted.

If flow is achieved within 3 hours, considerable myocardial salvage can occur with beneficial effects on ventricular function and mortality with additional long-term benefit from the presence of an open infarct related artery (IRA). When reperfusion is achieved after 3 hours myocardial salvage is progressively reduced and recovery of ventricular function is dependant on established collateral flow. Beyond 6 hours myocardial salvage is minimal or absent with the major benefit being that related to an open IRA.³ Reperfusion can be achieved using a strategy of fibrinolysis or primary PCI. Door to balloon times should be <90 minutes.1++A

Primary PCI vs fibrinolysis

Infarct artery patency rates at 90 minutes with PCI are superior to fibrinolysis (90% vs 60%). In a recent meta-analysis of 23 trials comparing PCI to fibrinolysis (which included the SHOCK trial which compared stabilisation with immediate revascularisation for cardiogenic shock).^{4,5} PCI appeared superior in reducing short-term mortality, reinfarction, and stroke. However, for patients presenting very early after symptom onset the outcomes with fibrinolysis may be superior.

In the PRAGUE⁶ study for patients randomised to receive streptokinase within 3 hours of symptom onset, the 30-day mortality was similar to that with primary PCI. Theoretically, based on the GUSTO-1⁷ results, where patients treated with tPA had a 1% absolute reduction in mortality compared with patients treated with streptokinase, an accelerated tPA regimen could achieve a 1% lower (absolute) mortality than PCI. In the CAPTIM⁸ study patients who received (pre-hospital) fibrinolysis within 2 hours of symptom onset had improved outcomes compared with primary PCI. Thus for patients presenting <3 hours after symptom onset fibrinolytic therapy may be the treatment of choice for mortality reduction. For patients presenting >3 hours and <12 hours after symptom onset primary PCI appears to be superior and is the reperfusion therapy of choice.

The choice of strategy adopted at any given institution, however, depends on a number of factors (Table 2).

Elderly patients

The optimal reperfusion strategy in the elderly is not defined.^{7,9} In a recent re-analysis of the Fibrinolytic Trialists Enrollment Group overview of patients >75 years there was a significant 15% relative reduction in mortality equating to 34 lives saved per 1000 patients treated; larger than the 16 lives saved per 1000 in patients aged <55 years.¹⁰ Although the risk of intracranial haemorrhage increases with age, most elderly patients who suffer an intracranial haemorrhage die (and are not counted in the mortality benefit) and the risk of non-fatal strokes with major disability occurring is small.¹⁰ In patients up to the age of 84 tPA has been shown to be superior to streptokinase for reducing the composite of mortality and non-fatal disabling stroke.⁷

Choice of fibrinolytic

In the absence of contraindications (Table 3) a fibrin specific agent (tPA, TNK, rPA (see Table 4) is most effective in patients <84 years,1++A⁷ or patients previously

administered streptokinase because of formation of antibodies and concerns about lack of efficacy.^{2++B¹¹} Streptokinase is cheaper but less effective than fibrin specific agents (Table 4). If cost is an issue, streptokinase is a suitable alternative for some patients.

Streptokinase is a vasodilator and may cause hypotension in 10% of patients. This should be managed by head down tilting, with consideration to giving iv sodium chloride 0.9% 250 mL boluses x 2-3. Allergic or febrile reactions to streptokinase may also occur and should be treated with hydrocortisone 100 mg iv and/or promethazine 12.5–25 mg iv stat. For severe anaphylaxis adrenaline sc/iv should be administered (which is otherwise absolutely contraindicated in the setting of an acute MI because of the risk of VF).

If major haemorrhage occurs with either streptokinase or tPA: apply local pressure and if appropriate consider reversing the effects of heparin with protamine and administering 1–3 units fresh frozen plasma.

Monitoring

Continuous ECG monitoring should be performed during infusion of fibrinolytic therapy and 12-lead ECGs should be recorded to give assessment of ST segment recovery. These are recommended to be performed at 90 minutes and 3 hours after first starting the infusion of fibrinolytic therapy.^{D4} To obtain a peak troponin level as a guide to infarct size troponins should be measured at least twice in the 24 hours and at 24–36 hours CKMB should be measured at ≈24 hours to aid detection of reinfarction as troponin T levels remain elevated for 10–14 days.^{D4}

Adjunctive therapies

Oxygen should be administered to keep the saturations around 96% (higher doses of oxygen increase afterload via arterial vasoconstriction. Sublingual GTN and morphine should be administered for pain relief (observe BP and RR) or fentanyl. IV antiemetics should be given with morphine (metoclopramide 10 mg or cyclizine 25 mg).^{D4}

Aspirin

All patients should immediately receive aspirin 150–300 mg which should be chewed if enteric-coated and 75–150 mg continued indefinitely (if there are no contraindications). This recommendation is based on the collaborative meta-analysis of randomised trials of antiplatelet therapy showing no relation of dose with efficacy¹² and information from other studies showing increased bleeding with increasing aspirin doses.^{1++A¹³}

Clopidogrel

Administration of clopidogrel should be considered at presentation in all patients with STEMI. For patients treated with fibrinolysis who are <75 years it is recommended that a loading dose of 300 mg followed by 75 mg daily be given for 2 weeks.¹⁴ For patients over 75 years receiving fibrinolysis or patients of any age not receiving fibrinolysis, consideration should be given to commencing 75 mg of clopidogrel at presentation and continued for 2 weeks.^{1++A¹⁵}

For patients undergoing primary PCI clopidogrel can be given (with a loading dose of 300 mg–600 mg) at presentation or after defining the coronary anatomy and continued for up to 12 months depending on the type of stent used.^{1+A}

Clopidogrel is relatively expensive but several studies have shown it to be cost effective.^{16–18} It is not currently funded except for patients undergoing stenting.

Table 1. Risk stratification of STEMI patients using the TIMI – STEMI risk score² (*Referenced to average mortality [95% confidence intervals])

TIMI Risk Score for STEMI	
History	
Age 65–74	2 points
•75	3 points
Diabetes, hypertension or angina	1 point
Examination	
SBP <100	3 points
HR >100	2 points
Killip II-IV	2 points
Weight <67 kg	1 point
Presentation	
Anterior STE or LBBB	1 point
Time to treatment >4 hours	1 point
Risk score = Total	(0-14)
Risk Score	Odds of death by 30D*
0	0.1 (0.1-0.2)
1	0.3 (0.2-0.3)
2	0.4 (0.3-0.5)
3	0.7 (0.6-0.9)
4	1.2 (1.0-1.5)
5	2.2 (1.9-2.6)
6	3.0 (2.5-3.6)
7	4.8 (3.8-6.1)
8	5.8 (4.2-7.8)
>8	8.8 (6.3-12)

Table 2. Preferred reperfusion strategy for STEMI

Primary PCI preferred	Thrombolysis preferred
Primary PCI capable catheterisation laboratory available (ED to balloon time <90 minutes, appropriate operator and team experience)	Primary PCI capable catheterisation laboratory not available
Duration of symptoms \geq 3hours	Duration of symptoms <3hours (and delay to laboratory)
Cardiogenic shock	
Significant heart failure Killip \geq 3	
Contraindications to fibrinolysis (Table 3)	Difficult vascular access

Table 3. Contraindications to fibrinolysis

<p>Absolute contraindications</p> <ul style="list-style-type: none"> • Any prior intracranial haemorrhage • Known structural cerebral vascular lesion • Known malignant intracranial or spinal neoplasm or arteriovenous malformation • Ischaemic stroke within 6 months • Neurosurgery within 6 months • Suspected aortic dissection • Active bleeding or bleeding diathesis (excluding menses) • Significant closed-head or facial trauma within 3 months • Uncontrolled hypertension on presentation (SBP >180 mmHg or DBP >110 mmHg) • Recent internal bleeding within 6 weeks • Major surgery or major trauma <2 weeks
<p>Relative contraindications</p> <ul style="list-style-type: none"> • Transient Ischaemic Attack <6 months • Traumatic cardiopulmonary resuscitation <2 weeks • Non compressible vascular puncture • Pregnancy • Active peptic ulcer • Current use of anticoagulants with an international ratio >2: the higher the INR, the higher the risk of bleeding

Table 4. Fibrinolytic agents

Variable	Streptokinase	Alteplase tPA*	Retepase rPA	Tenecteplase TNK-tPA
Molecular weight	47,000	70,000		
Administration	Infusion (1.5 MU over 30 minutes)	Infusion (weight based up to 100 mg over 90 minutes)	10 units over 2 min repeated after 30 minutes	Weight adjusted bolus 30-50 mg over 5-10 seconds
Fibrin specific	No	Yes++	Yes+	Yes+++
Systemic fibrinogen depletion	+++	+	++	Minimal
Bleeding (non-cerebral)	+++	++	++	+
Haemorrhagic stroke	+	++	++	++
Antigenic	Yes	No	No	No
Hypotension with administration	Yes	No	No	No
TIMI grade 3 flow at 90 minutes (%)	32	54	60	63
Cost	+	++	+++	++++

*Bolus 15 mg infusion 0.75 mg/kg over 30 minutes (maximum 50 mg), then 0.5 mg/kg not to exceed 35 mg over the next 60 minutes to an overall maximum of 100 mg

Antithrombotic therapy

Heparin

Adjunctive heparin therapy is recommended to be administered immediately with tPA and as an option with streptokinase. (Some hospitals may prefer not to use heparin with streptokinase particularly if patients are elderly and/or have a small inferior MI).

The dose of heparin has recently been adjusted downwards because of concerns about the risks of intracranial haemorrhage with fibrinolytic therapy and a bolus of UFH of 60 units/kg (maximum 4000 units) followed by an infusion of 12 units/kg/h (maximum 1000 units/h) with the infusion rate adjusted according to the APTT at 3h and the heparin infusion adjusted to achieve an APTT of 50-70sec is used.¹⁹ The infusion should continue for 48 hours.

Bedside APTTs are strongly preferred because of the immediate availability of the result. Other antithrombotics such as enoxaparin, fondaparinux and bivalirudin are currently being tested in clinical trials.

Glycoprotein IIb/IIIa inhibitors

These are not recommended with fibrinolytic therapy. For PCI and stenting abciximab is recommended.²⁰

β-blockers

IV β-blockers are recommended to be considered for administration immediately or following initiation of fibrinolysis in patients who are haemodynamically stable without heart failure (Killip III or IV) and without contraindications (asthma, systolic BP <110 mmHg, heart rate <50 minutes, Mobitz Type II 2nd degree or 3rd degree heart block)²¹ and oral therapy continued indefinitely—e.g. metoprolol 5 mg IV bolus every 2 minutes up to 15 mg followed 15 minutes later by 50 mg orally or atenolol 10 mg IV bolus followed 15 minutes later by 50 mg orally. For patients with heart failure it is recommended that β-blockers (carvedilol or metoprolol) be begun when the patient is stable for 24-48 hours.^{22,23}

ACE inhibitors

All patients with evidence of heart failure, anterior infarction or a history of previous infarction should be considered to receive oral ACE inhibitors beginning 2 hours after admission if the systolic BP is >100mmHg usually commencing with a low dose of a short acting drug and then increasing over several days to maximally tolerated doses.^{24,25} In all other patients ACE inhibitors are recommended to be begun on day 1 and continued long term.^{1++A}

If a choice has to be made between β-blockers and ACE inhibitors because of hypotension, ACE inhibitors are the preferred initial therapy (because of their effect on remodelling). If patients are intolerant of ACE inhibitors they should be started on an angiotensin receptor blocker.²⁶

Lipid modifying therapy

Initiation of statin therapy should be begun in-hospital (e.g. simvastatin 40 mg or atorvastatin 80 mg) with an aim to reduce the LDL to 1.6 mmol/L.1++A²⁷⁻²⁹

Nitrates

Nitrates are appropriate for the control of angina and hypertension.D4

Calcium channel blockers

There is no evidence that calcium antagonists improve prognosis following myocardial infarction, but they can be used for symptomatic angina in combination with a beta-blocker. Heart rate limiting calcium channel blockers are preferred if patients cannot tolerate a beta-blocker e.g. verapamil or diltiazem.1-B³⁰

Warfarin

Patients with pedunculated or mobile left ventricular thrombus should be anticoagulated for 3-6 months with repeat echocardiography at this time to determine if continuation of anticoagulation is appropriate. Anticoagulation of patients with low ejection fractions and no LV thrombus is controversial and treatment should be individualised. There is no need to anticoagulate patients with transient AF (<24 hours). Anticoagulation and rate control may be preferred for patients with AF and other risk factors (over 60, hypertension, diabetes, heart failure, EF \leq 35%, prior thromboembolism, persistent atrial thrombus) rather than anticoagulation for 3 weeks, and cardioversion (or TOE guided), although for younger patients this may be appropriate. Ongoing warfarinisation may still be appropriate for some patients who are initially returned to sinus rhythm.1++A

Failed fibrinolysis

In patients with continuing ischaemia or haemodynamic instability, after lytic therapy, rescue PCI should be undertaken as soon as possible.D4 Lack of resolution of ST segment elevation by 30% of baseline at 90 minutes is also considered to be indicative of failed reperfusion but has less evidence for its support as an indication for rescue PCI.

Stenting and adjunctive devices for PCI

Stenting is recommended. Drug eluting stents are indicated in small vessels, long lesions, bifurcation or ostial lesions, bypass grafts and patients with diabetes.1++A

Rotablation is recommended for fibrotic or heavy calcified lesions that cannot be adequately dilated before stenting.D4

Distal protection devices are indicated for use in saphenous vein grafts and where there is a high thrombus load.1++A Randomised trials are testing these devices. Other approaches such as aspiration systems are also being tested.

Facilitated PCI

Facilitated PCI is defined as planned PCI soon after fibrinolysis. A number of trials are investigating various fibrinolytic and glycoprotein IIb/IIIa regimens. These approaches cannot be recommended at present.

Angiography in patients who have received thrombolytic therapy

There are two approaches. One is ischaemia-driven if ischaemic symptoms or ischaemic ECG changes occur despite medical therapy or ischaemic changes occur during exercise stress testing or pharmacologic or stress echo imaging. This is the most common approach in New Zealand.

The other approach is to perform angiography in all patients who would be candidates for revascularisation. Routine angiography and PCI as appropriate on significant stenoses may provide prognostic information and enable patients to be discharged home early and reduce ischaemic events post discharge.^{D4} This approach is supported by the GRACIA 1 trial where an invasive strategy within 24 hours (median 16.7 hours) of thrombolysis, compared with an ischaemia guided strategy resulted in a lower incidence (9% vs 21%) of the primary end-point of the combined rate of death, reinfarction or revascularisation at 1 year and there was a trend for a reduction in death and MI, 7% vs 12% (RR 0.59, 0.33–1.05).³¹ There are a number of ongoing trials evaluating the most appropriate timing for angiography.

Surgical revascularisation (CABG)

The success of PCI and fibrinolysis for STEMI has meant that the need for urgent surgical reperfusion is limited to a very few select circumstances although it may be used as the primary reperfusion strategy in 2-5% of patients with STEMI:

- Failed PCI (primary or rescue) with ongoing symptoms and/or haemodynamic compromise.
- In patients who require surgical management of severe mitral regurgitation due to ischaemic papillary muscle rupture or repair of ventricular septal rupture, or sub acute rupture.
- Patients who are unsuitable for fibrinolysis or PCI who have persistent or recurrent ischaemia refractory to medical therapy.
- Patients <75 years (and selected older patients without important comorbidity) who develop cardiogenic shock within 36 hours of STEMI, have left main or severe 3 vessel coronary artery disease and can undergo CABG within 18 hours of the development of shock.⁵
- Patients with $\geq 50\%$ stenosis of the left main stem. This may change with increasing experience with left main stem PCI.

Diabetes mellitus

Diabetics are a high-risk group and all patients with a blood glucose >11 mol/L and a suspected or definite MI or unstable angina with an Ischaemic ECG should be treated aggressively with an insulin, glucose and potassium regimen.³² There are several appropriate regimens. At this stage without a clear optimal strategy, local units are advised to discuss this therapy with colleagues, and to institute a local policy.**1-A**

Complications of myocardial infarction

The majority of deaths in hospitalised patients with STEMI are due to LV pump failure and mechanical complications. Compared to the pre-reperfusion era, ventricular tachyarrhythmias are now less common.

Mechanical complications

A number of mechanical complications may occur including Mitral regurgitation, ventricular septal defect and free wall rupture—all of which require urgent echocardiography, and may require urgent insertion of an intra aortic balloon pump and often an urgent surgical consultation.

Arrhythmias

Ventricular or atrial arrhythmias are frequent. Local CCUs have standard protocols for treatment.

Ongoing ischaemia

If patients have ongoing ischaemia (an ECG should be obtained during symptoms to document the degree and extent of ischaemia) expeditious angiography should be considered.

Other complications

Delayed complications include post myocardial infarction syndrome and Deep Vein Thrombosis/Pulmonary Embolism.

Cardiogenic shock

The presence of shock due to left ventricular dysfunction following MI implies ischaemia/infarction of a large area of myocardium and is associated with 70–80% in-hospital mortality. Shock is defined as hypotension (BP \leq 90 mmHg or requiring inotropes to keep the BP $>$ 90 mmHg for 30 minutes) unresponsive to fluid loading and usually with associated decreased tissue reperfusion and decreased urine output. The SHOCK trial has shown that mortality is reduced to ~50% when aggressive support measures including administration of fibrinolytic therapy, intra aortic balloon counter-pulsation, mechanical ventilation and early revascularisation are performed.⁵ In patients without important comorbidity the interventional team, including an anaesthetist should be contacted immediately and oxygen, appropriate ventilation and inotropic support should be begun immediately and emergency angiography should be undertaken.1++A For patients where PCI is not appropriate, surgery should be considered.1++A³³

Heart failure

Furosemide should be given to decrease breathlessness. All patients should be placed on evidence based therapies including ACE inhibitors,²⁴ spironolactone^{34,35} and β -blockers.^{22,23} If patients are intolerant of ACE inhibition an ARB should be prescribed.1++A Enoxaparin 50 mg/day should be given to prevent deep vein thrombosis and pulmonary embolism.1+A Digoxin should be considered for patients

in sinus rhythm who continue to be symptomatic as it has been shown to decrease rehospitalization.**1+A**³⁶

Right ventricular infarction

Right ventricular infarction is usually diagnosed clinically or by ST elevation in right precordial ECG leads or on echocardiography. Patients may have raised jugular venous pressure, hypotension and clear lung fields. It is important that all patients get adequate fluids—i.e. at least 2 litres in the first 24 hours. If patients are hypotensive a fluid challenge should be given—e.g. 200 mL of IV saline over 10–15 minutes. Swan Ganz catheterisation may help monitor volume status.**4D**

Reinfarction

Approximately 2–6% of patients experience reinfarction in hospital and this is associated with increased mortality and more frequent heart failure, cardiogenic shock and ventricular arrhythmias. Urgent PCI should be considered. In hospitals without PCI facilities readministration of a fibrin-specific agent (50% of dose in first 24 hours) should be considered, followed by urgent transfer for PCI.**1+A**³⁷

Testing for inducible ischaemia

All patients who have not had angiography or have had incomplete revascularisation should undergo testing for inducible ischaemia—e.g. by treadmill, stress echo, or nuclear imaging prior to hospital discharge.**D4**

Echocardiography

Pre-discharge assessment of left ventricular function is necessary to assess left ventricular function in all patients if this has not been assessed by other means.**D4**

Holter monitoring

Routine Holter monitoring is not recommended.**D4**

Resource availability

It is recognised that in New Zealand there are limitations on resources. Pharmacoeconomic analyses are planned to determine the appropriate levels of funding in New Zealand for patients with STEMI.

Rehabilitation

All patients should be referred to the Rehabilitation Service and be encouraged to attend rehabilitation programmes, to stop smoking, undergo regular exercise, (30 minutes of brisk walking or equivalent on most days of the week), to achieve ideal weight, and to have a cardioprotective diet, and to aid compliance with medications.**1++A**

Advice about return to work and sexual activities should be tailored to the individual patient. The National Heart Foundation of New Zealand has several excellent patient information brochures. For driving guidelines, refer to page 56 of the “Medical Aspects of Fitness to Drive” book issued by the Land Transport Safety Authority.

Conclusion

It is very important that patients with STEMI receive some form of reperfusion therapy as quickly as possible along with the other evidence based therapies and that access across New Zealand be equitable, particularly for Maori. These guidelines are the evidence base for best practice management of patients with ST-elevation acute coronary syndromes.

Author information: ST-Elevation Acute Coronary Syndrome Guidelines Group (refer to Appendix 1 below), nationwide; The New Zealand Branch of The Cardiac Society of Australia and New Zealand, Wellington.

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Appendix 2

LEVELS OF EVIDENCE



1++	High quality of meta-analysis, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is casual.
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is casual.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not casual.
3	Non-analytic studies—e.g. case reports, case series.
4	Expert opinion.

Following assessment of the level of evidence for individual papers, recommendations were given a grade from A to D as below. This grading system departs from the Scottish Intercollegiate Guidelines Network (SIGN) system which was derived primarily for treatment guidelines and revises ranking according to therapy or prognosis. Questions relating to prognosis were considered a feature of this guideline to determine how to tailor cardiac rehabilitation services according to individual patient needs. For further details on the SIGN system see www.sign.ac.uk.

Grades of Recommendation	
A	<p>For therapy: At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, OR</p> <p>A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.</p> <p>For prognosis: At least one meta-analysis, systematic review, or large high quality cohort study rated as 2++ and directly applicable to the target population, OR</p> <p>A body of evidence consisting principally of studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results.</p>
B	<p>For therapy: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results, OR</p> <p>Extrapolated evidence from studies rated as 1++ or 1+.</p> <p>For prognosis: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results.</p>
C	<p>For therapy: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, OR</p> <p>Extrapolated evidence from studies rated as 2++</p>
D	<p>Evidence levels 3 or 4, OR</p> <p>For therapy: Extrapolated evidence from studies rated as 2+, or expert opinion.</p>



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Non ST-elevation acute coronary syndromes: New Zealand management guidelines

Non ST-Elevation Acute Coronary Syndrome Guidelines Group and the New Zealand Branch of the Cardiac Society of Australia and New Zealand

Glossary

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndromes
AHA	American Heart Association
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CREDO	Clopidogrel for the Reduction of Events During Observation
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
ECG	Electrocardiogram
ESC	European Society of Cardiology
FRISC-II	Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease
hsCRP	High sensitivity C-reactive protein
HPS	Heart Protection Study
ICTUS	Invasive versus conservative treatment in unstable coronary syndromes
IHD	Ischaemic heart disease
ISAR	Intracoronary Stenting and Antithrombotic Regimen trials
LMWH	Low-molecular weight-heparin
LV	Left ventricular
MI	Myocardial infarction
NSTEACS	Non ST-elevation acute coronary syndromes
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PCI	Percutaneous coronary intervention
RITA	Randomised Intervention Trial of Unstable Angina (RITA-3)
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial
TACTICS	Treat Angina With Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction
TNI	Troponin I
TNT	Troponin T
UFH	Unfractionated heparin

Purpose

These guidelines apply to the management of patients with non-ST elevation acute coronary syndromes (NSTEACS). The purpose of these guidelines is to provide a summary of the most up to date New Zealand and overseas evidence and to make recommendations based on the evidence that will lead to the best practice for patients with NSTEACS in New Zealand. The guideline is aimed at all health providers who care for patients with NSTEACS.

These guidelines are based on the Cardiac Society of Australia and New Zealand (2000) Guidelines on the Management of Unstable Angina¹ as well as a meeting held in Queenstown in May 2001, to which doctors from every major New Zealand hospital, recommended by the Head of Department, were invited to attend. The aim of

this meeting was to discuss the management of patients with NSTEMACS, to define guidelines and to develop a New Zealand Audit. The meeting was initiated by the Cardiac Society of New Zealand with a Grant from Roche Pharmaceuticals. The choice of content of the meeting and the organisation was completely independent.

For a detailed description of the levels of evidence cited in this guideline please see Appendix 2. These guidelines are intended for best clinical practice. Where physicians or hospitals are not able to meet the guidelines it is important that there is documentation that there have been communications between clinicians and managers clearly defining the clinical implications of any resource shortages.

Early risk stratification

Introduction

Risk assessment of patients with NSTEMACS plays an important role in predicting patient prognosis. This also enhances the cost-effectiveness of patient care by enabling evidence-based treatments including antiplatelet, antithrombotic, and revascularisation therapies to be targeted at the patients who are most likely to benefit from their use. The clinical history, examination findings, electrocardiographic changes, and blood levels of cardiac marker and troponins are all critical factors in determining risk.²⁻⁹

Risk assessment should be considered a dynamic process and patients should be assessed when first seen, after several hours, 6–8 hours, 24 hours and prior to discharge. The presence of continuing symptoms and response to therapy are important in risk assessment. Refractory ischaemia or evidence of ongoing (including silent) ischaemia on electrocardiogram (ECG) monitoring should mandate early angiography. Risk assessment may be enhanced by determining the number and severity of flow-limiting coronary artery stenoses and the presence or absence of left ventricular impairment. Risk assessment in patients with NSTEMACS allows prediction of the low, intermediate or high risk of death or nonfatal myocardial infarction (MI) and particularly the risk of events occurring in the short term.

The important features contributing to risk assessment are shown in Table 1. Various risk scores can also be used—e.g. The Thrombolysis In Myocardial Infarction TIMI risk score (Table 2).¹⁰

Measurement of markers of myocardial necrosis, inflammation, and natriuretic peptides

Cardiac markers

In patients presenting with symptoms within the last 24 hours suggestive of acute myocardial ischaemia cardiac troponins T or I have the best sensitivity and specificity for the diagnosis of MI and these are the markers of choice.^{11,12} In both short- and long-term follow-up studies, the magnitude of troponin elevations has correlated consistently with the risk of death and the composite risk of death or nonfatal MI^{2,8,13,14} and troponin levels have been shown to be more powerful prognostic indicators than CKMB levels (Table 3).^{13,15}

Table 1. Short-term risk of death or nonfatal MI in patients with unstable angina³

Feature	High Risk (At least 1 of the following features must be present)	Intermediate Risk (No high-risk features but must have 1 of the following features)
History	Accelerating tempo of ischaemic symptoms in preceding 48h	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use
Character of pain	Prolonged ongoing (>20 min) rest pain PCI last 6 months	Rest angina (<20 min or relieved with rest or sublingual nitroglycerine)
Clinical findings	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD. Pulmonary oedema, most likely related to ischaemia. New or worsening mitral regurgitation murmur S3 or new/worsening rales. Hypotension, bradycardia, tachycardia	
	Age >75yrs Diabetes Associated syncope Associated haemodynamic instability (Systolic BP <90mmHg, cool peripheries, diaphoresis) Known poor LV function (EF <40%)	Age >65-75yrs
ECG findings	Angina at rest with transient ST-segment changes >0.05mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia Deep T wave inversion (≥ 3 min in ≥ 3 leads)	T-wave inversions $\bullet 0.2$ mV in 3 leads Pathological Q waves
Cardiac markers	Elevated troponins (eg, TnT $\geq 0.03\mu\text{g/L}$)	

Table 2. Thrombolysis in myocardial infarction (TIMI) risk score¹⁰

Factor	Points
Age >65 years	1
>3 Risk Factors for IHD	1
Prior coronary stenosis >50%	1
>0.5mm ST deviation on ECG	1
>2 anginal events in prior 7 days	1
Aspirin use in prior 7 days	1
Elevated cardiac markers	1

Table 3. Serum markers for non-ST acute coronary syndromes

- Cardiac troponin T or I are considered the serum markers of choice.
- The presence in the serum of cardiac troponin T or I indicates myocyte necrosis.*
- The levels of cardiac troponins correlate with early risk of cardiac death and myocardial infarction.
- Measurements of cardiac troponin levels should be repeated after 6-8 hours, particularly if the baseline levels are normal.
- Myoglobin, heart fatty acid binding protein and CKMB (mass) are earlier markers of myocardial damage.
- Elevated cardiac troponin levels predict response to therapy with LMWHs, glycoprotein IIb/IIIa antagonists, and the benefit of an early invasive strategy.
- In patients with a recent (<14 days) MI, elevated troponins could be due to myocardial damage sustained in the initial MI. CK or CKMB is more useful in this setting to diagnose recurrent MI.

*See Table 4 for exceptions

Troponins may be the only markers required if utilised in a chest pain pathway with patients undergoing a 6-8 hour observation period.¹⁶ Point of care testing is recommended when hospital logistics cannot consistently deliver laboratory-assayed results within 1 hour.¹⁷

Troponins are very sensitive markers of myocyte necrosis, and elevated levels can occur in settings other than spontaneous myocardial ischaemia or percutaneous coronary intervention (PCI) (Table 4).⁵ Apart from acute coronary syndromes (ACS), the most frequent causes of elevated troponin levels are atrial or ventricular tachycardia (often with hypotension and an increased myocardial oxygen demand), pulmonary emboli with right ventricular infarction, and cardiac failure¹⁸ with myocardial necrosis due to neurohumoral changes and elevated left ventricular end-diastolic pressure. Other causes of elevated troponin levels include cardiac surgery, myocarditis, and renal failure.

The diagnostic criteria for MI for troponin T is a discrimination level of 0.03µg/L, there are different cutpoints for troponin I.¹⁹ The levels of troponins predict the benefits of therapy with low molecular weight heparins (LMWH),²⁰ glycoprotein IIb/IIIa antagonists,²¹ and of an early invasive/revascularisation strategy.²² The use of troponins to diagnose reinfarction is problematic in the 2 weeks after an initial MI as these markers have a long half-life (up to 14 days) and CKMB or CK should be measured in these circumstances.D4

Inflammatory markers

There has been extensive research into the roles of inflammation and inflammatory markers in NSTEMACS. The levels of high sensitivity C-reactive protein (hsCRP), interleukin-6 and more recently CD-40 ligand (which has prothrombotic effects) have been shown to have independent prognostic information.²³ Elevated levels of other inflammatory markers such as adhesion molecules,²⁴ interleukin-7²⁵ and matrix-metalloproteinases (including pregnancy associated plasma protein A)²⁶ also have been observed in patients with NSTEMACS. Conversely, levels of the anti-inflammatory cytokine, interleukin-10 have been shown to be reduced and patients with higher levels of interleukin-10 suffer fewer events during follow-up.²⁷ There have been no prospective trials of therapies aimed at modulating the levels of these markers. Neither the current ACC/AHA,³ ESC treatment guidelines for NSTEMACS²⁸ or the guidelines of The Australian and New Zealand Cardiac Society¹ recommend the measurement of inflammatory marker levels. Nor does this guideline recommend measurement, but recognises that in the near future with further evidence inflammatory markers may have an important role in risk assessment and choice of therapy.

Natriuretic peptides

In observational studies of patients with NSTEMACS, brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels have been shown to be independent prognostic factors for mortality and myocardial infarction. Elevation of BNP levels may be related to ischaemia causing myocardial stretch.²⁹⁻³¹ In the FRISC-II substudy NT-proBNP levels measured at admission predicted the benefit of revascularisation and added prognostic information to that obtained from clinical and ECG information and from markers of myocyte necrosis and

inflammation.³⁰ However in the TACTICS trial revascularisation did not provide more benefit for patients with elevated BNP levels (>80 ng/L) at admission.³² The results may relate to the enrolment of higher risk patients in FRISC-II and issues of statistical power. To enhance risk stratification and targeting of therapies, measurement of BNP or NT-proBNP levels may be considered but are not currently recommended.²⁹

Initial medical management

The recommended pathway of triage and indications for hospitalisation in patients with NSTEMI is summarised in Figure 1. An ECG and bloods for troponins, full blood count and lipids should be obtained within 10 minutes of presentation. If a chest pain unit pathway is used patients should be observed and have repeat measurements of troponins at 6–8 hours. Some patients will develop elevated troponins up to 12 hours after symptom onset. Early discharge decisions can then be made based on clinical features, including the presence or absence of recurrence of ischaemia, troponin levels, electrocardiographic changes, and testing for inducible ischaemia as appropriate, usually with exercise testing. Table 5 summarises the recommended dosage regimens for various antiplatelet and antithrombotic therapies (for more details see Appendix 2). Where to manage patients is an important consideration. It is recommended that all high risk patients should be managed in a CCU or CCU step-down until further risk stratification shows them to be at lower risk or revascularisation is performed.

The very important role of nurses in the management of these patients is acknowledged and highly valued.

Analgesia

Sub-lingual nitroglycerine is recommended for symptoms of ischaemia.**D4** Morphine or omnipon together with an antiemetic should be used to relieve severe pain.**D4** Intravenous nitroglycerine can also achieve symptomatic relief and be used for blood pressure lowering.**D3**

Antiplatelet agents

Aspirin—Aspirin reduces progression to MI and cardiac mortality by about 50%³³ and all patients without contraindication should immediately receive aspirin 150-300mg, 1++A which should be chewed if enteric coated. Long-term, lower doses of 75-100mg in enteric coated formulations to maintain efficacy and to minimise bleeding risk should be given indefinitely.^{33,34}

Clopidogrel—The CURE trial³⁵ and the separately reported PCI-CURE³⁶ results provide important evidence for the use of clopidogrel in patients with NSTEMI regardless of whether they are managed conservatively or invasively. In the CURE trial which randomised 12,562 patients (77% managed conservatively), clopidogrel reduced the incidence of death, non-fatal MI and stroke by 20% over an average 9-month follow-up period (9.3% with clopidogrel vs 11.5% with placebo, P<0.001). There were also reductions in the rates of revascularisation, as well as need for thrombolytic therapy and intravenous glycoprotein IIb/IIIa inhibitors in the clopidogrel group.

Figure 1. Early triage of patients presenting with probable/possible ischaemic symptoms including chest discomfort

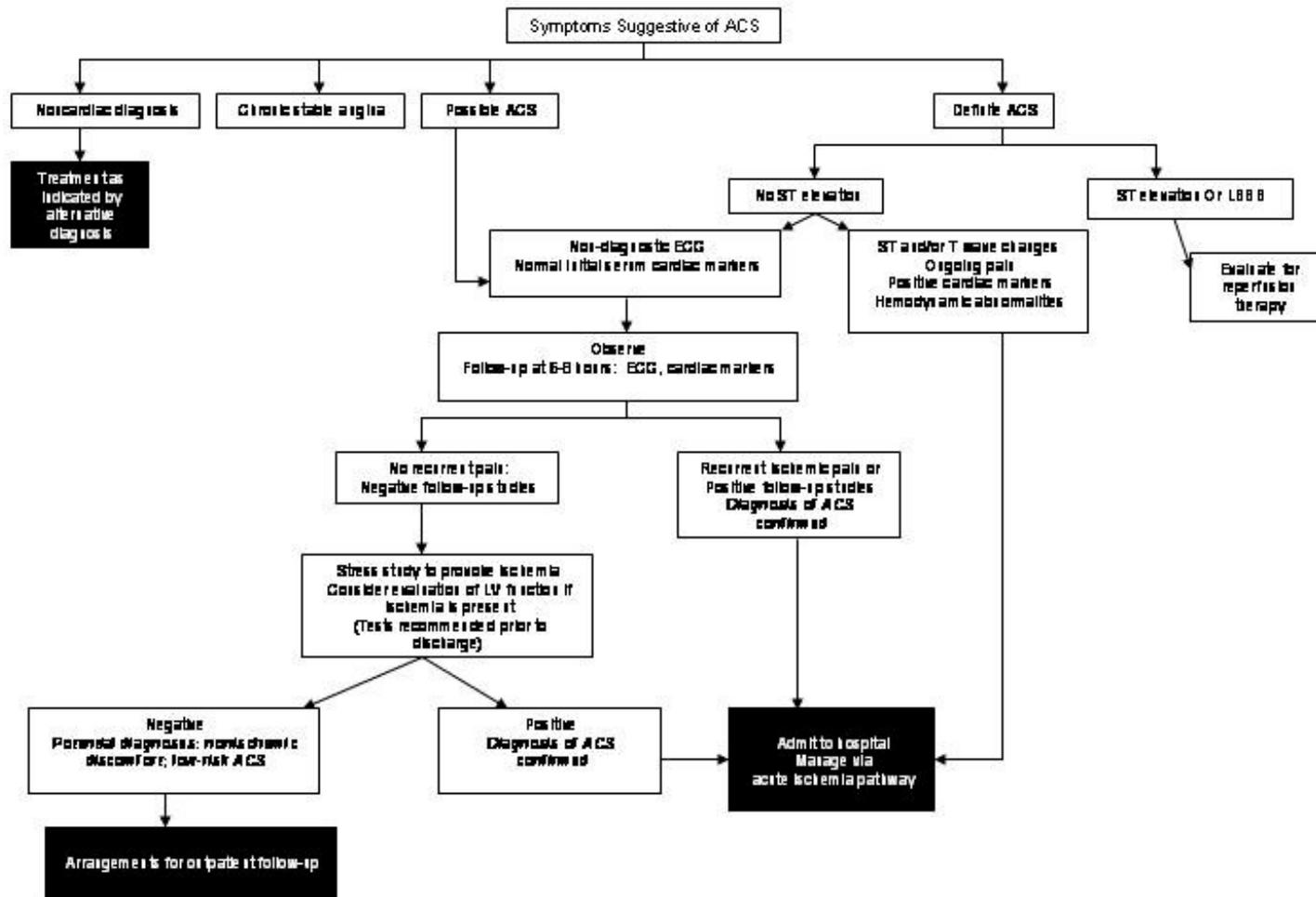


Table 4. Causes of elevated troponin levels in clinical settings other than ACS or PCI⁵

<p>Ischaemic causes other than plaque fissuring or rupture</p> <ul style="list-style-type: none"> • Coronary embolism (red cell or platelet thrombi, vegetation, atrial myxoma, calcification) • Coronary spasm • Coronary dissection • Aortic dissection • Transplant vasculopathy 	<p>Myopericarditis</p> <ul style="list-style-type: none"> • Rheumatic fever • Rheumatoid arthritis • Systemic vasculitis • Post-viral
<p>Cardiac surgery</p> <ul style="list-style-type: none"> • Left ventricular venting • Inadequate cardioplegia • Traumatic atrial cannulation • Manipulation of the heart • Ischaemia-related causes such as conduit or native vessel occlusion 	<p>Infiltrative diseases of the myocardium</p> <ul style="list-style-type: none"> • Amyloidosis • Sarcoidosis
<p>Miscellaneous</p> <ul style="list-style-type: none"> • Tachyarrhythmia • Hypertension • Congestive heart failure • Renal failure • Drug toxicity (e.g. adriamycin, 5-fluorouracil, etc) • Hypothyroidism • Pulmonary embolism with right ventricular infarction • Sepsis (including sepsis occurring with shock) • Transient ischaemic attack, stroke or subarachnoid haemorrhage • Pheochromocytoma • Rhabdomyolysis with myocyte necrosis 	<p>Traumatic</p> <ul style="list-style-type: none"> • Atrioventricular ablation • Defibrillation • Chest wall trauma

Table 5. Clinical use of antithrombotic therapies

Oral antiplatelet therapies	
Aspirin	Initial dose of 150-300mg nonenteric formulation followed by 75-150 mg/day of an enteric formulation
Clopidogrel (Plavix)	A loading dose of 4-8 tablets (300-600 mg) should be used when rapid onset of action is required, followed by 75 mg/day.
Heparins	
Heparin (UFH)	Bolus 60U/kg (maximum 4000 U) IV followed by infusion of 12U/kg/h (modified to achieve an aPTT of 50-75 seconds) with laboratory measurements and 60-85 with bedside measurements.
Enoxaparin (Lovenox)	1 mg/kg subcutaneously every 12 h; the first dose may be preceded by a 30 mg IV bolus.‡
Dalteparin (Fragmin)	120 IU/kg subcutaneously every 12 h (maximum 10,000 IU twice daily)
Glycoprotein IIb/IIIa antagonists	
Tirofiban (Aggrastat)	0.4 µg/kg/min for 30 minutes followed by infusion of 0.1 mcg/kg/h for 48 to 96 h* and for 12-24 hours post PCI
Eptifibatide (Integrilin)	180 mcg/kg bolus followed by infusion of 2.0 µg/kg/min for 72 to 96 h* and for 12.24 hours post PCI
Abx cimab (ReoPro)	0.25 mg/kg bolus followed by infusion of 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 to 24 h post PCI. Abx cimab should not be used as upstream treatment unless coronary anatomy is known and the patient is scheduled for PCI

* Different dose regimens were tested in recent clinical trials before percutaneous interventions

‡ Adjustment required for age ≥75 years and renal dysfunction – see pharmacy guidelines.

There was an excess of major bleeding with clopidogrel (3.7% vs 2.7%, P=0.003) but life-threatening bleeding was not increased. In patients undergoing CABG within 5 days of receiving clopidogrel, there was an increase in major bleeding from 6.3% to 9.6%, p=0.05. This compares with 7 major events per 1 000 patients (cardiovascular death, MI or stroke) prevented within the first 24 hours with clopidogrel.

In the PCI-CURE trial with 2658 patients, pre-treatment with clopidogrel for 10 days prior to PCI reduced 30-day composite of death, non-fatal MI and urgent target vessel revascularisation by 30% after PCI (4.5% vs 6.4%, P=0.03).³⁶ Long-term administration of clopidogrel after PCI for 12 months was associated with a lower rate of cardiovascular death, MI, or any revascularisation (p=0.03), and of cardiovascular death or MI (p=0.047). Overall (including events before and after PCI) there was a 31% reduction cardiovascular death or MI (p=0.002). Long-term benefit of clopidogrel plus aspirin after PCI in patients with chronic stable angina was also shown in the CREDO trial.³⁷ At 1 year, the composite endpoint of death, myocardial infarction or stroke was reduced by 27% in the clopidogrel group. Greater benefit was achieved in patients receiving clopidogrel >6 hours prior to PCI.

In the CAPRIE trial³⁸ in patients with previous MI, stroke or peripheral vascular disease clopidogrel had an 8.7% greater benefit than aspirin on reducing vascular death, MI and ischaemic stroke. Clopidogrel is therefore a useful alternative to aspirin when there is intolerance to aspirin.1++A

Clopidogrel (300-600mg orally and then 75 mg daily) should be considered in all patients at intermediate or high risk in addition to aspirin or as an alternative to aspirin and continued for 9 months according to appropriate funding.1+A There are two approaches, one is to give clopidogrel at the time of stenting after the coronary anatomy is known and the other is to give it to all patients prior to angiography, except those in whom urgent coronary artery bypass grafting (CABG) is likely as there is increased bleeding if clopidogrel has been given within 5 days of surgery.³⁵ These patients include those with ECG changes suggestive of $\geq 50\%$ left main stenosis (i.e. ST deviation in ≥ 2 coronary artery territories), known coronary anatomy from a previous angiogram which is inappropriate for PCI, the presence of multiple regional wall motion abnormalities on echocardiography, haemodynamic instability or heart failure. All of these patients should be considered for expeditious angiography.

Clopidogrel is expensive but several studies have shown it to be cost effective.³⁹⁻⁴¹ It is not currently funded except for patients undergoing stenting.

Glycoprotein IIb/IIIa antagonists—Patients with ischaemic ST depression on an ECG (≥ 0.5 mm), those with elevated troponin levels and those with diabetes have a worse prognosis and have been shown to have better outcomes with administration of intravenous glycoprotein IIb/IIIa antagonists. In a meta-analysis of glycoprotein IIb/IIIa inhibitors involving a total of 31,402 patients not routinely scheduled for PCI a 9% reduction of death or non-fatal MI was reported in the active treatment group (10.8% vs 11.8%, P=0.015).⁴² Patients with elevated troponins had an 18% reduction in death and MI equating to 20 events reduced for 1000 patients treated.

Diabetics have been shown to have a reduction in mortality with glycoprotein IIb/IIIa administration.⁴³ It is recommended that administration of either tirofiban or eptifibatide be considered in these high risk groups of patients as well as in patients with recurrent ischaemic symptoms and continued until the time of early coronary

angiography.1++A These agents have been shown to be cost effective but are not available in some hospitals.^{13,44-46}

Combination of antiplatelet therapy—The optimal antiplatelet therapy for patients with non ST-elevation acute coronary syndromes is not defined. There are no randomised clinical trial data comparing triple therapy (aspirin, clopidogrel and a glycoprotein IIb/IIIa antagonist) with double therapy—i.e. with aspirin plus clopidogrel or with aspirin plus a glycoprotein IIb/IIIa antagonist. There is in-vitro evidence showing greater inhibition of platelet function with combined therapy and there is non-randomised information⁴⁷ in non-ACS⁴⁸ and³⁶ in ACS showing improved efficacy with modest increases in bleeding.

Other antiplatelet agents—Dipyridamole does not confer any additional reduction in coronary events when added to aspirin and is not recommended.D4

Antithrombotic agents

Antithrombotic therapy is recommended in intermediate or high risk patients with either unfractionated heparin (UFH) or LMWH1++A with the preferred therapy being enoxaparin because a meta-analysis of all enoxaparin trials shows a 9% reduction in death and MI at 30 days compared to therapy with UFH (see Table 5 for suggested doses noting that APTT ranges are reagent specific and individual hospitals may have a different target range).⁴⁹

The recent SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularisation and glycoprotein IIb/IIIa Inhibitors) trial showed similar outcomes with UFH compared with enoxaparin on a background of high usage of clopidogrel and glycoprotein IIb/IIIa antagonists and an invasive strategy with a modest increase in bleeding. There was no significant increase in transfusions but there was an increase in TIMI major bleeding (See Appendix 3) (non CABG related) in all patients 1.7% UFH, 2.4% enoxaparin; p=0.025. In patients undergoing PCI there were similar TIMI major bleeding rates of 2.8% in patients receiving UFH vs 2.7% in patients receiving enoxaparin on a background of aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors. Either enoxaparin or UFH should be continued until catheterisation or for 48 hours but in view of increased bleeding and events if patients are switched from one antithrombotic agent to another, patients should continue on the initial antithrombotic agent.1++A

β-blockers

Although there is no strong evidence base in NSTEMI patients β-blockers may reduce progression to MI. IV β-blockers are recommended for patients at high risk and for those with continuing ischaemia if there are no contraindications (asthma, systolic BP <110 mmHg, heart rate <50 min or AV block) and oral therapy should be continued indefinitely.++B

Calcium channel blockers

If β-blockers are contraindicated, diltiazem should be given.D4 Calcium channel blockers that increase heart rate should not be used without concomitant β-blockers therapy.D4

Lipid modifying therapy

Initiation of statin therapy should begin in hospital in all ACS patients in order to enhance compliance and to reduce events. **1++A** Use of a fixed dose of simvastatin (40 mg) has been shown to reduce events by over 20% in HPS in non ACS patients.⁵⁰ Achievement of an LDL level of 1.6mmol/L with atorvastatin (80 mg) has been shown to reduce by 16% a composite endpoint of death, MI, readmission with unstable angina, revascularisation and stroke compared to an LDL level of 2.5mmol/L achieved with pravastatin therapy (40 mg).⁵¹

ACE inhibitors

All patients with evidence of heart failure, should receive oral ACE inhibitors beginning 2 hours after admission if the systolic BP is >100 mmHg using (e.g. 6.25 mg tds, or equivalent medication) and then increasing over several days to maximally tolerated doses. **1++A** In patients who are at high risk, ramipril and perindopril have been shown to reduce death and MI.^{52,53} In patients at low risk because of low cholesterol levels, non smoking, controlled blood pressure, previous revascularisation, and high usage of aspirin, beta-blockers, and statins, trandolapril has been shown not to be beneficial.^{53,54} ACE inhibitors should be commenced during hospitalisation and continued indefinitely. **1++C**

Early angiography and revascularisation

The FRISC-II trial demonstrated superiority in higher risk patients of an invasive approach with PCI or CABG after initial medical treatment with the low molecular weight heparin dalteparin and aspirin for 4-7 days with a reduction in mortality at 1 year from 3.9% to 2.2% p=0.01612. The TACTICS trial⁴ randomised 2220 high risk patients with aspirin, unfractionated heparin and tirofiban to an early invasive strategy with angiography within 4–48 hours followed by revascularisation if the anatomy was suitable, or to a more conservative strategy with catheterisation only for recurrent ischaemia or a positive stress test. Death, non-fatal MI and rehospitalisation for ACS at 6 months occurred in 15.9% of patients in the invasive arm and 19.4% in the conservative arm (P=0.025). The benefit of an invasive approach was confined to medium and high-risk patients who had elevated troponins, ST segment changes or diabetes.

RITA 3⁵⁵ also showed benefit of an invasive strategy in high risk patients treated with enoxaparin for 3 days prior to intervention. The ISAR Cool study⁵⁶ showed that an immediate invasive approach in 410 patients with either ST depression or elevated troponins (time to angiography of 2.4 hours) together with aspirin, clopidogrel, UFH and tirofiban resulted in lower rates of MI (5.9% vs 10.1%) compared with delaying PCI while on the same therapy for 72 hours. In the ICTUS (Invasive vs Conservative Treatment in Unstable Coronary Syndromes) study (Hot Lines ESC Munich 2004) a very high rate of intervention (73%) showed no advantage over a selective invasive strategy (47%).

An early invasive strategy within 48–72 hours together with intensive antithrombotic therapy is strongly recommended for patients with elevated troponin levels (or other cardiac markers of myocardial necrosis) **1++A**, patients with ST segment changes, diabetes, patients with recurrent or continuing ischaemic symptoms at rest or on mild

exertion despite medical therapy (beta-blocker or calcium channel blockers) and patients with interstitial or pulmonary oedema.**D4**

Several comorbidities such as renal failure are relative contraindications for angiography and revascularisation. Advanced age is not an absolute contraindication for angiography and PCI. Because of data²² showing reduced readmissions, PCI may be of particular value in the elderly.⁵⁷ Increasing stroke rates with surgery makes surgery unattractive in the very elderly.

In patients going to the catheterisation laboratory without pre-treatment with glycoprotein IIb/IIIa antagonists, it is recommended that administration of eptifibatid or abxici mab in the laboratory be considered, especially in patients with diabetes or the presence of angiographic thrombus.**1++A**

It is recommended that troponin positive patients waiting for surgery should be on clopidogrel and have it stopped 5 days before surgery.**1++B**

Secondary prevention

All patients should be referred to rehabilitation services. All patients without contraindication should be on aspirin, a β -blocker, a statin and an ACE inhibitor indefinitely and if funding allows clopidogrel for 9 months. Patients should also stop smoking, achieve ideal weight, and exercise 30 minutes/day.

Resource availability

It is recognised that in New Zealand that providing expensive pharmaceuticals and equitable provision of an invasive strategy for Maori and in rural populations will be challenging.⁵⁸ However, it is recognised that an invasive approach has been shown to be cost effective^{44,46} and it is expensive to keep patients in hospital for long periods awaiting diagnostic testing or to have these patients discharged with a high risk of reinfarction or readmission to hospital. Extensive cost effective analyses are planned to determine appropriate levels of funding in the New Zealand setting for patients with NSTEMACS.

Conclusion

In New Zealand cheap and readily available therapies such as aspirin, beta blockers and ACE inhibitors are under prescribed.⁵⁹ It is important that these treatments are used in as many patients as possible and treatment such as PCI in patients at high risk should also be equitably available to all New Zealanders.

Author information: Non ST-Elevation Acute Coronary Syndrome Guidelines Group (refer to Appendix 1 below), nationwide; The New Zealand Branch of The Cardiac Society of Australia and New Zealand, Wellington

Appendix 1. Non ST-Elevation Acute Coronary Syndromes Guidelines Group

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Appendix 2

LEVELS OF EVIDENCE

1++	High quality of meta-analysis, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is casual.
2+	Well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is casual.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not casual.
3	Non-analytic studies—e.g. case reports, case series.
4	Expert opinion.

Following assessment of the level of evidence for individual papers, recommendations were given a grade from A to D as below. This grading system departs from the Scottish Intercollegiate Guidelines Network (SIGN) system which was derived primarily for treatment guidelines and revises ranking according to therapy or prognosis. Questions relating to prognosis were considered a feature of this guideline to determine how to tailor cardiac rehabilitation services according to individual patient needs. For further details on the SIGN system see www.sign.ac.uk.

Grades of Recommendation	
A	<p>For therapy: At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, OR</p> <p>A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.</p> <p>For prognosis: At least one meta-analysis, systematic review, or large high quality cohort study rated as 2++ and directly applicable to the target population, OR</p> <p>A body of evidence consisting principally of studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results.</p>
B	<p>For therapy: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results, OR</p> <p>Extrapolated evidence from studies rated as 1++ or 1+.</p> <p>For prognosis: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results.</p>
C	<p>For therapy: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, OR</p> <p>Extrapolated evidence from studies rated as 2++</p>
D	<p>Evidence levels 3 or 4, OR</p> <p>For therapy: Extrapolated evidence from studies rated as 2+, or expert opinion.</p>

Appendix 3. TIMI major bleeding criteria—Bleeding is associated with ≥ 5 g/dL decrease in haemoglobin (each unit of packed red blood cells or whole blood transfused counting as 1g of haemoglobin) or a $\geq 15\%$ absolute decrease in haematocrit (each unit of packed red blood cells or whole blood transfused will count as 3% points) or it is intracranial (confirmed by magnetic resonance imaging or computer tomography).

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Severe hypothermia in association with sodium valproate overdose

Philip Robinson, Chris Abbott

Drug overdose is frequently a contributing factor in cases of hypothermia. We report the case of a 22-year-old man who overdosed on sodium valproate and developed severe hypothermia. Impaired thermoregulation including both hypothermia and heat intolerance have previously been described in relation to therapeutic sodium valproate administration. However there has not been a reported case of severe hypothermia associated with sodium valproate overdose.

Case report

A 22-year-old man was brought to the Emergency Department of Nelson Hospital by ambulance having overdosed on sodium valproate. He had become unresponsive the previous evening during a party, and flatmates had assumed this was due to alcohol intoxication and left him to recover. He lay fully clothed inside. The overnight temperature fell to 9°C. The next morning he remained unresponsive and was doused with cold water in an attempt to rouse him. This was unsuccessful and eventually an ambulance was called to take him to hospital, approximately 15 hours after the overdose. Police subsequently confirmed that 40 Epilim EC 200mg tablets were unaccounted for.

On arrival at hospital his Glasgow Coma Score was 3/15. He was apnoeic, bradycardic (pulse 50/min), hypotensive (systolic blood pressure 85 mmHg) and hypoglycaemic (blood glucose 3.1 mmol/L). Core temperature measured rectally was 27°C. There was no evidence of alcohol consumption.

The ECG showed slow atrial fibrillation and prominent Osborne (J) waves. An arterial blood gas on arrival showed a pH of 7.13, a pCO₂ of 77 mmHg, a pO₂ of 258 mmHg, and a base excess of -7 mmol/L. Haematology showed haemoglobin of 180 g/L but the full blood count and coagulation profiles were otherwise unremarkable. Biochemistry was notable for a sodium level of 156 mmol/L. Electrolytes and renal function were otherwise normal; amylase was 75 U/L and serum creatine kinase was 6,235 U/L.

Toxicology revealed an ethanol concentration of 0 mmol/L, paracetamol of less than 20 umol/L, salicylate of 0.1 mmol/L, and a valproate concentration of 8,700 umol/L.

Initial management in the Emergency Department included intubation and ventilation with 100% oxygen. He also received thiamine, glucose, and naloxone. Rewarming therapy included the following; removal of wet clothing, drying of the skin, and warmed resuscitation environment, humidified oxygen, and IV fluids. Further external rewarming therapy included use of a Bair Hugger® forced-air-rewarming blanket and a radiant heat lamp. Invasive rewarming included warmed bladder lavage.

The patient was transferred to the intensive care unit and progressively rewarmed over the next 12 hours by which time his temperature reached 36°C. At 6 hours post-

admission, his electrocardiograph reverted to sinus rhythm. Haemodialysis was considered but not instituted in view of the improving clinical picture. His creatine kinase peaked at 15,795 U/L 19 hours post-admission. By day 2, the patient was extubated and transferred to a general medical ward. He subsequently recovered fully with no residual neurological deficit.

Discussion

Hypothermia is defined as a core temperature of less than 35 degrees centigrade. It can occur at any age, in any season and in any setting.

Factors involved in hypothermia include:

- Increased heat loss (e.g. exposure and vasodilatation),
- Decreased heat production (e.g. age, endocrine disease, and immobility), and
- Impaired thermoregulation (e.g. secondary to injury, infection or drugs).

Hypothermia in this case was undoubtedly multifactorial in aetiology. This man was exposed to a low overnight temperature and was unconscious and immobile. These environmental factors alone are unlikely to have been the sole cause of hypothermia in this previously healthy man with no comorbidities. The haematological, biochemical, and electrocardiographic abnormalities noted are consistent with the recognised features of hypothermia.

Hypernatraemia is explained by the sodium content of valproate. Elevated creatine kinase is consistent with prolonged immobility and rhabdomyolysis.

The severity of hypothermia seemed greater than might be expected in the circumstances and the impact of sodium valproate in this case is of interest. Thermoregulatory derangement including both hypothermia and heat intolerance have been described in relation to therapeutic sodium valproate administration.¹⁻²

Zachariah et al, in *Neurology* 2000, report four cases of hypothermia induced by therapeutic valproic acid that improved dramatically on discontinuation of the drug. They suspect the apparent hypothermic effect of valproic acid relates to its Gamma-Aminobutyric Acid (GABA) agonistic effect. There is experimental animal evidence for the role of GABA in thermoregulation.³⁻⁴ The core temperature of rats has been reduced by GABA, and by sodium valproate experimentally, at least partly by activation of GABA receptors.⁵

Zachariah et al conclude that valproate can have reversible effects on temperature control in humans and that humans occasionally develop hypothermia at therapeutic dose.

While hypothermia associated with sodium valproate has been reported in animal studies, and in case reports in humans at therapeutic dose, we could find no previous reports of hypothermia associated with valproate overdose (Literature search on 7th Feb 2005. MEDLINE 1966-Week 4 Jan 2005 & EMBASE 1988-Week 6 Jan 2005. Search terms: valproate, valproic acid & hypothermia).

The New Zealand drug regulatory data sheet on Epilim EC and the NZ National Poison Centre datasheet on sodium valproate do not refer to hypothermia as an effect of either therapeutic use or overdose.⁶⁻⁷ Three case series of valproate overdose have

been published including a total of 427 patients and none have reported hypothermia as an effect.⁸⁻¹⁰

Hypothermia is frequently multifactorial in aetiology. Sodium valproate affects the neurochemical processes involved in hypothermia. Cases of hypothermia have been reported with therapeutic dosing of valproate, and therefore it seems likely sodium valproate was a significant contributing factor in the development of severe hypothermia in this case.

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Systemic side effects from topical imiquimod

Carl Hanger, Judith Dalrymple, David Hepburn

Topical imiquimod (Aldara™) has recently become available in New Zealand and has been used to treat several skin conditions including actinic keratoses, basal cell carcinoma (BCC), lentigo maligna, molluscum contagiosum, and common warts.¹

It has a novel mode of action as an immune response modifier.¹ It is thought to owe its activity to the induction of interferon alpha (IFN- α) and tumour necrosis factor alpha (TNF- α). Heightened activation of these substances *in vivo* might be expected to give systemic side effects and this does occur with oral administration.² However, topical application of imiquimod has been reported to be well tolerated with systemic reactions absent or mild.^{3,4} Local reactions such as erythema, scabbing, and crusting are commonly reported—and increasing severity of these may be associated with higher clearance rates of skin lesions.⁵

We report on a patient who had a systemic reaction to topical imiquimod, which was severe enough to prompt referral to a medical outpatient clinic for further work-up. Application of the Naranjo method⁶ for estimating the probability of adverse drug reactions (ADR) suggests that topical imiquimod is a ‘probable’ cause of this man’s symptoms. The referring general practitioner (GP) suspected an underlying malignancy or depression.

Case report

This case involved a fit and active 78-year-old man who regularly walked 10–15km each week. He had a past history of ischaemic heart disease (myocardial infarct 1999, but no angina since), hypertension, melanoma excised from just below his right ear 1999 (no recurrent disease), and a hip replacement in early 2004. There were perioperative problems with dislocation of the hip, with some associated weight loss, but this was regained in the subsequent months. He had no known drug allergies.

He presented to one of us (DH) with a basal cell carcinoma (BCC) on his right temple in early September 2004 and was prescribed topical imiquimod 5% daily for a 6-week period. After 2–3 weeks of applying imiquimod, he felt generally unwell, with ‘flu-like’ symptoms and extreme tiredness. He lost his appetite, lost weight, had postural hypotension symptoms, and was quite low in mood. In early October 2004, he had some night sweats which lasted for 1 week only. His GP referred him to the Older Persons Health Service (Princess Margaret Hospital, Christchurch) for an urgent review due to the severity of his symptoms, the associated 7 kg weight loss, and blood results which showed a markedly raised erythrocyte sedimentation rate (ESR).

When seen in late October (2 weeks after cessation of topical imiquimod), he was still complaining of all the above symptoms, but he felt they might be improving as his appetite had lifted. There was still a 6 cm diameter inflamed area (with scab formation) over his temple. There was no associated lymphadenopathy, signs of temporal arteritis, or local recurrence of melanoma. The remainder of examination

was normal except for postural hypotension (150/70 mmHg down to 105/55 mmHg). Administered drugs were bendrofluazide 5 mg, atenolol 100 mg, aspirin 150 mg, and doxazosin 4 mg daily. Due to the postural symptoms, his bendrofluazide was stopped. He attributed his symptoms to the cream and as there was no evidence to support an alternative hypothesis, we agreed on a 'wait and watch approach'.

When seen 3–4 weeks later, he felt completely normal again and had resumed his long walks each week. All of his symptoms had resolved. He had put on 2 kg and the area on his temple had healed with no residual erythema and the BCC had disappeared. In the interim, he had had a normal CT head scan, chest X-ray, and an ultrasound of his upper abdomen showed small gallstones but no dilatation of the bile ducts.

Sequential blood tests (see Table 1) showed resolution of all the abnormal inflammatory markers and liver tests. Tests for thyroid function, immunoglobulin levels, prostate specific antigen, folate, and autoantibodies were all normal.

Table 1. Sequential blood test results following cessation of topical imiquimod

Date	Haem (g/L)	ESR	CRP	ALT (0–35)	AST (0–35)	Ferritin (20–500)	Serum protein electrophoresis	Vit B ₁₂ (120–450)
Mid-October	115	108	–	52	39	–	–	–
28/10/2004	119	69	N†	N	N	831	Inflammatory reaction	148
22/11/2004	120	32	N	N	N	425	N	95
9/12/2004	129	20	–	–	–	–	–	69*

*Different laboratory with normal range (100–570); †=Normal; Haem=haemoglobin; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase.

Discussion

The raised inflammatory markers, together with his systemic upset, initially pointed to a significant intercurrent illness as the cause of his symptoms, but to date none has been found. Reported dose limiting toxicities of oral imiquimod include fatigue, fever, malaise, increased transaminases, hypotension, vomiting, and depression.² The timing of both the symptom onset and cessation, together with the cluster of symptoms previously reported with oral administration, strongly suggest that this was a severe systemic reaction to topically applied imiquimod.²

Topical imiquimod is reported to have minimal systemic absorption (<1%), with only a small number of mild systemic upsets.² However our case would suggest that these systemic side effects can be quite severe, with a marked inflammatory reaction. There was no evidence that he used more the prescribed amount, or used occlusive dressings, both of which might increase toxicity. We hypothesise that the absorption through very inflamed and vascular skin of the upper face and scalp may be greater than early studies indicate.⁷

As the t_{1/2} of oral imiquimod is 2.5 hours,⁸ the time to resolution was somewhat slower than we would have anticipated.⁹ His symptoms had started to improve within 2 weeks of cessation, but his inflammatory markers took much longer to resolve. This

long resolution phase may reflect the complex chain of events initiated by imiquimod, rather than just the plasma $t_{1/2}$ of imiquimod.¹⁰

Low vitamin B₁₂ can cause tiredness and dizziness, but each of his symptoms has resolved completely without any B₁₂ supplementation. Thus, it seems very unlikely that his consistently low B₁₂ levels are the cause of his symptoms. The temporal association of low B₁₂ with his systemic upset raises the possibility that the latter caused the former. Topical imiquimod may alter B₁₂ concentrations via its induction of INF- α and TNF- α , but the mechanism is not clear.¹¹ Irrespective of this, we believe he should have B₁₂ supplements to avoid the known haematological and neurological complications of B₁₂ deficiency, but it is unclear how long these should be given for.

To establish a causal relationship between a drug and an ADR, several factors must be considered. A definite causal relationship is very rarely established so it is the probability of causality that is assessed. Use of a systematic, reliable, and validated method reduces the variability of these assessments. We chose to apply the Naranjo method⁶ for estimating the probability of adverse drug reactions. This method ranks the probability of adverse drug reactions as definite, probable, possible or unlikely.

Our assessment suggests that topical imiquimod is a 'probable' cause of this man's symptoms, satisfying requirements of timing, dechallenge, and a pattern of adverse effects consistent with reports from oral use. Topical application of imiquimod appears to have been very effective at treating his BCC, so we do not want to discourage its appropriate use. Rather we wish to highlight a potentially serious adverse effect for prescribers to be aware of and to advise patients about.

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Capturing data on medicines usage: the potential of community pharmacy databases

Kathleen Ryan, Pauline Norris, Gordon Becket

Abstract

Aims The initial aim of the research projects was to examine the geographic distribution, patronage patterns, and loyalty of prescription clients around individual community pharmacies. A second aim was to explore the geographical and socioeconomic variation in the use of prescription medicines and prescribing trends both between and within therapeutic classes.

Methods Geographic Information Systems (GIS) technology (including the tabulating, geocoding, and mapping functions) was used to analyse the information that is held in community pharmacy databases.

Results These studies demonstrated the use of this technology to show variation in local use of prescription medicines, at both an individual level and a population level, through the analysis of data already held in community pharmacy databases.

Conclusion The use of GIS technology and pre-existing community pharmacy databases enables improved data capture on the prescription—and medication-related behaviour of health-service consumers.

There have been several strong calls for better information on medicines usage, including distribution, inappropriate use and misuse, and its impact on New Zealand primary and secondary healthcare costs.¹⁻⁴ Electronic technology makes collation of health information possible and much work has already been done on the technological development^{2,5,6} and the ethical and legal implications⁷⁻¹² of e-health information capture, transfer and utilisation. Simultaneously, there is an international movement towards increased involvement in public health and health promotional activities for community pharmacy.¹³⁻¹⁶

In his call for the streamlining of electronic information systems between various bodies within the health sector, David Moore, at that time the General Manager of PHARMAC (Pharmaceutical Management Agency—the body responsible for purchasing medicines on behalf of the state) stated that pharmacists “may have the best overall view of prescribing patterns”.¹

Community pharmacy databases do indeed hold a wealth of largely untapped information that is often overlooked. Also, community pharmacy databases overcome many of the limitations of the other databases.

In this paper, we argue that community pharmacy databases may be the most appropriate databases for providing information on medicines usage because of the amount, accuracy, and completeness of the information already stored and the ease with which it can be captured and analysed. To illustrate this claim, we demonstrate how Geographic Information Systems (GIS) technology has been used in a series of studies to utilise and analyse the information stored in community pharmacy

databases to provide information on medicines usage. Furthermore, for the above reasons (of quantity, quality, ease of capture, and access), we suggest that community pharmacy may be the most appropriate point of contact with patients for the collection and verification of universal electronic health information.

Background

Medicines usage databases—Various databases^{4,17} that provide some of the required information already exist. Each has its own unique strengths and limitations. At present, however, there is much duplication in the capture of some information and neglect or incomplete capture of other information, such as ethnicity and National Health Index (NHI) numbers.

For instance, HealthPAC (the Ministry of Health's Health Payments, Agreements and Compliance unit of the Ministry of Health) holds a record of all of the prescriptions for which pharmacists have been reimbursed under the pharmaceutical benefits scheme. The only pharmaceutical data that is collected and kept by HealthPAC is that which is needed for paying the pharmacist, and for trying to deter fraud.

Data that are recorded include the identity of the pharmacy and the prescriber, the name of the drug, dosage form, dose, frequency, total quantity, whether the patient has a Community Services Card (CSC) which entitles a low income patient to government subsidy, whether the patient is under 6 or over 65, and other factors that entitle a patient to reduced co-payments. However, this database does not capture unsubsidised, below subsidy or Over-The-Counter (OTC) medicines or any kind of patient information such as name, gender, age, address, ethnicity or diagnostic data.

Also, the HealthPAC database has no unique identifier which could be used to determine the number of patients for whom prescriptions are reimbursed or the number of prescriptions per patient, as opposed to the actual number of prescriptions reimbursed.

Similarly, there is a GP database (compiled by the Royal New Zealand College of General Practice [RNZCGP] Dunedin Research Unit from 42 general practice primary care computers) which includes a file of prescribed medicines (including the date of prescription, the medicine prescribed, the form, strength, dose and quantity) but which does not contain the name or address of the patient and in which until recently ethnicity data was not recorded.^{4,18}

The imminent integration of NHI numbers into GPs' electronic record systems will go some way towards addressing these shortcomings. The GP database represents only 6.7% (as at 31 December 2001) of New Zealand's population and primary care practitioners are added and deleted over time. The GP database does not record any information from private hospitals. The prescription of a medicine does not equate to its use. The GP database records what has been prescribed, not what was prescribed but not dispensed, nor what was dispensed but not collected. Similarly, collection of a medicine is not a measure of consumption.

Community pharmacy databases have become more common since the 1990s, primarily arising from computerisation of the legally required record of all medicines dispensed but also as a result of the electronic pricing of prescriptions by HealthPAC which superceded the transmission of paper prescriptions. Consequently, information is captured for 100% of patients for whom medicines are dispensed.

A typical community pharmacy database contains five domains of data:

- Demographic information about the patient (name, address, date of birth, family association, NHI number - if known - and subsidy status, such as possession of a community services or high user health card),
- The patient's medication history (drugs dispensed including strength, dosage (form, amount and frequency), quantity and date of dispensing),
- The drugs themselves (generic and brand name, therapeutic group identification as per the British National Formulary, sometimes adverse drug reactions)
- The prescriber (name, address, prescriber identification)
- Account information (prescription fees, part charges).

Although data about dispensing of a medicine is not an accurate measure of medication use, it is at least one step closer to consumption than a written prescription (as captured by the GP database), and compliance with chronic medications can be tracked through repeat dispensing frequency data.

Community pharmacy databases can also overcome some of the limitations of the HealthPAC data in that they enable linking of prescribing, dispensing and socioeconomic data (through name, address, ethnicity and deprivation score) on an individual patient basis. Another important difference between the information held in community pharmacy databases and that held in the HealthPAC database is that community pharmacy databases capture the provision of non-subsidised medicines.

Furthermore, they can be used, and sometimes are, to capture OTC medicines usage. The weakness of community pharmacy databases, as with most other databases, lies in the inaccuracy and inconsistency of the entry of information, in this case at the pharmacy level. National Health Index (NHI) numbers are not always entered and patients are sometimes entered under several names (for example John Smith, J M Smith or Mr J Smith) which results in the very time consuming task of matching names to address entries.

Similarly, the databases are rarely 'cleaned', and may contain deceased or relocated individuals. However, in spite of these limitations, community pharmacy databases may provide an important link in the attempt to achieve standardised national health information.

Geographic information systems (GIS) technology—GIS is a technology that enables the storage, analysis, and display of information in geographical terms. Several sets of information can be layered, one on top of the other, depending upon the purpose.

For example, a basic map can be produced with layers containing information about the location of rivers, roads, railways, local authority boundaries etcetera and this can be further overlaid with information on people, materials, vehicles, buildings, the weather or even the distribution of a toxic gas cloud after a chemical spillage. The various sets of information are stored as tables or databases and it is the combination of these tables that produces the layering of the information.

Geocoding is the electronic form of matching a database of addresses to a reference database of geographical information, such as the streets and suburbs within the local

area, essentially sticking pins in a map—by the millions! The reference database may also contain other information such as census or socioeconomic data. For example, geocoding offers a means of obtaining information about the geographical spread of, say, pharmacy customers by determining the physical location of each record in a pharmacy computer database.

The combined data sets can then be used for spatial or geographic analysis or to produce a map or model, enabling much finer detail than possible using manual methods. In this example, maps can be produced showing where customers live, what medications they have been dispensed, the frequency of dispensing and their socioeconomic status.

The studies reported here describe a series of research projects that demonstrate the potential use of the data stored in community pharmacy databases to provide information on medicines usage. This leads to a discussion of the issues that access to this type of health information raises. One of the initial areas to be addressed, in providing better information on medicines usage, is consumer behaviour with respect to access to pharmaceuticals. It has generally been assumed that consumers patronise the pharmacy nearest to where they live and that they attend only one pharmacy for their prescription medicines.

The first two studies address prescription customer pharmacy patronage and loyalty patterns. Once information has been obtained regarding consumer access to medicines then it is apposite to consider the frequency of dispensing and the distribution of particular medicines. The third study addresses the issues of dispensing frequency and distribution of medicines.

Methods and Results

Geographic Information Systems (GIS) technology (including tabulating, geocoding and mapping functions) was used to analyse the information held in community pharmacy databases. Addresses from the pharmacy database were matched against a reference database (provided by Land Information New Zealand), in this case, containing a list of the streets and suburbs within the local area. The combined data sets were then used for spatial or geographic analysis to produce a map of where customers lived showing much finer detail than possible using manual methods. The smallest unit, a meshblock, containing a median of about 90 people, was considered the most appropriate unit to use.

Study 1—The first study¹⁹ was designed to examine the geographic distribution and patronage patterns of prescription clients around individual community pharmacies. Prior to this study, in New Zealand, there was a lack of information about the geographical areas served by pharmacies. It was assumed that pharmacies drew on populations who lived in their immediate area. Community pharmacy databases were used to test this assumption.

Addresses of clients for whom prescriptions had been dispensed were downloaded from 12 NZ pharmacies, including four from central city locations, four suburban and four rural. For each pharmacy, a random sample of 1067 addresses was selected and electronically geocoded. Using this sample size ensured that the proportion of people living within specific meshblocks could be estimated (with 95% confidence) to within

3% of the actual level. The matching was represented in two visual forms, firstly, as a spreadsheet table and, secondly, as a series of maps for each pharmacy.

Because of the sensitive nature of the spreadsheets and geocoded maps produced in Study One the results for the individual pharmacies cannot be included in this paper. However, these individual results were collated to give a national picture of pharmacy patronage for various types of pharmacies.

Figure 1. Hypothetical map of a simulated suburban pharmacy

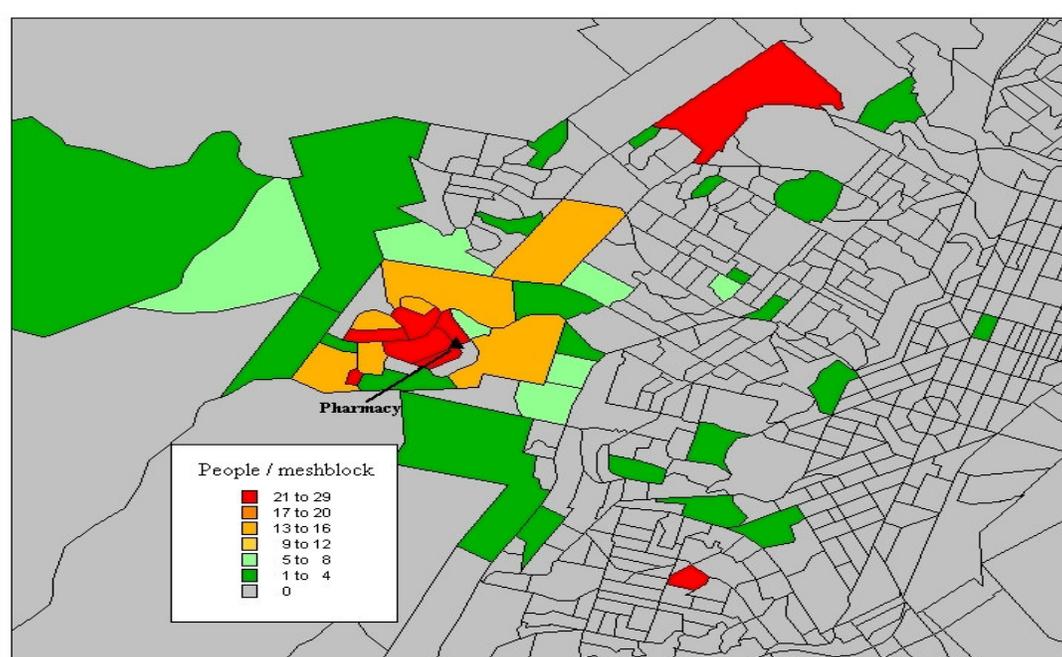


Figure 1 is a simulated example of the type of presentation produced. It shows a typical customer distribution pattern around a suburban pharmacy with customers mainly living in the same suburb as the pharmacy and surrounding residential suburbs. There are also a few outlying, high-density meshblocks that can be variously explained as containing rest homes or hospitals serviced by the pharmacy or customers belonging to a prescription-charge reimbursement scheme.

The pattern was different for central city pharmacies that had a broad scattering of low-density customers throughout the entire city with few customers living in the immediate vicinity. Rural pharmacies' customers came in high numbers from the township and in lower numbers from the surrounding countryside. Some pharmacies attracted customers from considerable distances. Therefore, it cannot be assumed that pharmacies draw their customers from the immediate vicinity; different types of pharmacy have different types of customer patronage patterns.

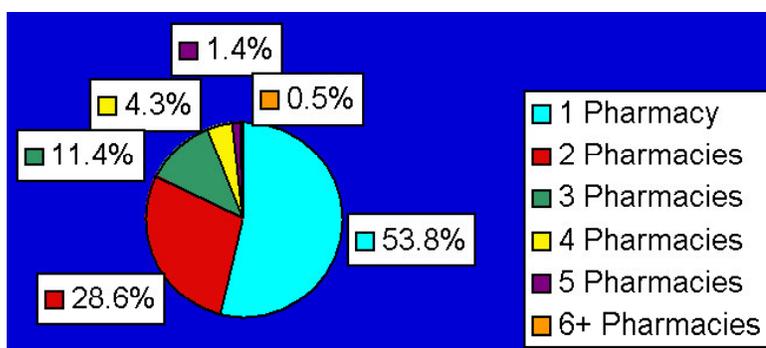
Study 2—The second study was designed to examine the loyalty of prescription clients by tracking the visits of specific clients to all pharmacies in a particular area. This study further tested the assumption that people go to the pharmacy nearest to

where they live and the added assumption that people go to one pharmacy only for their prescription medicines.

Seventy-two percent of the pharmacies in one municipal region of New Zealand agreed to participate. The names and addresses of prescription customers from each pharmacy for the past two years were downloaded and combined into one large database of over 300,000 records. These records were then sorted by surname and sampled to produce nine sets for cross matching. These sets were selected systematically by choosing nine surnames at random and then taking the following slice of 2500 names for comparison to the original individual databases.

Figure 2 shows the proportion of customers in a large town who had visited one, two, three or more pharmacies in the previous two-year period. In essence, it is a measure of customer loyalty.

Figure 2. Pharmacy customer loyalty in a single municipality.



It can be seen from Figure 2 that only just over half (53.8%) of all pharmacy prescription customers were loyal to one pharmacy. More than a quarter of customers visited two pharmacies and over a tenth visited three. Although only 0.5% of customers visited six or more pharmacies this was over 500 people in the two-year period in the region studied. In other words, almost one-fifth of pharmacy customers visited three or more pharmacies to have their prescriptions filled.

Figure 3. Customer loyalty by category of pharmacy.

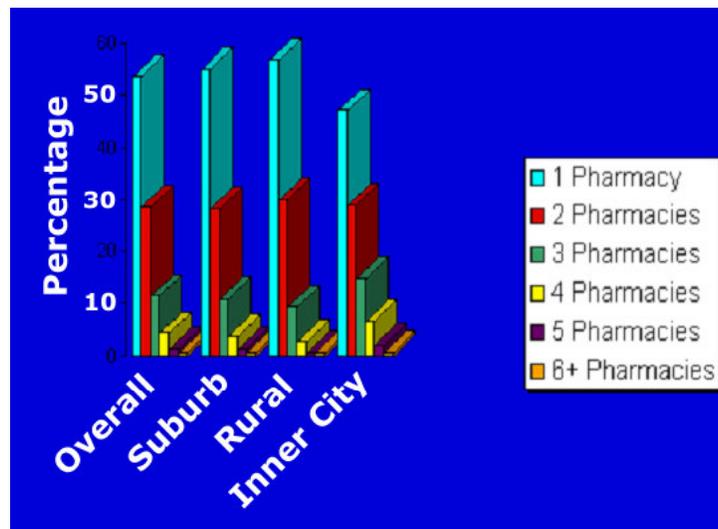


Figure 3 shows the loyalty of customers for the different types of pharmacies. It can be seen that the proportion of customers loyal to one pharmacy is greatest for rural pharmacies at 57% and lowest for central city pharmacies at 47%. It can also be seen that central city pharmacies have a higher proportion of customers who visit two or more pharmacies than do the other types of pharmacy. Unexpected, though, is the substantial proportion of customers from rural pharmacies who travel large distances to visit other pharmacies.

Study 3—The third study was designed to explore geographical and socioeconomic variation in the use of prescription medicines and prescribing trends between and within therapeutic classes of medicines.

The entire database of one community pharmacy was downloaded and all of the dispensings for 1 year were chosen for analysis. This represented over 6000 individuals receiving over 37,000 prescriptions. This study was only attempting to demonstrate potential, not to produce meaningful findings. In order to get significant results, data from all of the pharmacies in the area would be needed. The use of PersonID, a unique identifier assigned to each patient, allowed the cross-linking of tables, such as prescribed medicine and address. This enabled mapping of the distribution of any particular drug or class of drugs from that pharmacy. The addition of socioeconomic data, in the form of NZ Deprivation Index scores for each meshblock, produced information about the socioeconomic status of those sectors of the population who had received various medicines.

Figure 4. Distribution of azithromycin (simulated data)

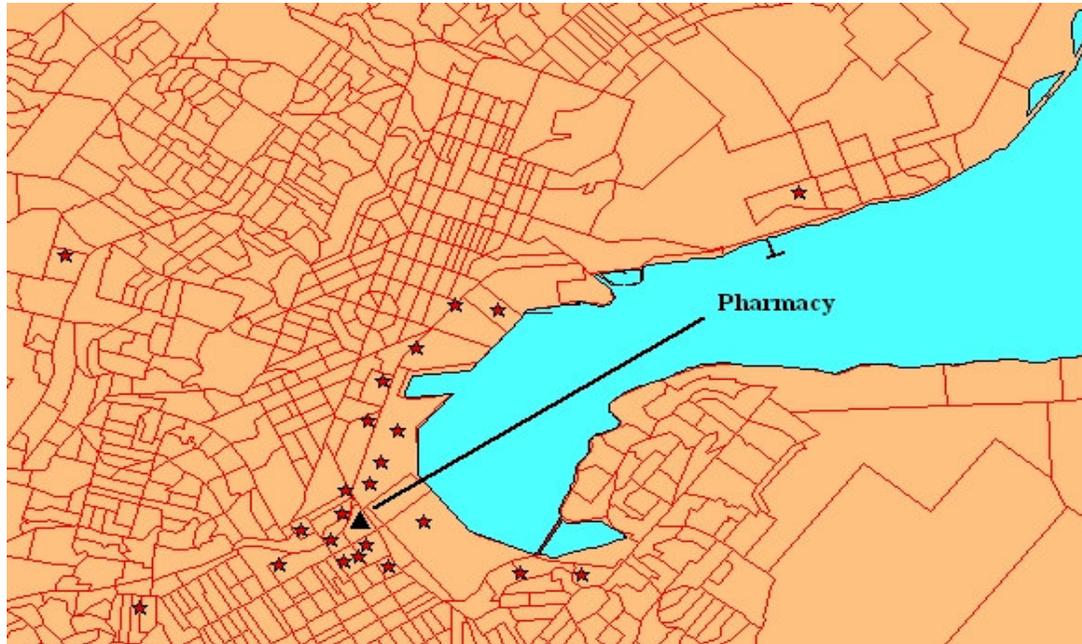


Figure 4 shows the distribution, by meshblock, of azithromycin from a single pharmacy for a single year. Because of the sensitive nature of this data we have provided a simulation of the actual findings. Azithromycin is used to treat chlamydia, so the map also approximates the geographic distribution of people treated for that sexually transmitted disease. In this instance, the map shows the prevalence of this drug usage in one suburb. Such a distribution pattern has implications for targeting public health educational material, in this case about sexually transmitted diseases.

Figure 5 shows the frequency of dispensings of an antidepressant for each of the locations. It shows a quite different distribution pattern from that of the medicine in Figure 4. It can be seen that 19 households received one dispensing of this drug during the year while only one household received seven dispensings. With monthly dispensings of antidepressants being the norm at the time, it would appear that many people were not completing the minimum recommended 6-month treatment regimen. Some dispensings may have been captured towards the beginning or end of a course or some people may have changed to another antidepressant but there is still some discrepancy and this study is merely illustrative of possibilities not definitive.

Figure 5. Distribution and frequency of dispensings of an antidepressant

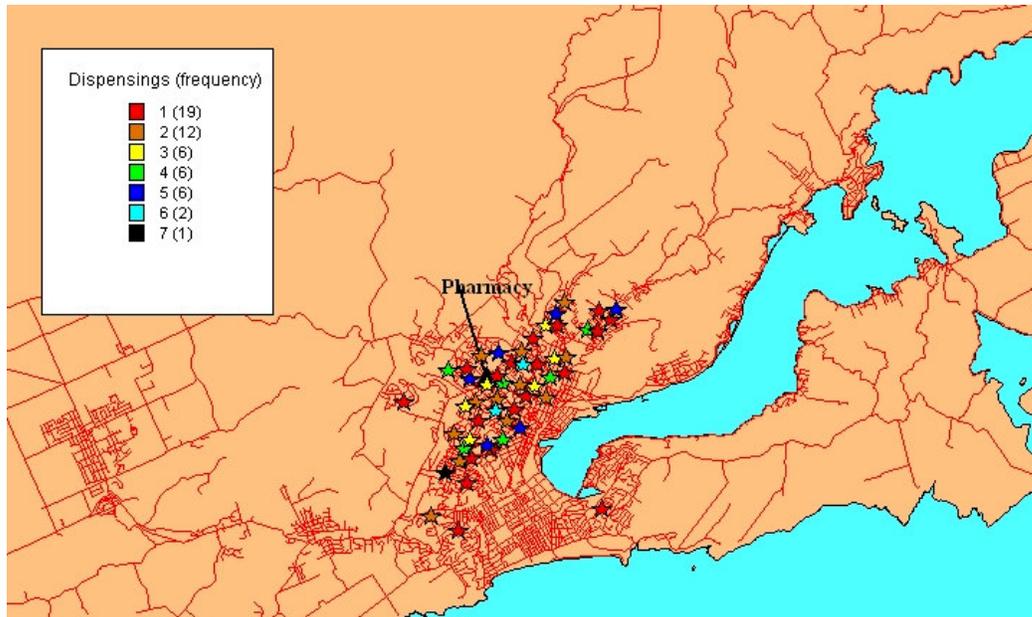


Figure 6. Distribution (by socioeconomic status) of antidiabetic medicines and related equipment

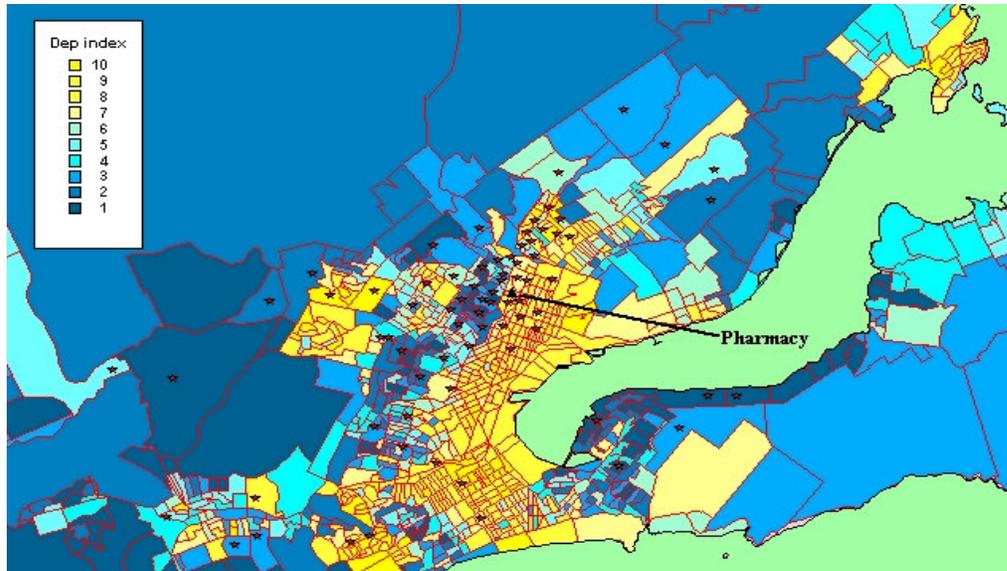


Figure 6 shows the distribution of dispensed anti-diabetic medications and paraphernalia overlaid onto the deprivation score by meshblock. The poorer areas of the city appear yellow and the wealthier blue. It must be stressed that this map utilises the data from one pharmacy only with the aim of demonstrating potential rather than significant findings. In this case, the dispensings are scattered fairly evenly over areas

with both high and low deprivation scores. This study is incomplete as yet but demonstrates the possibilities for documenting and monitoring the distribution of prescription medicines by both prescriber and therapeutic class and their use by geographic location and socioeconomic status.

Discussion

At the community level, it cannot be assumed that customers go to the pharmacy in the immediate vicinity of their dwelling; nor can it be assumed that customers are loyal to one pharmacy. Customer loyalty and patronage patterns have implications for levels of care, with the possibility that, for customers visiting many pharmacies, no pharmacist has a complete overview of the customer's medication history. At the population level, information about geographic and socioeconomic variation in prescribing patterns between and within therapeutic classes and by prescriber provides better understanding about the use of medicines. Knowledge about the distribution of pharmaceuticals and consumer access to pharmaceutical services allows for future policy development.

The above studies demonstrate the potential of the data stored in community pharmacy databases to provide information on medicines usage. Geographic information systems technology applied to community pharmacy databases has enabled the development of a body of knowledge about the delivery of pharmaceutical services in the community.

These studies demonstrate the ability to show local variation in the use of prescription medicines at individual and population levels by analysing the data already held in community pharmacy databases. Ethical issues notwithstanding, national data could potentially be collected via access to all community pharmacy databases. The GIS software used in these studies may in future be modified and incorporated into community pharmacy computer systems. Finally, access to this type of information would enable analysis of the effect of pharmaceuticals on secondary care costs and aid the appropriate allocation of resources¹. Work still needs to be done on the ethical issues surrounding access to personal health information held in health care databases, the transfer of such information between health professionals, its security and the use of the NHI number. Within the NZ community, there is very little awareness of the capture, storage and use of personal health information or the existence of national databases²⁰. Patient rights and patient responsibilities in terms of state funded health care need to be debated publicly.

It could be argued that patients, as consumers of state-funded health care, have certain obligations to the funder, such as the provision and use of data for purposes of monitoring, research or resource allocation. Duplication of data collection and incomplete capture of data could be avoided if community pharmacies were set up to collect a comprehensive national minimum dataset. Community pharmacies are ideally positioned, both in terms of physical location and technological ability, to become key players in the capture, verification, transfer and utilisation of e-health information on medicines usage.

Conclusion

Community pharmacy offers one of the most appropriate points of contact with health services' consumers for more complete data capture than is currently occurring. With

more universal use of NHI numbers, the future development of electronic health records and the electronic transfer of prescriptions, added to the already operational electronic submission of pharmaceutical subsidy payment claims, community pharmacy databases could be an important link in the capture of standardised information on medicines usage.

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Going against the flow: the impact of PHARMAC not funding COX-2 inhibitors for chronic arthritis

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Abstract

COX-2 inhibitors have come under a lot of scrutiny lately, with questions raised regarding class effects and the risk-benefit of these pharmaceuticals. From 1999 to 2003 the New Zealand Pharmaceutical Management Agency (PHARMAC) evaluated the evidence on COX-2 inhibitors, including their efficacy, cost-effectiveness and budgetary impact. In September 2003 PHARMAC decided not to list celecoxib, rofecoxib and meloxicam on the Pharmaceutical Schedule. This decision meant that at least 18 other pharmaceuticals were able to be funded or have access extended, resulting in 437 'statistical lives' saved per year, with net health gains, and savings for District Health Boards. Had PHARMAC funded COX-2 inhibitors at the same time as Australia, it is estimated that this may have resulted in approximately 740 to 4220 excess myocardial infarctions (MIs) and approximately 330 to 1900 excess deaths from MI.

- Drugs:** cyclo-oxygenase 2 (COX-2) inhibitors—celecoxib (Celebrex) and rofecoxib (Vioxx).
- Indication:** pain and inflammation in osteoarthritis (OA) and rheumatoid arthritis (RA).*
- Recommended dose:** rofecoxib 25 mg per day; celecoxib 200 mg per day.

Clinical efficacy and safety

Two large pivotal trials have been conducted to assess the effectiveness of celecoxib and rofecoxib compared with conventional nonsteroidal anti-inflammatory drugs (NSAIDs) in reducing gastrointestinal (GI) complications - the Celecoxib Long-term Arthritis Safety Study (CLASS)¹ and Vioxx Gastro-selective Outcomes Research (VIGOR) study.²

These two trials found that COX-2 inhibitors are no more effective than conventional NSAIDs in reducing pain and improving physical and global functions in both OA and RA patients, but may be associated with a lower rate of GI complications and improved tolerability. However, it has been widely questioned whether the claims over GI safety were overstated, particularly as, controversially, only the more positive 6-month CLASS results were reported even though the 12-month results were available.³⁻⁸

The cardiovascular safety of COX-2 inhibitors has also been questioned since the VIGOR trial was published in 2000.^{3,9,10} This trial found a five-fold incidence of myocardial infarction (MI) in patients administered rofecoxib compared with the naproxen group (0.5% vs. 0.1% respectively).¹¹

These cardiovascular concerns were confirmed when rofecoxib was abruptly withdrawn from the market in October 2004, following the results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial indicating an increased risk of confirmed serious thrombotic events (including MI and stroke) in long-term use.^{12†}

A cumulative meta-analysis published in December 2004 based on 18 RCTs reported a relative risk of MI with rofecoxib of 2.24 (95% CI 1.24-4.02). The authors concluded that rofecoxib should have been withdrawn several years earlier.³⁵

It was later estimated that rofecoxib could have caused 88,000–140,000 excess cases of serious coronary heart disease in the United States, many of which were likely to have been fatal.¹³ If COX-2 inhibitors were funded in New Zealand, we estimate that this would have resulted in between 740 and 4220 additional MIs, with 330 to 1900 excess deaths from MI.‡

It seems likely that the increased cardiovascular risk is a class effect of COX-2 inhibitors.^{14,15} The evidence on COX-2 inhibitors, including their cardiovascular risk, was thoroughly reviewed by the Medicines Adverse Reactions Committee (MARC) in early 2005. The Committee concluded that there was an overall class effect for cardiovascular risk with COX-2 inhibitors, and that given the limitations of the available data, all COX-2 inhibitors should be treated comparably and any restrictions placed on the products should be similar across the range of products (<http://www.medsafe.govt.nz/profs/adverse/minutes121.htm>).¹⁶

Background to PHARMAC's Decision

PHARMAC first received an application to list celecoxib in 1999. An application for the listing of rofecoxib was received in 2000. As with all applications PHARMAC receives, these applications were reviewed by PHARMAC's Pharmacology and Therapeutic Advisory Committee (PTAC).§

PTAC considered that the place in therapy and safety profile of COX-2 inhibitors still needed to be fully elucidated from post-marketing experience. The committee considered that COX-2 inhibitors were expensive and agreed that the additional expenditure over NSAIDs could not be justified considering the modest decrease in serious GI complications. In addition, the committee considered that patients at high risk of adverse events, including gastro-intestinal ones, would still have to be considered at high risk if treated with COX-2 inhibitors, hence targeting specific subgroups of patients would be difficult. However, at the time, PTAC considered that there was no clinical reason not to list these pharmaceuticals, hence PHARMAC staff continued to evaluate these drugs.

A rapid economic analysis was undertaken in 2002 to assess whether the benefits of COX-2 inhibitors (in terms of any reduction in GI bleeds) would compensate for the substantially higher price, compared with other pharmaceuticals PHARMAC has funded. This rapid analysis indicated that this class of drugs was not cost-effective when compared with other pharmaceuticals PHARMAC had funded. The analysis also indicated that given the available budget they were unaffordable.

PHARMAC and PTAC continued to keep up-to-date with the growing amount of international literature regarding the efficacy and safety profile of COX-2 inhibitors

and were aware of the increasing cardiovascular concerns associated with COX-2 inhibitors.

In 2003 PHARMAC was asked to share its work on COX-2 inhibitors with District Health Board (DHB) hospitals. A summary discussion document was written and distributed to DHB hospitals in April 2003

(<http://www.pharmac.govt.nz/pdf/Cox2.pdf>) highlighting the clinical evidence, cardiovascular concerns, cost-effectiveness and economic impact of COX-2 inhibitors.¹⁷

In September 2003 PHARMAC consulted with medical groups, pharmaceutical suppliers and interested parties on a proposal not to fund COX-2 inhibitors. Following this consultation, the PHARMAC Board resolved to decline the listing of celecoxib, rofecoxib and meloxicam on the Pharmaceutical Schedule.

Government Policy

PHARMAC's objective, as outlined in the NZ Public Health and Disability Act 2000, is to secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the funding provided.¹⁸

PHARMAC evaluated the evidence on COX-2 inhibitors, including efficacy and cost-effectiveness. PHARMAC also calculated that funding COX-2 inhibitors would exceed \$30 million per year. Based on this evidence PHARMAC concluded that for all patients that the cost of COX-2 inhibitors was significant and the benefits relatively minimal when compared with other pharmaceuticals awaiting funding.

PHARMAC must work within a fixed budget. Had COX-2 inhibitors been funded, then for the relevant time period this would have meant not funding or extending access for at least 18 pharmaceutical treatments, including extending access to statins and alendronate, venlafaxine, leflunamide, newer antiepileptic agents, and 3/4ths of extending access to olanzapine.** We calculate that by funding these pharmaceuticals rather than COX-2 inhibitors, the equivalent of 437 'statistical lives' were saved per year†† (i.e. if COX-2 inhibitors had been funded then the equivalent of 437 lives would have been lost per year from not receiving other pharmaceutical treatments).‡‡

These investments also nominally saved an extra \$17 million to the health sector; funding COX-2 inhibitors would have meant not realising these nominal savings.§§

Overall, the decision not to fund COX-2 inhibitors ultimately resulted in greater health gains from the pharmaceutical budget than would have been achieved otherwise. In fact, if COX-2 inhibitors were funded, this would have achieved a small net health loss, due to excess MIs.†††

Economic Analysis

In early 2002 PHARMAC staff undertook a rapid economic analysis for celecoxib using the 6-month CLASS data (indicative results described above).¹⁹ A detailed analysis on celecoxib and rofecoxib was then completed for PHARMAC in December 2003.

The results of the detailed analysis indicated that the cost per quality adjusted life year (QALY) of COX-2 inhibitors (celecoxib and rofecoxib) compared with conventional

NSAIDs for patients with a high-risk of GI haemorrhage was over \$1 million. For average risk patients, there was no overall benefit and higher total costs (i.e. negative risk-benefit ratio due to impact of MIs), with -0.00161 QALYs lost per patient per 5 years of treatment. The cost/QALY of celecoxib alone compared with conventional NSAIDs in high-risk patients was \$450,000. This suggested that COX-2 inhibitors were not cost-effective compared with other pharmaceuticals that could have been funded at the time.²⁰⁻²⁴ §§§

These results are consistent with several other analyses internationally.²⁵⁻²⁷

We acknowledge that COX-2 inhibitors can provide benefits for the subgroup of patients who are at high risk of GI bleeds and cannot tolerate or do not respond to conventional NSAIDs. However, we consider that it is still not cost-effective to fund COX-2 inhibitors for this subgroup when compared with other pharmaceuticals that could be funded – reflecting the trade-offs between improved GI symptoms and sequelae versus cardiovascular adverse effects. As well, these patients are still at risk of GI haemorrhage with COX-2 inhibitors, and as PTAC noted previously, targeting would be difficult.

Current Situation: New Zealand

There are currently five COX-2 inhibitors available in New Zealand – celecoxib (Celebrex), etoricoxib (Arcoxia), meloxicam (Mobic), lumircoxib (Prexige), and parecoxib (Dynastat).****

The Medicine Adverse Reactions Committee (MARC) has examined the evidence on the safety of COX-2 inhibitors, and recommended that they stay on the market but with considerably stronger warnings and requirements by pharmaceutical suppliers to collect and report information on their usage.²⁸ These recommendations have been accepted by the Ministry of Health. This decision was based on the argument that for some patients these medicines are the best treatment option. However the stronger warnings reflect MARC's view that an increased risk of heart attacks and strokes can occur with all COX-2 inhibitors. This decision was consistent with recommendations made by the European Medicines Evaluation Agency, and the Australian Therapeutic Goods Administration.

COX-2 inhibitors are being used in New Zealand despite PHARMAC not funding them. COX-2 inhibitors are funded by ACC (PHARMAC understands this to be in the region of \$1.1 million per year), whilst Pfizer has been reported as estimating that 11,600 patients received celecoxib during 2004.¹⁶

Current Situation: International

Australia

In Australia celecoxib and rofecoxib were listed on the Pharmaceutical Benefits Scheme (PBS) in August 2000. The rapid uptake of celecoxib and rofecoxib following their listing was unprecedented—800,000 prescriptions were written in the first 30 days, and 1.5 million prescriptions were written by the end of the first four months. This had a significant effect on the health budget, costing Aus\$205 million in the 2000/01 financial year.²⁹ COX-2 inhibitors were identified as a major reason for the health budget blowout in Australia in 2002.^{30,31}

Following the withdrawal of rofecoxib, the Therapeutic Goods Administration (TGA) undertook an urgent evaluation of COX-2 inhibitors.³² The results of this review were considered by the Australian Drug Evaluation Committee (ADEC), which made a number of recommendations to restrict the use of these drugs in Australia, including the introduction of explicit warnings in product information about the increased risk of cardiovascular adverse events. It also recommended that COX-2 inhibitors be prescribed only when other treatments cannot be tolerated or have caused serious adverse effects. In addition, celecoxib and meloxicam should not be prescribed to patients with increased risks of cardiovascular events and treatment should be limited to the shortest time needed. The TGA is also advising patients to review their treatment and dosage regime with their doctor.

Dispensings for COX-2 inhibitors in Australia during July 2005 (n=155,321) were 31% of their levels during the beginning of 2004.²⁹

Europe

The European Medicines Agency (EMA) recommended the suspension of the marketing authorisation for valdecoxib (Bextra) and new contraindications and warnings for other COX-2 inhibitors.^{33,34}

- A contraindication introduced for all COX-2 inhibitors in patients with ischemic heart disease or stroke;
- A warning introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for high risk patients;
- Doctors are advised to use the lowest effective dose for the shortest possible duration of treatment;
- Additional or strengthened warnings regarding risk of hypersensitivity reactions.

Comment

PHARMAC will continue to review the evidence on new pharmaceuticals, to try to ensure that maximum health gains can be obtained from the budget available.

Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Rachel Grocott declares no conflicts.

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Endnotes:

*PHARMAC has not assessed COX-2 inhibitors for use post-operatively.

†The APPROVe study was a multi-centre, randomised, placebo-controlled, double-blind study to determine the effect of 3 years treatment with rofecoxib on the recurrence of neoplastic polyps of the large bowel in 2600 patients with a history of colorectal adenoma. In this study 25 patients taking placebo versus 45 patients taking rofecoxib experienced a confirmed serious thrombotic event. The absolute event rates were approximately 3 per 400 patient years for placebo and 6 per 400 patient years for rofecoxib, i.e. an absolute increase in risk of approximately 3 thrombotic events per 400 patient years of treatment. The difference in event rates was only apparent after 18 months of treatment.

‡This estimate is based on uptake patterns in Australia. Between August 2000 (when celecoxib was funded on the Pharmaceutical Benefits Scheme (PBS)) and October 2004 (when rofecoxib was withdrawn) there were 25,101,929 dispensings for celecoxib and rofecoxib in Australia (PHARMAC analysis of PBS services and cost data at http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml). Had New Zealand funded COX-2 inhibitors at the same time, the total usage of COX-2 inhibitors over the 51 month time period would have been 416,518 person-years. It is assumed that 50% of usage would be for rofecoxib and 50% celecoxib. The estimate does not take into account the number of patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded). The proportion of patients administered various NSAIDs was based on script data between 2001-2002 financial year. Excess cases of MI were calculated using methods similar to those of Graham et al [Lancet 2005;3365:475-81]. The relative risk of MI with rofecoxib (RR 2.24) is based on the results of the Juni et al. meta-analysis on 18 RCTs on rofecoxib [Lancet 2004;364:2021-9], and the relative risk of MI with celecoxib (RR 1.4) was based on the results of the Moore et al meta-analysis [Arthritis Res Ther 2005;7:R644-65]. The (weighted-average) risk of MI for patients administered NSAIDs was calculated from the VIGOR and CLASS trials and the TennCare observational study [(Ray et al. Lancet 2002;359:118-23)]. The analysis assumes case fatality rates for MI of 44-45% [sources: NZ 28-day case fatality rate calculated from Auckland Regional Coronary Outcomes Study (ARCOS) data (Robert Beaglehole and Alistair Stewart, personal communication 1996), registrants aged 35 to 64 years 1986 to 1992 (no. deaths with 28 days / no. registrants); United Kingdom Heart Attack Study Collaborative Group (Norris RM. BMJ 199;316:1065-70; American Heart Association statistics cited by Graham et al Lancet 2005)].

§PTAC is a group of clinicians that considers clinical evidence and provides independent and objective advice to PHARMAC on the clinical consequences of funding decisions.

<http://www.pharmac.govt.nz/ptac.asp>

**This analysis calculates that, based on Australian uptake rates, expenditure in the first year may have been NZ\$33.4 million (PHARMAC analysis of PBS data with 4,594,187 COX-2 inhibitor dispensings in the first 12 months in Australia; assumes \$1.20/patient/day cost). This compares with 18.7 pharmaceutical investments between 1999/00 to 2003/04 giving the same estimated spending over the first 12 months. These investments, in order of total quality-adjusted life years (QALYs) gained during the first 12 months that they were funded, were: statins; alendronate and etidronate for severe osteoporosis; levonorgestrel-releasing intrauterine devices and tranexamic acid for heavy menstrual bleeding; imatinib for chronic myeloid leukemia + GIST; lamivudine for chronic Hepatitis B infection; venlafaxine for refractory depression; 3/4ths of olanzapine for schizophrenia; leflunomide for rheumatoid arthritis; naltrexone for alcohol addiction; topiramate and gabapentin for refractory epilepsy; anastrozole for advanced breast cancer; etanercept for juvenile rheumatoid arthritis; tacrolimus for immunosuppression post any organ transplant; eformoterol (LABA) for asthma.

††In this context, each 'life saved' is a statistical life, and each saved life is equivalent to living a full quality of life for 36.4 remaining years expected for the average New Zealand citizen. The present value is 9.7 years after discounting at 10% (the discount rate used by PHARMAC for economic analyses for decisions up until July 2005). 'Statistical lives' are calculated from total quality-adjusted life years (QALYs) estimated for decisions, by dividing total QALYs by the above 9.7 discounted years lost prematurely per average death. Further information about QALYs is available at <http://www.nzma.org.nz/journal/116-1170/362/> and <http://www.pharmac.govt.nz/pdf/QALYExplanation.pdf>

‡‡In this analysis approximately 4,231 QALYs would have been lost in the first 12 months alone had PHARMAC not funded the 18.7 new investments but had instead funded COX-2 inhibitors. This equates to 906 QALYs per million population per year. This estimate does not take into account patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded).

§§According to PHARMAC's economic analyses for the 18.7 investments, spending the \$33.4 million over the first 12 months would mean fewer health sector costs elsewhere through reduced use of other pharmaceuticals, hospitalisations, disability support services, etc., to the tune of \$17.0 million (i.e. offsets of 51%). Hence the net cost to DHBs of these 18.7 investments was \$16.4 million over the first 12 months. By contrast, funding COX-2 inhibitors would have meant savings to the health sector of \$9.3 million through reduced costs of conventional NSAIDs. Hence, the net savings to DHBs through the 18.7 investments rather than COX-2 inhibitors would have been \$7.6 million over the first 12 months (the difference between the \$17.0 million and \$9.3 million, with rounding). This estimate does not take into account patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded).

†††On average perhaps 454 (range 136-772) additional MIs and 204 (60-347) excess deaths from MI during would have occurred in New Zealand during the first year of COX-2 inhibitor funding – using the same methods as earlier in endnote ‡ (based on Graham et al Lancet 2005) and an estimated 76,232 patients predicted to use COX-2 inhibitors in New Zealand within the first 12 months (PHARMAC analysis of PBS services data). Taking into account the number of major GI bleeds prevented from the use of COX-2 inhibitors (approximately 225 – based on the incidence rates in CLASS and VIGOR) this results in an overall risk-benefit ratio of COX-2 inhibitors 2.6:1. However, due to a lower case-fatality rate with major GI bleeds (approximately 12% - see Economic analysis section) compared with MIs (44-45%), the risk-benefit ratio of COX-2 inhibitors in preventing death is 9.9:1 (i.e. patients administered COX-2 inhibitors are approximately 10-times more likely to die from MI compared with a major GI bleed). Hence any QALY gains from fewer GI bleeds would be offset by greater QALY losses from excess MIs. This estimate does not take into account patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded).

‡‡‡Patients with a high risk of GI haemorrhage were defined for the purposes of the economic analysis here as persons with a history of GI ulcer events.

§§§Cost/QALYs of other pharmaceuticals that could have been funded at the time (1999/00 to 2003/04) included: Extending access to erythropoietin beta for anaemia of chronic renal failure (2002/2003) \$-40,000/QALY; Access for olanzapine for schizophrenia - existing patients with risperidone failure (1999/2000) \$-5,748/QALY; Extending access to alendronate for osteoporosis (2003/2004) \$-3,395/QALY; Listing of levonorgestrel-releasing IUS for heavy menstrual bleeding (2002/2003) \$750/QALY; Listing of lamivudine for chronic Hepatitis B infection (1999/2000) \$1,500/QALY; Extending access to tranexamic acid for heavy menstrual bleeding (2001/2002) \$2,185/QALY; Extending access to statins for cardiovascular risk (dyslipidaemia) (2001/2002) \$2,495/QALY; Listing of alendronate for severe osteoporosis (1999/2000) \$3,545/QALY; Listing of naltrexone for alcohol addiction (2003/2004) \$3,600/QALY; Extending access to anastrozole for breast cancer (advanced) (2002/2003) \$4,000/QALY; Listing of venlafaxine for refractory depression (2003/2004) \$4,000/QALY; Extending access to etidronate for osteoporosis (2003/2004) \$6,492/QALY; Extending access to alendronate for osteoporosis to 1+# (BMD<-3.0) (2000/2001) \$12,426/QALY; Extending access to tacrolimus for immunosuppression post any organ transplant (primary treatment or rescue therapy) (2003/2004) \$12,500/QALY; Listing of leflunomide for rheumatoid arthritis (2001/2002) \$14,086/QALY; Listing of gabapentin for refractory epilepsy (2000/2001) \$15,000/QALY; Listing of topiramate for epilepsy (refractory) (2000/2001) \$18,500/QALY; Listing of imatinib for chronic myeloid leukemia + GIST (2002/2003) \$18,900/QALY; Extending olanzapine for schizophrenia to new cases (1999/2000) \$27,467/QALY; Listing of eformoterol for asthma symptom control (2000/2001) \$40,000/QALY; Listing of etanercept for juvenile rheumatoid arthritis (2003/2004) \$40,000/QALY.

****Valdecocix (Bextra) was voluntarily withdrawn in April 2005 due to concerns about an increased risk of serious skin reactions.

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Modern medical literature

This extract comes from a speech read before the Wellington Division, B.M.A., by W. Kington Fyffe, M.D., M. R. C. P., and published in the New Zealand Medical Journal 1905, Volume 4 (18), p307.

It is well in these days, when discovery is added to discovery, and invention to invention, to occasionally look backwards and take stock of what we have left behind. It may be that in the refuse forgotten and thrown away there may be a gem buried, and, like the Chinese, we may possibly get gold from the outcast tailings of the mine. I venture to think sometimes that too much time is spent in what is called "keeping up with modern medical literature," which might be occupied in absorbing the ripe experience of our great-grandfathers in the science.

And here let me deplore the lack of great writing, the power of fine composition, in our modern medical writers, which their forefathers possessed. Since Sir James Paget died we have had no medical Chrysostom.

All our text-books are crammed full of facts put together at the expense of the English language, and to our disgrace as an educated profession. The language is slipshod, and the meaning often most involved. It is true there are exceptions to the rule, but, taken generally, the tendency in modern medical literature is to sacrifice style and finish to the everlasting fact expressed in the baldest and worst possible English.

Who nowadays opens a medical book for pleasure? One may do so to look up a point, or to try and get light thrown on an obscure case, but not for any other reason.



Acute abdominal pain and palpable mass

K Sudeep, M John

A 32-year-old lady was referred for evaluation of an abdominal swelling that appeared following an episode of acute abdominal pain and shock 2 weeks prior to the current presentation. She was healthy prior to this episode. Clinical examination revealed a few pigmented papular lesions on the cheek and the left-sided large abdominal mass.

Figures 1 and 2 show a computed tomographic (CT) scan performed 2 weeks after the acute episode.

Questions—What do the figures show?. What is the diagnosis?

Figure 1

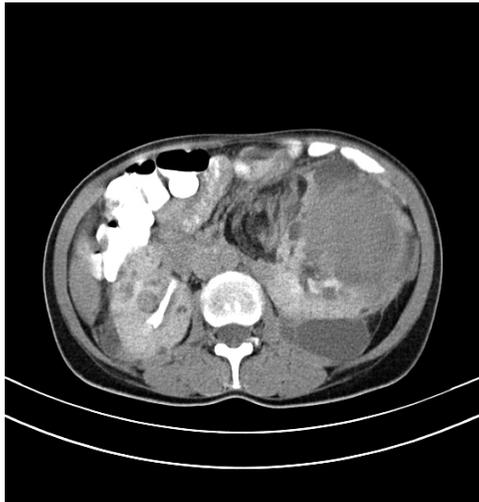
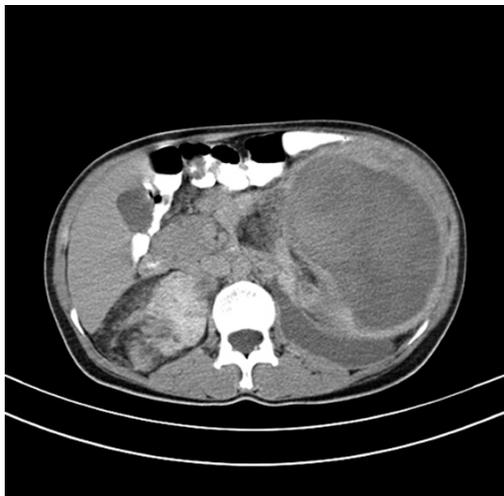


Figure 2



Answers and discussion

The CT shows a large haematoma causing compression of the left kidney with bilateral large renal angiomyolipomas, characterised by fat density tissue within the kidneys. Vertebral sclerotic lesions were also seen. The facial lesion of the patient was biopsied and was suggestive of an angiofibroma. The patient underwent drainage of the organised haematoma and partial nephrectomy on the left side.

The presence of renal angiomyolipomas with sclerotic bone lesions and facial angiofibromas are diagnostic of tuberous sclerosis. The diagnosis of tuberous sclerosis is dependent on the presence of major and minor features. The major features are tubers, sub-ependymal nodules (SEN), sub-ependymal giant cell astrocytomas (SEGAS), cardiac rhabdomyoma, retinal hamartomas, renal angiomyolipomas, pulmonary lymphangiomyomatosis, shagreen patch, facial angiofibroma (adenoma sebaceum), and unguis fibromas.

The minor features proposed are dental pitting, bone cysts, hypomelanotic macules, pulmonary lymphangiomyomatosis, gingival fibromas, hamartomatous rectal polyps, and cerebral white matter radiation lines on MRI. Definite tuberous sclerosis is diagnosed in the presence of two major features or one major plus two minor features.

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Low-dose aspirin in the primary prevention of cancer?

Basic research and observational evidence as well as results from trials of colon polyp recurrence suggest a role for aspirin in the chemoprevention of cancer. The proposed mechanism for aspirin's effect on cancer lies with its effect on the cyclooxygenase 2 (COX-2) enzyme, which is linked to inflammation and related to tumor growth through its effect on apoptosis, cell migration, and angiogenesis. That's the theory, but the results from a randomised trial involving 39,876 healthy U.S. adult women (The Women's Health Study) do not confirm the theory. The outcome of this large-scale, long-term trial suggest that alternate day use of low-dose aspirin (100 mg) for an average 10 years of treatment does not lower risk of total, breast, colorectal, or other site-specific cancers.

Oh well, what about statins and cancer?

JAMA 2005;294:47-55

Statins and cancer

Yes you've guessed it. Statins target 3-hydroxy-3-methylglutaryl coenzyme A reductase, thereby blocking endogenous synthesis of cholesterol and have proven worth in reducing cardiovascular harm. But researchers have also been exploring the effects of statins on molecular carcinogenesis, such as their ability to inhibit proliferation, angiogenesis, and metastasis and promote apoptosis—and apparently they do.

In addition, in a recent retrospective study it is claimed that the use of statins was associated with a 47% reduction in the risk of colorectal cancer. Sounds good—but bear in mind that basic research and observational study were not confirmed in the analogous aspirin and cancer prevention story.

N Engl J Med 2005;352:2184-92 & 2238-9

PET scans

Antiquated regulations and the refusal to fund positron emission tomography (PET) scans means patients are denied a diagnostic tool that is standard in most industrialized countries. Who said that? Well on this occasion it was the Canadian Association of Radiologists (CAR) and the Canadian Society of Nuclear Medicine. As it happens there are 12 PET scanners in Canada, including 2 at private clinics in Quebec and British Columbia. Of the remaining 10, only 3 are available for clinical use; the others operate under research protocols for clinical trial participants. You will recall that we have no PET scanners in New Zealand, so we don't feel that bad about Canada's plight. The antiquated regulation concerns the lack of availability of fluorodeoxyglucose (FDG), the radioactive tracer used to highlight molecular activity on the imaging scans.

CMAJ 2005;172:1670-71

Patients with suspected osteoporosis

Osteoporosis is very common in the elderly—particularly in females. How far should it be investigated? Routine blood tests, serum calcium and vitamin D, X-ray spine and bone density scan—yes all of these—but anything else?

A Danish group suggest that patients presenting with osteoporosis should be tested for M (monoclonal) component in serum. Why? Because some will have myeloma. In their study, 18 of 366 (4.9%) patients with osteoporosis had M components in their serum. Accordingly, as 1 in 20 patients with newly diagnosed osteoporosis had multiple myeloma or monoclonal gammopathy of undetermined significance, they feel that serum electrophoresis is a reasonable screening test. Seems good sense.

BMJ 2005;330:818–20

Acute infective conjunctivitis in children

Acute sticky or red eye in children is common. How best managed—eye swab and chloramphenicol eye drops?—or just the drops?—or nothing? Most probably just get the drops. However, we now have a randomised double-blind placebo-controlled trial to help us decide.

A recently reported study included 326 children aged 6 months to 12 years with a clinical diagnosis of conjunctivitis who were recruited from 12 general medical practices in the UK. Eye swabs were taken for bacterial and viral analysis, and half of the children had chloramphenicol eye drops and the rest had placebo drops. And the results (at 7 days)—cure in both groups in more than 80% of cases. And the eye swabs were non-contributory.

The message is clear.

Lancet 2005;366:37–43



New Zealand Quality of Healthcare Study, what about hindsight bias?

I have followed with interest the series of papers coming out of the New Zealand Quality of Healthcare Study. The most recent¹ covered adverse events arising during surgical care.

Both that study and its Australian counterpart (The Quality in Australian Health Care Study) assessed the preventability of adverse events. This was done without reference to the effect of hindsight bias.

As part of the American Society of Anesthesiologists Closed Claims Study² this was studied by providing reviewers with cases where the outcome had been changed.

The reviewers' assessment of preventability was affected by the outcome to the order of a third. The reviewer was more likely to say a complication was preventable if there was a poor outcome, and vice versa.

A preventable complication sounds like a bad thing to both professional and lay reader. Might I suggest that reference to hindsight bias would set some boundaries around the figures quoted in this work and that this factor should be incorporated in future work.

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2. Caplan RA. Posner KL. Cheney FW Effect of outcome on physician judgments of appropriateness of care. JAMA. 1991;265:1957–60.